

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209229Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

Summary Basis of Approval

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Reviewers	Pamela Horn, M.D., Medical Officer Yi Ren, Ph.D., Statistical Reviewer David Petullo, M.S., Statistical Team Leader Celia Winchell, M.D., Medical Team Leader, Cross-Disciplinary Team Leader Sharon Hertz, M.D., Division Director Mary Thanh-Hai, M.D., Office Director
Review Completion Date	May 15, 2018
Established/Proper Name	Lofexidine hydrochloride
(Proposed) Trade Name	Lucemyra
Applicant	US WorldMeds
Dosage Form(s)	tablet
Applicant Proposed Dosing Regimen(s)	0.72 ¹ mg four times a day for up to 14 days
Applicant Proposed Indication(s)/Population(s)	Mitigation of symptoms associated with opioid withdrawal; facilitation of completion of opioid discontinuation treatment
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults

This memo serves as the primary clinical and statistical review, the Cross-Disciplinary Team Leader review, and the Supervisory review of this application.

¹ Expressed as hydrochloride salt, this dose is 0.8 mg qid, 3.2 mg/day. This review primarily refers to the drug in terms of the salt.

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1. Executive Summary

1.1 Product Introduction

Lofexidine is an alpha-2 adrenergic agonist intended for the mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment. The product should be used as part of a long-term treatment plan for managing opioid use disorder following discontinuation of opioids. If approved for the proposed indications, lofexidine would be the first non-opioid approved for treating opioid withdrawal and the only product approved for the facilitation of completion of opioid discontinuation treatment. Currently, the only product approved for managing opioid withdrawal is methadone. There is widespread off-label use of buprenorphine and clonidine for managing opioid withdrawal

1.2 Conclusions on the Substantial Evidence of Effectiveness

The application provides substantial evidence that lofexidine is effective for mitigating symptoms of withdrawal associated with abrupt opioid discontinuation based on two adequate and well-controlled clinical trials that demonstrated a clinically meaningful and statistically significant treatment effect on opioid withdrawal symptoms in patients with opioid use disorder after abrupt opioid discontinuation as measured by an instrument that assessed patient-reported symptoms of opioid withdrawal, as well as an effect on retention through the treatment period.

1.3 Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Lofexidine is indicated for the mitigation of symptoms associated with abrupt withdrawal from [REDACTED] (b) (4) [REDACTED] opioids. I recommend approval, if the Applicant and Division arrive at agreed-upon labeling.

Withdrawal is not life-threatening but in patients with opioid use disorder (OUD), which is a life-threatening disease, it serves as a barrier to entering into treatment and stopping opioid use. In patients with physical dependence but not addiction, withdrawal can be very uncomfortable and distressing. Current treatment options for abrupt withdrawal include methadone, buprenorphine, and clonidine. In the clinical situations where it is possible, a slow taper with the opioid on which the patient is physically dependent is preferred to abrupt withdrawal.

The data meet the standard for substantial evidence for effectiveness for the mitigation of withdrawal symptoms. A difference in benefit between OUD patients and patients discontinuing opioid analgesics would not be expected provided that the discontinuation was abrupt and the indication need not be restricted to OUD patients. The indication should be restricted to abrupt or acute withdrawal of short-acting opioids because long-acting opioids and opioid taper were not studied and the benefit of the studied clinical situations cannot be extrapolated to these situations. The 2.88 mg per day dose (3.2 mg per day as hydrochloride salt) did not confer additional benefit over the 2.16 mg per day dose (2.4 mg per day as salt).

Lofexidine is associated with hypotension, bradycardia, orthostatic hypotension, dizziness, syncope, rebound hypertension and QT prolongation. The risks of the 2.88 mg per day² regimen exceed the 2.16 mg per day regimen³. There are not adequate data to assess the risks of lofexidine beyond 7 days of consecutive use.

In patients where a non-opioid medication is clinically appropriate, who are not at undue risk for clinically significant cardiovascular adverse effects, and who are experiencing or are expected to experience clinically important opioid withdrawal symptoms, the benefit-risk of lofexidine is favorable. The benefit-risk for lofexidine may also be favorable for patients at increased risk for the cardiovascular adverse effects of lofexidine provided that they can be adequately monitored and that their withdrawal could interfere with reaching their treatment goals or is otherwise clinically significant enough to justify the risk.

Approval of lofexidine will add another non-opioid to the armamentarium. The benefit and risk profile of lofexidine is informed by adequate and well-controlled data and there are data to inform dosing both in the general patient population and in special populations. There are not data

² 3.2 mg/day as hydrochloride salt

³ 2.4 mg/day as hydrochloride salt

available to directly compare the regimen studied in the lofexidine program to the other available treatment options and an advantage over other options has not been established.

Strategies to minimize risk to patients include beginning patients at a maximum dose of 2.16 mg per day⁴ with the option to increase dosing, proper patient selection including selection of patients where opioid withdrawal symptoms are causing or are expected to cause significant distress or to interfere with treatment goals and selection of patients where the cardiovascular and cardiac electrophysiological effects of lofexidine would not be expected to place subjects at undue risk, increased cardiovascular monitoring in patients with additional risk factors for cardiovascular adverse events, and patient counseling and emphasis on continued engagement in treatment in patients with OUD.

I recommend that the Applicant be required to conduct an adequate and well controlled postmarketing study of lofexidine in patients discontinuing opioid analgesics by way of a slow taper. The study should be designed in order to meet the goals of assessing the benefit conferred by lofexidine in patients undergoing a slow analgesic taper, which is an expected off-label use, and to collect data in a sufficient number of subjects to assess the safety of lofexidine beyond 7 days of consecutive use.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Withdrawal from physical opioid dependence is characterized by anxiety, dysphoria, agitation, sweating, disturbances of thermoregulation, insomnia, yawning, lacrimation, and rhinorrhea, followed by muscle and joint aches, piloerection, nausea, vomiting, diarrhea, and abdominal cramping. The severity and time course of the withdrawal syndrome depends on the abruptness of opioid cessation or reduction, the level of physical dependence, and the pharmacokinetic properties of the opioid. 	Mitigating symptoms of opioid withdrawal would benefit patients with physical dependence to opioids who discontinue opioid use, both in those patients with OUD in conjunction with long-term management of OUD and in patients using opioids for analgesia

⁴ 2.4 mg/day as hydrochloride salt

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> • Withdrawal is not life-threatening but in patients with opioid use disorder (OUD), which is a life-threatening disease, it serves as a barrier to entering into treatment and stopping opioid use. • In patients with physical dependence but not addiction, withdrawal can be very uncomfortable and distressing. • After completing opioid discontinuation, a patient is at increased risk of an opioid overdose should they resume opioid use. For patients with opioid use disorder, continued maintenance treatment with an agonist is preferred when possible. 	
Current Treatment Options	<ul style="list-style-type: none"> • Methadone; For detoxification treatment of opioid addiction (heroin and other morphine-like drugs); Oral, 40 mg per day in divided doses, gradual taper; Associated with respiratory depression, misuse and diversion, QT prolongation; Restricted to use in a certified opioid treatment program or inpatient setting • Buprenorphine/naloxone; Used off label for withdrawal management; Up to 8/2 mg to 16/4 mg SL per day (Suboxone and its generics), taper; Associated with respiratory depression, misuse and diversion • Clonidine; Used off label for withdrawal management; 75-300 ug tid; Associated with rebound hypertension, hypotension, bradycardia 	<p>There is a role for a non-opioid in withdrawal management when OUD patients are not candidates for maintenance treatment with an agonist or are preparing to begin antagonist treatment and for patients discontinuing opioid analgesics. Lofexidine is very similar to clonidine and recommendations for clonidine use in withdrawal management are varied and based on data that has not been reviewed for the purpose of making a determination of whether it meets the regulatory standard for substantial evidence of effectiveness</p>
Benefit	<ul style="list-style-type: none"> • The benefit of lofexidine in mitigating withdrawal symptoms was demonstrated in two adequate and well-controlled studies by measuring the symptoms in a patient-reported outcome measure (SOWS-Gossop) and in the proportion of subjects that completed the treatment period in the studies in the active group compared to placebo • The benefit observed at the 3.2 mg per day (as hydrochloride salt) assigned dose was based on an average actual dose of 2.5 mg per day. The benefit observed at the 2.4 mg per day (as hydrochloride salt) assigned dose was based on an average actual dose of 1.9 mg per day. 	<p>The data meet the standard for substantial evidence for effectiveness for the mitigation of withdrawal symptoms A difference in benefit between OUD patients and patients discontinuing opioid analgesics would not be expected provided that the discontinuation was abrupt and the indication need not be restricted to OUD patients The indication should be restricted to abrupt or</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>The benefit observed was not different between the 2.4 mg per day dose and the 3.2 mg per day dose.</p> <ul style="list-style-type: none"> • The studies were limited to subjects with OUD in acute, abrupt withdrawal from heroin and short-acting prescription opioids and did not evaluate patients without OUD being treated for pain, patients undergoing a taper of opioids, or patients discontinuing long-acting opioids • Physical dependence on short-acting opioid analgesics were represented in the patient populations studied, the benefit observed on the SOWS-Gossop was not based on symptoms of the withdrawal syndrome that would be expected to differ substantially between OUD patients and patients physically dependent on analgesics, and the mechanism of action of lofexidine would not be expected to result in differential benefit between patient populations • None of the submitted data include direct comparisons of lofexidine to the other current treatment options • The data do not include data on discontinuation of long-acting opioids • Off-label use is expected in the setting of gradual taper of opioid analgesics, and to a lesser extent, taper of long-acting opioids and taper of OUD patients 	<p>acute withdrawal of short-acting opioids. The 3.2 mg per day dose did not confer additional benefit over the 2.4 mg per day dose.</p>
<p>Risk and Risk Management</p>	<ul style="list-style-type: none"> • The main risks of lofexidine are hypotension, bradycardia, orthostatic hypotension, dizziness, syncope, rebound hypertension and QT prolongation. • Opioid overdose risk increases following completion of opioid discontinuation. Labeling should include a warning of this risk and a recommendation for patient counseling and emphasis on continued engagement in treatment in patients with OUD • There were clinically important differences in the incidence and clinical significance of bradycardia and orthostatic hypotension 	<p>Lofexidine is associated with hypotension, bradycardia, orthostatic hypotension, dizziness, syncope, rebound hypertension and QT prolongation. Strategies to minimize risk to patients include beginning patients at a maximum dose of 2.4 mg per day with the option to increase dosing, proper patient selection including selection of patients where opioid withdrawal symptoms are causing or are</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>between the 2.4 mg per day dose and the 3.2 mg per day dose.</p> <ul style="list-style-type: none"> • There are no data comparing rebound hypertension with the 2.4 mg per day dose and the 3.2 mg per day dose. • Use should be avoided in patients with comorbidities or concomitant medications where the cardiovascular and cardiac electrophysiological effects of lofexidine would place the patient at undue risk • Vital sign and ECG monitoring is warranted in patients at increased risk for clinically significant bradycardia, hypotension, rebound hypertension and clinically significant QT prolongation. • None of the submitted data include direct comparisons of lofexidine to the other current treatment options 	<p>expected to cause significant distress or to interfere with treatment goals and selection of patients where the cardiovascular and cardiac electrophysiological effects of lofexidine would not be expected to place subjects at undue risk, increased cardiovascular monitoring in patients with additional risk factors for cardiovascular adverse events, and patient counseling and emphasis on continued engagement in treatment in patients with OUD</p>

1.4 Patient Experience Data

Patient experience data were included in this application. Refer to OND's Clinical Outcome Assessments Staff consult review for an evaluation of the data submitted in support of this application.

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	<input checked="" type="checkbox"/> Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	<input checked="" type="checkbox"/> Patient reported outcome (PRO)	
	<input type="checkbox"/> Observer reported outcome (ObsRO)	
	<input type="checkbox"/> Clinician reported outcome (ClinRO)	
	<input type="checkbox"/> Performance outcome (PerfO)	
	<input checked="" type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
	<input type="checkbox"/> Input informed from participation in meetings with patient stakeholders	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Other: (Please specify)	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

2 Therapeutic Context

2.1 Analysis of Condition

Physical dependence to opioids is an expected physiological response to chronic opioid exposure, associated with a down-regulation of endogenous endorphins and dynorphins. Abrupt cessation of opioids in physically dependent patients results in acute withdrawal symptoms. The time of onset, peak and duration of these symptoms depends on the elimination half-life of the opioid that was used prior to cessation, but the symptoms are essentially the same irrespective of the specific opioid. The earliest symptoms are anxiety, dysphoria, agitation, sweating, disturbances of thermoregulation, insomnia, yawning, lacrimation, and rhinorrhea, followed by muscle and joint aches, piloerection, nausea, vomiting, diarrhea, and abdominal cramping. Opioid withdrawal symptoms occur both in patients who have been using opioids appropriately, and in patients with Opioid Use Disorder (OUD). In patients with OUD, the occurrence of withdrawal symptoms and the relief of withdrawal when opioids are used are important drivers of continuing use. Concern about withdrawal prevents some patients with OUD from seeking treatment, and symptoms of withdrawal contribute to relapse in patients attempting to recover from OUD.

The Diagnostic and Statistical Manual (DSM 5) criteria for diagnosing opioid withdrawal state that it must occur in the setting of cessation or reduction in opioid use that has been heavy and several weeks or longer in duration and be characterized by at least three of the following:

- Dysphoric moods
- Nausea or vomiting
- Muscle aches
- Lacrimation or rhinorrhea
- Pupillary dilation, piloerection or sweating
- Diarrhea
- Yawning
- Fever
- Insomnia

2.2 Analysis of Current Treatment Options

In patients using opioid analgesics appropriately, opioid withdrawal is typically managed by slow taper of the analgesic. However, in patients with OUD, treatment with tapering doses of opioids to achieve an opioid-free state was defined under the Narcotic Addict Treatment Act of 1974 (NATA) as “detoxification,” and such treatment can be administered only:

1. Using methadone, in specially-licensed clinics (opioid treatment programs, OTPs)
2. Using buprenorphine, in either OTPs, or in office-based practices of physicians who have received a waiver under the Drug Addiction Treatment Act of 2000 (DATA) to provide this treatment
3. When a patient is admitted to a medical facility for a co-occurring medical problem

The term detoxification is no longer used by many addiction medicine professionals, who prefer the term “withdrawal management.”

For most patients with OUD, the maintenance use of either mu agonist, partial agonist, or antagonist medications (combined with psychosocial treatment) is considered superior to withdrawal management (combined with psycho-social treatment), followed finally by psychosocial treatment on its own. Withdrawal management is generally believed to be associated with higher rates of relapse to illicit opioid use compared to maintenance treatment options.

However, long-term medically-assisted treatment (MAT) of OUD with methadone, buprenorphine, or naltrexone is not always available, and not always desired by the patient. Short-term medically-assisted withdrawal with methadone or buprenorphine may also not be accessible to many patients, or may require a longer period of treatment than the patient prefers. Naltrexone treatment is initiated safely only after an opioid-free interval, and therefore, patients seeking this treatment often first undergo withdrawal management without opioid agonists. In such circumstances, management of opioid withdrawal symptoms using non-opioid medications is an option. A variety of “comfort medications” to treat each symptom (e.g., OTC analgesics, anti-diarrheals, anti-emetics, etc.) are often used, either by health care providers or by patients themselves. The most commonly-used non-opioid medication to manage the overall withdrawal syndrome is clonidine, an alpha antagonist antihypertensive that is not labeled for treating opioid withdrawal. Because of the pharmacologic similarity between clonidine and lofexidine, the Agency evaluated its extent of use using available data. A summary of the findings may be found in the attached Drug Utilization review.

Table 1 Available Therapies for Withdrawal Management

Product Name	Relevant Indication	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Methadone	For detoxification treatment of opioid addiction (heroin and other morphine-like drugs)	Oral, 40 mg per day in divided doses, gradual taper	Not described in product label	Respiratory depression, misuse and diversion, QT prolongation	Restricted to use in a certified opioid treatment program or inpatient setting
Buprenorphine/naloxone	Used off label for withdrawal management	Up to 8/2 mg to 16/4 mg SL per day (Suboxone and its generics), taper	Not approved for withdrawal management	Respiratory depression, misuse and diversion	
Clonidine	Used off label for withdrawal management	75-300 ug tid	Not approved for withdrawal management	Rebound hypertension, hypotension, bradycardia	

Given the high rate of relapse after withdrawal management that is not followed by long-term treatment, medications for relief of symptoms of withdrawal may not be considered, strictly speaking, to treat addiction. However, there are circumstances in which symptomatic relief of withdrawal could play an important role in the treatment of patients with OUD. These include:

1. Patients who desire treatment with antagonist medications and require an opioid-free interval before initiating treatment. These may include patients whose profession does not permit agonist treatment or patients with other personal or medical reasons for preferring antagonist treatment.
2. Patients who desire treatment but do not have access to maintenance with agonists or antagonists
3. Patients who seek treatment with other non-opioid “relapse prevention” treatments or strategies that may be developed in the future.
4. Individuals addicted to illicit drugs who are admitted to a residential setting (hospital for medical condition, jail, “drug-free” housing situation) where maintenance treatment of addiction or short-term withdrawal management treatment with an opioid taper is not offered or is not available
5. Patients discontinuing agonist or partial agonist MAT, either after achieving long-term stability, or due to personal or medical reasons

This final scenario deserves mention. MAT may continue indefinitely for some patients, but certain patients may reach a point where the decision to taper off MAT is appropriate. In other circumstances, patients may have financial or administrative reasons to discontinue MAT. In these situations, MAT does not (and should not) end abruptly; a taper of MAT medications is undertaken to minimize withdrawal and, ideally, to reduce the risk of relapse. The non-opioid medications described above that are used to treat opioid withdrawal are often used during this end-of-treatment taper. It may be reasonably anticipated that lofexidine would be used in the same way. However, it is important to note that no studies have been performed to determine whether the addition of lofexidine to an end-of-treatment taper provides any benefit in terms of reduction in symptoms or increased likelihood of successfully reaching an opioid-free state.

In addition to patients with OUD, patients with painful conditions taking opioids for analgesia may develop a physical dependence to opioids, and upon discontinuation or reduction in the opioid analgesic, may experience withdrawal symptoms. It may also be reasonably anticipated that lofexidine would be used to treat opioid withdrawal in this setting and like the end-of-MAT-treatment scenario described above, no studies have been performed to assess if lofexidine offers a benefit in this setting.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Lofexidine was studied in the 1970s for hypertension, opiate and alcohol withdrawal, and menopausal flushing at doses up to 1.6 mg/day lofexidine hydrochloride. An NDA for hypertension submitted 1983 received a non-approval action, in part for lack of efficacy.

3.2 Summary of Presubmission/Submission Regulatory Activity

Reviewer Comment: Note that in the development program, lofexidine doses were expressed in terms of the hydrochloride salt. In this review, descriptions of the studies and the results retain this terminology. The labeling for this product will express doses in terms of lofexidine. The following equivalencies may be useful for reference

<i>Lofexidine HCl (development program)</i>	<i>Lofexidine (labeling)</i>
0.2 mg tablet	0.18 mg tablet
0.8 mg dose	0.72 mg dose
2.4 mg/day regimen	2.16 mg/day regimen
3.2 mg/day regimen	2.88 mg/day regimen

In 1995, working closely with NIDA, a US agent for Britannia, submitted IND 47,857. Based on pilot dose-finding studies, development focused on a 3.2 mg/day dose.

The dose regimen selected for the first pivotal study was 3.2 mg/day, given as 4 x 0.2 mg tablets q.i.d., studied for 4 or 5 days, in inpatients. The initial study was conducted in patients who were initially stabilized on morphine, and used a withdrawal scale that emphasizes objective symptoms, rather than signs. Although the Applicant was advised that the study might not support the claim they were currently seeking (palliation of symptoms), they opted to conduct it as designed because they felt the selected endpoint was the best-established, and planned to collect subjective measures as secondary endpoints to guide future studies that would be more symptom-oriented. Note that an effect on various subjective measures was not established in that study. Additionally, objective signs of withdrawal demonstrated resurgence to pre-treatment levels after discontinuation of lofexidine, demonstrating that the studied course of treatment was apparently too brief. The Division advised the Applicant in interactions during the development program that because of these design elements and results, this study could not serve as one of

the two adequate and well-controlled studies required for demonstration of substantial evidence of effectiveness.

A second study, Study 3002, was conducted, again as inpatient, but in the more realistic scenario of starting treatment without initial stabilization on morphine⁵ and using a patient-reported symptom measure. This study also was five days long, providing no safety data supporting use of lofexidine at the proposed dose of 3.2 mg/day beyond 4-5 days. This is 25% higher than the maximum dose used at the peak of titration in patients in the UK. Even some of the patients in acute opioid withdrawal (a state associated with elevations in blood pressure and pulse) experienced hypotension, bradycardia, and syncope on the 3.2 mg dose in the clinical studies. The safety in patients who are in later stages of withdrawal, as the acute symptoms begin to resolve, was not established in this study.

The Applicant cited studies (Lin S, 1997) (Kahn A, 1997) (Carnwath T, 1998) indicating that lofexidine is comparable in efficacy to clonidine for treating withdrawal symptoms while producing less hypotension. However, it is essential to understand that these studies were conducted at maximum lofexidine doses of 1.6-1.8 mg/day while the clonidine doses administered were up to 0.6 to 0.9 mg per day, which corresponds to current off-label recommendations for dosing. There is no basis for assuming that the proposed dose of lofexidine, 3.2 mg/day, offers any safety advantage over clonidine.

There is one report of torsade de pointes in the UK post-marketing safety database, and three cases of QT prolongation that exceeded 40 ms in patients in a clinical trial involving adding lofexidine to methadone (Schmittner J, 2009). These cases occurred after a dose of 0.4 mg lofexidine was added to a stable methadone dose of 80 mg/day. Therefore, significant safety concerns exist regarding the appropriateness of lofexidine use during methadone taper. Use during methadone taper has not been studied, but as previously noted, it is a clinical scenario in which clonidine is used and in which off-label use could reasonably be expected.

Noting these issues, the Agency required the Applicant (now US World Meds or USWM) to undertake an additional controlled clinical trial, Study 3003-1, in which longer dosing and a lower dose were explored. Additionally, USWM was required to provide a dossier of information supporting the validity of the instrument used to measure subjective opioid withdrawal symptoms and was required to collect additional data on the effects of lofexidine administration and coadministration with methadone on QT interval.

The Applicant requested Fast Track designation in October 2016 on the basis that lofexidine was being developed as a treatment for a serious aspect of a life-threatening condition and had the potential to address an unmet need. The Division concurred that although the withdrawal experienced during opioid discontinuation in patients with OUD is not, in and of itself, a serious aspect of this condition, failure to complete opioid discontinuation due to the aversive experience of opioid withdrawal prevents patients from maintaining abstinence from the opioid to which

⁵ This design was necessitated by the use of the measurement scale selected in the first study, which was developed in patients starting from a common stable baseline.

they are addicted at an early and critical phase and prevents them from moving into the next phase of treatment of their addiction. The Division concurred that there is an unmet medical need for a non-opioid alternative to methadone or buprenorphine for facilitation of completion of withdrawal management for which there is substantial evidence of effectiveness. The Division concluded that while clonidine is widely used for withdrawal management, the evidence base for its dosing and benefit in aiding patients in completing opioid discontinuation would be unlikely to meet the standard of substantial evidence of effectiveness, as published studies typically did not include this endpoint. Therefore, a therapy that was approved based on substantial evidence of effectiveness in facilitating completion of withdrawal management, with adequate data to inform dosing recommendations and that could be used in situations where an opioid was not clinically indicated or was not available had the potential to offer a significant public health benefit and address an unmet need. The Division granted the request and designated the lofexidine program as a Fast Track development program for the facilitation of opioid discontinuation treatment in December 2016.

3.3 Foreign Regulatory Actions and Marketing History

Applications for use in hypertension were also submitted but not approved in several European countries. In the mid-1980's, an application was approved in UK for "for relief of symptoms in patients undergoing opiate detoxification" with minimal efficacy data due to a growing opiate problem in UK and lack of available treatment; the hypertension indication requested was not approved.

Britannia began marketing lofexidine in the UK in 1992⁶ under trade name Britlofex, with a regimen of 2.4 mg given in 3 or 4 divided doses, gradually titrated to target dose over 4 days and then used for a total of seven to ten days⁷. The company had sold (b) (4) packages that are supposed to be equal one "detox." A national survey of lofexidine use in the United Kingdom revealed that patients were titrated to a mean dose of 2.2 mg/day, with a median dose of 1.6 mg/day and a mean and median duration of use of 10 days (Akhurst, 1999).

⁶ Approval was in mid-80's but original marketing authorization holder never launched the product.

⁷ Note that this is a lower dose, a longer course of treatment than studied in clinical trials submitted to this NDA, and involves titration (not studied) and taper (included in one study).

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

Two sites were inspected for Study USWM-LX1-3003-1 and two sites were inspected for Study USWM-LX1-3002, chosen primarily on the basis of enrollment. Additionally, an inspection of the Sponsor was also conducted. No Form 483 was issued to any site and all were classified as No Action Indicated.

4.2 Product Quality

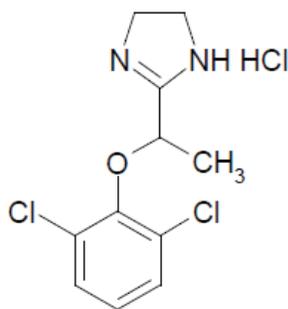
4.2.1 Drug Substance

The drug substance, lofexidine hydrochloride, is manufactured by (b) (4)

Lofexidine Hydrochloride

Molecular Formula: C₁₁H₁₃Cl₃N₂O

Molecular Weight: 295.6



Drug substance attributes are adequate for the proposed drug product formulation and manufacturing process. Lofexidine hydrochloride is freely soluble in water. Active Pharmaceutical Ingredient (API) solubility, particle size and polymorphic forms are not considered critical quality attributes (CQAs). The drug substance was found to be stable at (b) (4) months. However, lofexidine hydrochloride undergoes hydrolysis in presence of moisture.

The applicant provided general properties, specification, batch data and validated analytical methods for each of the starting materials. The proposed controls for raw materials, reagents, solvents, etc. are appropriate to adequately ensure the quality of the drug substance. The synthetic scheme in relation to final drug substance, manufacturing process

detail is adequate, and process parameters are supported by process development. The applicant provided adequate information on the origin, fate, control identification, and characterization of actual and potential impurities.

The stability data from three primary stability batches stored in a (b) (4) showed no change of stability indicating attributes under long-term condition for (b) (4) months and accelerated conditions for (b) (4) months. The drug substance appears to be stable under light, oxidative, acidic and basic conditions. However, the degradation was noted under strong acidic or basic conditions.

The applicant committed to continue the stability studies post-approval with primary stability batches.

4.2.2 Drug Product

Lofexidine 0.18 mg tablets will be provided as round, convex-shaped peach colored film-coated tablets debossed with “LFX” on one side and “18” on the reverse. All excipients used in the drug product composition, except Opadry OY-S-9480 (b) (4), are of USP/NF monograph standard. The colors in the coating composition Opadry OY-S-9480 are approved for pharmaceutical use.

Initially, three placebo batches and one additional active batch were manufactured and tested at a site in (b) (4) under a process development protocol to increase process knowledge and justify process ranges using Quality by Design (QbD) principles. Following (b) (4), in 2016 commercial manufacturing of lofexidine tablets transferred to Catalent Pharma Solutions (Winchester, KY). The manufacturing processes used at both sites were similar with comparable stability data for the drug product batches.

Drug product specifications agreed upon during the review cycle are adequate to ensure quality of the drug product at release and stability testing. A microbial limit test was included at release up on Agency’s request, and USWM agreed to test additional commercial batches, post approval, and provide data for Microbial limits test at release testing for review by the Agency. The test for Microbial Limits will remain part of the drug product regulatory and quality control specification until further review by the Agency.

A single presentation of (b) (4)-count HDPE bottle with (b) (4) was proposed as container-closure system for commercial distribution of lofexidine tablets 0.18 mg. A desiccant, a sachet (b) (4) was added to the bottle with the goal of (b) (4). Each (b) (4)-count bottle is placed in a carton, and multiple cartons placed in a shipper.

Desiccant is considered important to stability based on observations from stability studies. Tablets stored at 40°C/75% RH condition stuck to each other (b) (4). However, tablets stored at 30°C/ 65%RH did not exhibit any stickiness after 12 months. (b) (4)

(b) (4) at Catalent. The post-approval stability commitments

and stability protocols provided were deemed adequate to confirm the initially assigned tentative shelf-life of 36 months based on the primary stability data available thus far from the Catalent manufacturing site.

Late in the review process, USWM clarified that they (b) (4) -count bottle to be dispensed (b) (4) with desiccant in the bottle. In-use stability studies suggested that even a storage period of five days (anticipated duration of treatment for many patients) in a pharmacy vial would result in tablets sticking together. The clinical team did not agree that (b) (4) tablets would be the appropriate amount to dispense to each patient, and asked USWM to provide additional data to support (b) (4) packages.

USWM proposed to provide two package sizes, one containing 36 tablets (about a 3 days' supply at the recommended dose) and one containing 96 tablets, to be dispensed (b) (4). These presentations would be appropriate to meet the needs of most patients. The labeling will emphasize the need to keep the product in the supplied bottle with the desiccant in place.

4.2.3 Facilities

Following a review of the inspectional histories of the drug substance and drug product manufacturing and testing facilities, there are no outstanding concerns related to the demonstrated manufacturing and testing capabilities. The overall facility review recommendation is adequate for approval.

4.3 Clinical Microbiology

N/A

4.4 Nonclinical Pharmacology/Toxicology

The primary pharmacology of lofexidine and the structurally similar central alpha-2 adrenergic agonist, clonidine, were demonstrated to be practically identical via receptor binding and functional activity screens. Additional secondary pharmacology binding screens were conducted on lofexidine and its major human metabolites, LADP, LDPA, and 2,6-DCP. Lofexidine displayed moderate binding at additional serotonin and dopamine-related receptors, enzymes and transporters. In contrast, the metabolites did not show any significant binding to primary or secondary targets. Three major human metabolites have been identified that are also detected in the urine of rats, dogs, and rabbits. Studies are currently underway to confirm that these human major metabolites are produced in rats at adequate exposures to qualify the safety of these metabolites. Given the human experience and existing data in urine, this study can be submitted as a post marketing requirement.

4.4.1 Safety pharmacology

Many of the nonclinical studies in support of earlier human drug development were completed prior to Good Laboratory Practices. The Applicant has obtained these pre-GLP nonclinical studies to support this development program. General toxicology studies were conducted in the rat and dog, which characterize the toxicological effects of the drug. The following target organs were identified in repeat-dose toxicology studies conducted in rats and dogs: central nervous system (CNS), cardiovascular system, hepatic, and renal system. Additional treatment-related findings consistent with dehydration were noted. Likely related to drug-induced decreased lacrimation, there was severe ocular toxicity, characterized by keratitis and corneal

erosion/ulceration, observed in the 28-day rat study at the MD and HD in males and at all doses evaluated in females. Collectively, the existing toxicology studies suggest the potential for adverse effects that increase with duration of treatment, some of which could be explained by exaggerated pharmacological effects of sedation, reduced food consumption, hypotension and decreased tissue oxygenation, alterations in water balance, and decreased lacrimal secretions.

Some of the toxicities noted may well be more related to C_{max} and the physiological changes that occur with this drug following only once a day dosing. To support clinical studies of a duration longer than 14 days, the preGLP rat 90-day toxicology study should be repeated with a dosing regimen that more closely mimics the clinical setting.

4.4.2 Genetic Toxicology

The genetic toxicology of lofexidine was evaluated via two *in vitro* assays, an Ames bacterial reverse mutation assay and a L5178Y/TK^{+/-} mouse lymphoma assay, and one *in vivo* rat bone marrow erythrocyte micronucleus test. The Ames assay and the micronucleus test were negative; however, a positive result was observed in the mouse lymphoma assay. An *in vivo* comet assay testing stomach and liver has been requested and is underway. This study is still pending and may be submitted post marketing.

4.4.3 Carcinogenicity

Two carcinogenicity studies, a 2-year study in rats and an 18-month study in mice, were submitted in the Application; however, upon review these studies and consultation with the Executive Carcinogenicity Assessment Committee, these studies were deemed inadequate to support the safety of lofexidine with respect to carcinogenicity [REDACTED] (b) (4)

[REDACTED] The approved indication calls for up to two weeks of use.

4.4.4 Reproductive Toxicology

The reproductive toxicology of lofexidine was assessed via one new GLP study and four older non-GLP studies in rabbits and rats. A GLP toxicokinetics study was also conducted in rabbits. The human equivalent dose (HED) using body surface area-based allometry at the NOAEL for every toxicology study exceeded maximum recommended human dose (MRHD) of 2.88 mg/day. Although toxicokinetics evaluations were not performed in any of the non-GLP toxicology studies, toxicokinetics data were available from at least one study for rabbits (dams only), rats, and dogs, allowing for safety margins to be calculated comparing the exposure at the NOAEL's of toxicology studies to the human exposure at the MRHD. The safety margins based on exposure were approximately 10- to -20-fold more conservative than the HED-based margins for rats and dogs and approximately 500-fold more conservative for rabbits. The HED-based safety margins with respect to reproductive toxicology are all greater than one; however, the exposure-based margins are all significantly less than one, suggesting that there may be risks associated with lofexidine treatment during pregnancy.

Although some of these adverse effects may be due to maternal toxicity, the effects are treatment related and a direct or indirect effect cannot be ruled out. Given the adverse effects noted at what appear to be clinically relevant exposures, these studies raise concerns for potential treatment of pregnant women. Abrupt discontinuation of opioids is not recommended in pregnant women, so it is not anticipated that use of lofexidine for the labeled indication would be widespread in this population. However, additional reproductive developmental toxicology studies using dosing regimens better approximating the human dosing may be warranted to support use in pregnant women during opioid taper.

4.4.5 Manufacturing Excipients and Impurities

There are no concerns regarding the safety of the excipients, drug substance or drug product impurity specifications. The specifications for two of the drug substance impurities exceed the ICH qualification threshold; [REDACTED] (b) (4)

4.4.6 Post-marketing recommendations

The following non-clinical postmarketing requirements (PMRs) are recommended:

1. Conduct an in vivo comet assay testing lofexidine in the liver and stomach.

2. Conduct a pharmacokinetic study in the rat to characterize the plasma levels of lofexidine and the lofexidine metabolites LADP (N-(2-aminoethyl)-2-(2,6-dichlorophenoxy)propenamide), LDPA (2-(2,6-dichlorophenoxy)propionic acid), and 2,6-DCP (2,6-dichlorophenol) using a validated assay.
3. Conduct a juvenile animal study in rats from PND 36 to PND 90 to support pediatric drug development in children aged 12 to 17 years. The study will evaluate the effect of the drug on growth and development, reproductive (b) (4), bone development, and the central nervous system.
4. Conduct a juvenile animal study in rats from PND 7 to 90 to support pediatric drug development in children and neonates. The study will evaluate the effect of the drug on growth and development, reproductive (b) (4), bone development, and the central nervous system.
5. Conduct a juvenile toxicology in rats to evaluate the impact of lofexidine on early neuronal development during peak synaptogenesis to support pediatric studies in neonates and children under the age of 3.
6. Conduct a fertility and early embryonic development study in rats testing lofexidine administration to males and include histopathology of the testes and sperm assessments (count, motility, and morphology).
7. Conduct a 90-day GLP repeat-dose toxicology study in the rat testing lofexidine HCl to establish a NOAEL to support clinical studies that are longer than 14-days in duration. To avoid the potential confounding impact of C_{\max} -induced fluctuations in physiology, which could impact the NOAEL, dose the animals several times a day, as feasible, to mimic the clinical setting.

4.5 Clinical Pharmacology

Reviewer Comment: In this section, doses are expressed in terms of lofexidine hydrochloride salt

The clinical development program included 16 Phase 1 clinical pharmacology trials (i.e., absolute bioavailability and mass balance, single- and multiple-ascending dose, food effect, drug interaction, hepatic impairment, renal impairment, and QT studies).

Key clinical pharmacology review issues include (1) the appropriateness of the dosing instruction in general patients and (2) recommendations in specific patient populations (i.e., hepatic impairment, renal impairment).

The clinical pharmacokinetic features of lofexidine are summarized in the text below, excerpted from the clinical pharmacology review. Note that in the clinical pharmacology review, the salt dose (i.e., 0.2 mg/tablet) was used rather than the free base dose (0.18 mg/tablet):

Absorption: Following oral administration, peak lofexidine plasma concentration (C_{\max}) was attained at approximately 3 to 5 hours. Plasma lofexidine concentrations increased approximately proportionally with increasing doses following single dose administration of 0.2 to 0.8 mg and

four times daily administration of 0.2 to 0.8 mg lofexidine (i.e. total daily dose of 0.8 to 3.2 mg). The absolute bioavailability of a single oral lofexidine dose (0.4 mg in solution) compared with an intravenous infusion was 72% (90% CI: 58% to 85%). Ingestion of a high-calorie, high-fat meal slightly delayed the median (min, max) T_{max} from 5 (3, 7) to 6 (2, 10) hours but did not alter the C_{max} and AUC values of lofexidine so lofexidine may be administered with or without food. Results from in vitro study in Caco-2 cells suggested that lofexidine was not a substrate of P-gp.

Distribution: Mean volume of distribution values following the administration of an intravenous dose was 297.9 L, suggesting extensive distribution into body tissue. The protein binding of lofexidine in human plasma was approximately 55%. Lofexidine is not preferentially taken up by blood cells. In a study comparing the total radioactivity attributed to lofexidine and its metabolites in plasma and whole blood around T_{max} in healthy volunteers, it was determined that red blood cells contain approximately 27% of radioactivity in the plasma. The data from the incubation of whole blood samples mixed with various concentrations of lofexidine HCL suggested that lofexidine is not preferentially bound to blood cells, as evidenced by whole blood-to-plasma concentration ratios of less than 1.

Metabolism: Lofexidine is metabolized by CYP2D6, with CYP1A2 and CYP2C19 also capable of metabolizing lofexidine. Lofexidine and its major circulating metabolites (LADP, LDPA, 2,6-DCP) did not inhibit or induce major CYPs in vitro, with the exception of a slight inhibition of CYP2D6 by lofexidine, with an IC_{50} of 4551 nM (approximately 225 times the steady state C_{max} of lofexidine with 0.8 mg four times daily dosing). Interaction with CYP2D6 substrates is not expected to be clinically significant.

Elimination: Following an intravenous infusion of 0.2 mg lofexidine for 200 minutes, clearance of lofexidine is 17.63 L/h and the elimination half-life is 12 hours. A mass balance study of lofexidine (0.4 mg in solution) given orally showed nearly complete recovery of radioactivity in urine (93.5%) over 144 hours post-dose, with an additional 0.92% recovered in the feces over 216 hours post-dose, for a total recovery in the urine and feces of 94.4% of the administered dose. Thus, it appears that nearly all the administered dose was absorbed, and that the primary route of elimination of lofexidine and its metabolites was via the kidney. Renal elimination of unchanged drug accounts for approximately 15% to 20% of the administered dose.

Special populations concerns are addressed in the text below, excerpted from the clinical pharmacology review.

Hepatic Impairment: Lofexidine is extensively metabolized. Based on the results from a dedicated hepatic impairment study, mean C_{max} values were similar for subjects with normal, mild, and moderate hepatic impairment. Mean C_{max} values for subjects with severe hepatic impairment was approximately 67% higher than that for subjects with normal hepatic function. Mean AUC_{last} values in subjects with mild, moderate, and severe hepatic impairment were approximately 27%, 90%, and 200% higher, respectively, compared with subjects with normal hepatic function. A similar trend was observed for mean AUC_{inf} values. Mean $t_{1/2}$ values increased as the severity of hepatic impairment increased. They were 14.91, 16.78, 37.01, 48.21 hours in subjects with normal, mild, moderate, and severe hepatic impairment, respectively. The

sponsor's proposed maximum dosing regimen for mild, moderate, and severe hepatic impairment were 3 tablets QID, (b) (4)

(b) (4) respectively. Although they are reasonable from PK perspective, [the clinical pharmacology review team] suggested the (b) (4) dosing frequency for moderate and severe hepatic impairment with 2 tablets QID and 1 tablet QID (b) (4)

Renal Impairment: Based on the results from a renal impairment study with a reduced study design, mean C_{max} values were similar for ESRD and normal renal function subjects. An approximately 80% greater AUC_{last} values was observed for ESRD subjects compared with normal renal function subjects. Mean $t_{1/2}$ increased from 19.34 h in subjects with normal renal function to 26.41 h in subjects with ESRD. The impact of dialysis on the overall PK of lofexidine during a typical 4-hour dialysis was minimal.

Results from another renal impairment study with full study design, mean C_{max} , AUC_{last} , and $t_{1/2}$ increased with severity of renal impairment. Mean C_{max} increased by 24.2%, 17.2%, and 54.3% for subjects with mild, moderate and severe renal impairment, compared to subjects with normal renal function, respectively. Mean AUC_{last} increased by approximately 57.4%, 87.0%, and 172% for subjects with mild, moderate, and severe renal impairment, compared to subjects with normal renal function, respectively. Similar trends are found for AUC_{inf} . Mean $t_{1/2}$ was 14.24, 15.74, 20.63, and 22.29 hours in subjects with normal, mild, moderate, and severe renal impairment, respectively. The sponsor proposed dosage adjustment for different degrees of renal impairment based on the data obtained from 2 renal impairment studies. The sponsor's proposed maximum dosing regimen for mild, moderate, and severe renal impairment/ESRD on dialysis is (b) (4) (b) (4) respectively. Although they are reasonable from PK perspective, [the clinical pharmacology review team] suggested the (b) (4) dosing frequency for moderate and severe renal impairment/ESRD on dialysis with 2 tablets QID and 1 tablet QID, respectively, (b) (4). Because the increases in lofexidine AUC_{last} in subjects with mild (57%) and moderate impairment (87%) are similar, the same maximum dose is recommended for mild and moderate renal impairment, 2 tablets QID.

Body weight, age, gender, race: In the pivotal Phase 3 studies (3002 and 3003-1), doses were administered without adjusting for body weight, age, gender, race, or BMI. Based on the sparse PK samples collected in study 3003-1, race, ethnicity, and BMI did not appear to influence lofexidine plasma concentrations. On average, females had slightly higher plasma concentrations than males, which was accounted for by gender-related differences in body weight.

Drug-drug interactions: Drug-drug interactions were tested in PK studies with paroxetine, a strong inhibitor of CYP2D6, and with methadone, buprenorphine, or naltrexone, agents which might be co-administered with lofexidine in patients withdrawing from opioids. Lofexidine exposures were approximately 30% greater with co-administration of paroxetine. Co-administered oral naltrexone did not affect lofexidine PK, but lofexidine delayed naltrexone T_{max} , and slightly reduced the C_{max} of naltrexone (36%) and 6 β -naltrexol (19%), AUC values of naltrexone (8%), but did not affect the AUC values of 6 β -naltrexol. This effect is expected to be limited to oral naltrexone and an impact on depot naltrexone is not anticipated. Buprenorphine

and methadone PK were not altered by lofexidine in patients maintained on high doses of buprenorphine (16-24 mg/day Suboxone) or methadone (80-120 mg/day). Although these studies were not designed to evaluate if the PK parameters of lofexidine were altered by long-acting opiates, in both studies, lofexidine concentrations remained within the clinical range observed in the larger Phase 3 trials with short-acting opiates.

4.6 QT Interdisciplinary Review Team

Reviewer Comment: In this section, doses are expressed in terms of lofexidine hydrochloride salt

QT prolongation and decrease in heart rate have been observed for lofexidine. The cardiac conduction effects of lofexidine were reviewed by the QT interdisciplinary review team (QT-IRT). Overall, no large mean increase in the QTc interval has been observed in patients receiving lofexidine. This observation is supported by the presence of few QTc outliers (2 patients $QTc \geq 500$ [1 in placebo], 9 patients with $\Delta QTc \geq 60$ [3 in placebo]) and few adverse events of interest per ICH E14. However, no dose or exposure- response relationship could be identified in the submitted studies for QTc prolongation.

USWM had previously acknowledged the QT prolonging effects of lofexidine, and proposed that a thorough QT study of lofexidine in healthy volunteers would not be feasible due to the observed bradycardia and hypotension. The QT-IRT agreed with the sponsor. Specific QT protocols for to evaluate the effects in the presence of methadone and buprenorphine were conducted, and ECG monitoring was continued in clinical studies.

The mechanism of the observed QT prolongation is unknown. In vitro hERG data suggests that the observed QT prolongation is unlikely to be mediated via blockade of the hERG potassium channel.

There was one case report of significant QTc prolongation ($QTcF > 600$ ms) when co-administered with methadone in an investigator-sponsored study, which was not included in the ISS. In addition, there is a post-marketing case report of torsade de pointes for a subject receiving lofexidine and who had bradycardia (40 – 44 bpm).

ECG data collected in phase 3 suggests that lofexidine does not cause large mean increases in the QTcF interval, with the maximum increase occurring on day 1 for both treatment arms). While the QTcF effect appears to be lesser when comparing day 7 to day 1, this observation cannot be used to conclude an absence of QTc prolongation over time. There were few QTc outliers ≥ 500 or $\Delta QTc \geq 60$ ms, and, consistent with the results of other studies. There was an increase in the frequency of patients with bradycardia (<45 bpm) in the phase 3 trial (placebo: 3%; 2.4 mg: 7%; 3.2 mg: 20%). Bradycardia is a risk factor for torsade de pointes in the presence of QTc prolongation. The profound decrease in heart rate (~20 bpm) impacts the ability to interpret the observed QTcF prolongation.

Analysis of the QTc data collected in patients on stable doses of buprenorphine does not suggest that lofexidine causes a large increase in the QTc interval when comparing buprenorphine + lofexidine to buprenorphine alone. However, an increase in the QTc interval was observed when comparing methadone + lofexidine to methadone alone. Overall, the lofexidine-methadone study data suggest that lofexidine might increase the QTc interval compared to a methadone-alone baseline and based on a by-time analysis the maximum mean $\Delta QTcF$ was observed to be 7.9 ms. Additionally, a difference 20.4 ms was observed compared to lofexidine-placebo, however, this

was a secondary analysis and only a small number of subjects received lofexidine-placebo (n=7). In addition, a decrease in heart rate was observed in the lofexidine arm (maximum mean Δ HR was -18 bpm), but not in the placebo arm.

In addition, a DDI study with naltrexone was also conducted. In the naltrexone DDI study a single dose of 0.4 mg lofexidine was administered, and no difference between lofexidine alone compared to lofexidine + naltrexone was observed. However, as the study was conducted at a sub-therapeutic dose, the results cannot be extended to therapeutic dosing.

ECGs were also collected in patients with hepatic and renal impairment with a single lofexidine dose of 0.4 mg. The analysis of this data is limited to by-time analysis, due to the lack of an established concentration-QTc relationship for lofexidine. The hepatic and full renal impairment studies showed an increase in the maximum mean Δ QTc when comparing normal subjects to subjects with increasing degrees of organ impairment. However, the number of subjects included in each of the studies per organ impairment group is too small to draw any definitive conclusions.

4.7 Controlled Substances

The data pertinent to abuse potential of lofexidine was assessed by the Controlled Substances Staff. They concluded that the nonclinical assessment of lofexidine shows that it does not bind to or activate any receptors known to have abuse potential. No *in vivo* behavioral assays were conducted to determine the abuse potential of lofexidine; however, it does not have pharmacokinetic properties associated with drugs that have abuse potential such as rapid onset and high CNS penetrance.

Based on the adverse event profile in clinical trials, its pharmacological similarity with clonidine (a drug not scheduled under the Controlled Substances Act (CSA)), lofexidine's several year history of use in the United Kingdom without emergence of signals of abuse, the Controlled Substances Staff agreed with USWM that lofexidine does not warrant placement in any schedule of the CSA.

Review of the adverse event data was notable for the occurrence of withdrawal symptoms upon discontinuation of lofexidine including diarrhea, insomnia, anxiety, chills, hypertension, hyperhidrosis and extremity pain. Physical dependence may manifest separately from abuse liability and psychological dependence. This withdrawal syndrome does not, necessarily, imply abuse potential; however, tapering of the product at the end of treatment is recommended.

4.8 Clinical Outcome Assessment

During the clinical development program, the Clinical Outcome Assessment (COA) Staff commented on strengths and limitations of the Short Opiate Withdrawal Scale – Gossop (SOWS-Gossop), and identified various limitations of the instrument, most notably an exclusion of certain relevant symptoms associated with short-acting opioid withdrawal (e.g., nausea, vomiting, diarrhea, depression, anger and anxiety). USWM was also given guidance on how to assemble a dossier to support the use of the instrument in clinical trials and labeling.

The COA staff reviewed the dossier submitted by USWM to support the use of the SOWS-Gossop instrument, and concluded that the evidence submitted by the applicant for Agency evaluation of the PRO instrument’s psychometric properties (reliability, construct validity, and ability to detect change) generally appeared supportive. Although certain specific symptoms are not included in the instrument, and the vague term “feeling sick” is included, upon probing, most participants described “feeling sick” as nausea, vomiting, diarrhea, flu-like symptoms, cannot get out of bed, unwell, body aches, not feeling normal, or fever. Other descriptions included: no energy, exhausted, fatigue, no motivation, sweating, loss of appetite, dehydration, feeling like stuff was crawling all over me.

In the context of opioid withdrawal in patients with OUD, the term “feeling sick” may be adequately understood to mean “dope sick.” It is noted that this instrument may not be appropriate for populations who do not have an OUD diagnosis (e.g., patients undergoing analgesic taper).

5 Sources of Clinical Data and Review Strategy

Reviewer Comment: In this section, doses are expressed in terms of lofexidine hydrochloride salt

5.1 Table of Clinical Studies

The table below lists all studies in the clinical development program.

Table 2 Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route/ duration	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
3002	00235729	Randomized, double-blind, placebo-controlled inpatient study	Oral <ul style="list-style-type: none"> • LFX 3.2 mg/day (0.8 mg QID) for 5 days • PBO QID for 5 days All subjects received PBO on Days 6 and 7	Day 3 SOWS-Gossop score, time to dropout	264 (200M, 64F)	Dependent on short-acting opioids	15 sites in United States
3003-1	01863186	Randomized, double-blind, placebo-controlled for 7 days followed by open-label, variable-dose treatment for up to 7 additional days	Oral <ul style="list-style-type: none"> • LFX 2.4 mg/day (0.6 mg QID) for up to 7 days • LFX 3.2 mg/day (0.8 mg QID) for up to 7 days • PBO (QID) for up to 7 days All subjects could receive LFX at variable dose on Days 8-14	AUC SOWS-Gossop Days 1 through 7, completion status Day 7	602 (427M, 175F)	Dependent on short-acting opioids	18 sites in United States
<i>Phase 3 Studies to Support Safety</i>							
3001	00032942	Randomized, double-blind, Placebo-controlled Inpatient study with morphine lead-in and LFX taper	SC morphine <ul style="list-style-type: none"> • 3-day lead-in (100 mg/day) Oral LFX or PBO • LFX 3.2 mg/day (0.8 mg QID) or PBO QID on Days 4-7 • LFX 1.6 mg (0.4 mg QID) or PBO (QID) on Day 8 All subjects received oral PBO on Days 9 and 10		68b (59M, 9F)	Dependent on short-acting opioids	
3003-2	02363998	Open-label safety study	Oral LFX 3.2 mg/day (0.8 mg QID) for up to 7 days. LFX dose		286 (188M, 98F)	Dependent on short-acting or long-acting	

			could be lowered to 2.4 mg daily (0.6 mg QID) if required for tolerability reasons All subjects could receive LFX at tapering doses on Days 8-14			opioids	
Other studies included in the safety database							
0-1001	Open-label pilot study to assess PK of lofexidine administered IV						
1-1001	Open-label, crossover, comparative, bioavailability study						
1002	Open-label, dose escalation, crossover PK/safety study						
1003	Open-label, randomized, 2-way, crossover, ADME mass balance, and absolute bioavailability study						
1003-1	Open-label mass balance study						
1004	Open-label, randomized, 2-way, crossover food effect study						
1005-1	Pilot, multiple, ascending-dose study of electrocardiographic effects, safety, tolerability, and PK in methadone-maintained subjects						
1005-2	Randomized, double-blind, placebo-controlled, multiple ascending-dose, PK, safety, tolerability, and ECG effects study in methadone-maintained subjects						
1006	Randomized, double-blind, placebo-controlled, multiple ascending-dose study of electrocardiographic effects, safety, tolerability, and PK in buprenorphine-maintained subjects						
1007	Open-label, parallel-group, PK/safety study in hepatically impaired and NHF subjects						
1008	Open-label, parallel-group, PK/safety study in ESRD and NRF subjects (reduced design)						
1009	Open-label, single-sequence, 3-treatment PK/safety drug-drug interaction study of lofexidine and naltrexone						
1010	Open-label, single-sequence, 3-treatment PK/safety drug-drug interaction study of lofexidine and paroxetine						
1011	Open-label, crossover, pilot QTc effect study						
1012	Open-label, parallel-group, PK/safety study in normal renal function subjects and subjects with various degrees of renal impairment (full design)						
1013	Open-label PK/safety study to evaluate the relative exposures of lofexidine and its major metabolites in subjects seeking reduction in maintenance buprenorphine dose						
2001	Open-label with morphine lead-in (initial study and 2 substudies)						
2002	Randomized, double-blind, double-dummy, placebo-controlled, crossover study in subjects administered intramuscular naloxone after treatment with LFX, clonidine, and PBO						
2003	Blinded, placebo-controlled multiple-dose, hemodynamic and cognitive effects study in methadone-maintained subjects						
2004	Study 1 (Pilot) Open-label, optimum dose determination (Phase 1) Randomized, double-blind, placebo-controlled with dose taper						

	(Phase 2) Naltrexone maintenance Study 2 Randomized, double-blind, placebo-controlled study Naltrexone maintenance
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5.2 Review Strategy

The efficacy review was completed by Dr. Yi Ren and the safety review was completed by Dr. Pamela Horn.

Two of the three controlled Phase 3 studies are reviewed in detail in the efficacy sections: studies 3002 and 3003-1. (b) (4)

The safety review includes all studies in the clinical development program. Comparisons of incidence of safety outcome measures are made using the subset of data derived from the controlled phase of Phase 3 studies. (b) (4)

6 Review of Relevant Individual Trials Used to Support Efficacy

Reviewer Comment: In this section, doses are expressed in terms of lofexidine hydrochloride salt

6.1 USWM-LX1-3002

6.1.1 Study Design

This study initiated on June 16, 2006 and completed on Oct 26, 2007.

Overview and Objective

The primary objective was to investigate the efficacy of lofexidine hydrochloride, an alpha-2-adrenergic agonist, in reducing withdrawal symptoms in subjects undergoing opioid withdrawal management.

Trial Design

The trial was designed as an inpatient, randomized, multi-center, double-blind, placebo-controlled, parallel-group study. After an initial screening period, eligible subjects were to be admitted to an inpatient unit and randomized equally to receive either lofexidine (0.8 mg QID) or placebo QID for 5 days. All subjects were then to receive placebo for two days and then be discharged on Day 8 following the post-treatment assessments.

There were to be 264 subjects enrolled. Subjects were to meet the Diagnostic and Statistical Manual for Mental Disorders Fourth Edition (DSM-IV) criteria for current dependence on any opioid with a half-life similar to heroin or morphine based on the structured

clinical interview (SCID) and were to be experiencing withdrawal.

Key Inclusion Criteria

1. At least 18 years of age.
2. Dependent⁸ on heroin, morphine, Vicodin, Lortab, Lorcet, Percocet, Percodan, Tylox, hydrocodone by any route of administration or oxycodone (including oxycodone time-released formulation).
3. Subject report of opioid use for at least 21 of the past 30 days.
4. Score of 2 or greater on the Objective Opiate Withdrawal Scale-Handelsman (OOWS-Handelsman).
5. Positive urine toxicology screen for opiates and negative for methadone and buprenorphine.

Reviewer Comment: The criteria for defining a study population with an addiction to opioids appears to be acceptable. The OOWS-Handelsman is a clinician-rated assessment of physical signs that incorporates no subject report. Subjects were required to score 2 or higher out of a possible 13 points.

Subjects were to be excluded from participation for the following:

1. Pregnant or lactating women.
2. Self-reported methadone or buprenorphine use in the last 14 days.
3. Having a psychiatric disorder that the study physician believed would make study participation unsafe or treatment compliance difficult.
4. Addiction to another substance that requires detoxification.
5. Seizures, or anticonvulsant therapy use during the past 5 years.
6. Pancreatic disease such as Type 1 diabetes.
7. Liver disease or AST or ALT levels 5 times the upper limit of normal.
8. Gastrointestinal or renal disease that would affect absorption, metabolism or excretion of the study drug.
9. Clinically significant abnormal ECG such as second or third degree heart block, uncontrolled arrhythmia, or QTc interval > 450 msec for males, and > 470 msec for females.
10. Heart rate less than 45 bpm or symptomatic bradycardia.
11. Systolic blood pressure < 90 mmHg or symptomatic hypotension.
12. Blood pressure > 160/100 mmHg.
13. History of myocardial infarction.
14. Self-reported AIDS, active tuberculosis or active syphilis.
15. Clinically significant abnormal lab values.
16. Use of psychotropics, prescription analgesics, anticonvulsants, antihypertensives, antiarrhythmics, antiretrovirals, or cholesterol lowering medication in the past 4 weeks.

Due to the potential for drug-drug interactions, patients were prohibited from concomitant use of

⁸ The DSM-IV criteria for opioid dependence includes but is not limited to physical dependence. The criteria are designed to diagnose patients with addiction rather than mere physical dependence. The most recent version of the DSM has renamed the disorder to opioid use disorder with severity modifiers.

tricyclic antidepressants, alcohol, sedatives and anesthetics, and beta blockers.

Dosing was to occur at 8 am, 1 pm, 6 pm, and 11 pm. The protocol stated that the investigator could hold doses for standing systolic blood pressure of 90 or less.

Nicotine use was to be permitted in the study on an individual study site basis. A tobacco use diary was to be maintained by the study sites. Tobacco products were not to be used within one hour of scheduled vital sign assessments. Nicotine replacement therapy by patch, gum, inhaler or nasal spray was to be encouraged and was not restricted with respect to vital sign assessments.

Permitted Concomitant Therapy

1. Guaifenesin (for cough) (up to 2 tsp PO every 2 hours, PRN)
2. Alumina, Magnesia and Simethicone (for dyspepsia and nausea) (up to 30 mL PO every 4 hours, PRN)
3. Dioctyl sodium sulfosuccinate (for constipation) (up to 100 mg PO every 8 hours, PRN)
4. Psyllium hydrocolloid suspension (for constipation) (up to 1 tablespoon PO every 12 hours, PRN)
5. Bismuth sulfate (Pepto-Bismol) (for diarrhea) (up to 6 doses of 30 mL PO every 24 hours, PRN)
6. Acetaminophen (for headache, muscle aches, or other discomfort) (up to 4 doses of up to 650 mg PO every 24 hours)
7. Zolpidem (for insomnia) (up to 10 mg PO, PRN, may repeat 1 time if administered prior to 5:00 AM. Zolpidem must not be administered prior to 11:00 PM (which is the time of the last daily dose of lofexidine or placebo).
8. Nicotine replacement therapy (patch, inhaler, gum, nasal spray).

All other medications were to be approved by the medical monitor of the study prior to administration.

Cardiovascular Discontinuation Criteria

Subjects were to be discontinued for the following cardiovascular events:

1. New onset of clinically significant abnormal ECG (e.g., second or third degree heart block or uncontrolled arrhythmia, prolonged QTc interval).
2. Persistent symptomatic hypotension (hypotension not responding to bed rest, which leads to missing more than 2 doses of study medication in a day or 4 doses during the study).
3. Single occurrence of symptomatic bradycardia (heart rate less than 60 beats per minute, regardless of blood pressure) associated with chest pain, shortness of breath, or decreased level of consciousness.
4. Persistent Hypertension - Blood pressure 185/ 110 mm Hg or greater recorded on 3 separate occasions taken at least 5 minutes apart AND within a 1-hour time period.
5. Medical Intervention for Cardiovascular Event: Any medical intervention (nonmedication or medication inclusive) used for the treatment of any cardiovascular event, with the exception of a positional intervention in subjects displaying hypotension.
6. Any other clinically significant cardiovascular sign (QTc > 450 msec for males, and > 470 msec for females) or symptoms that would place the subject at risk.

Table 3 shows the assessments that were to be done during the study.

Table 3 Schedule of Assessments Study 3002

Activity	Outpt. Screen	BL		Study Day									
				Treatment Phase					Post-Treatment Phase				
				1	2	3	4	5	6	7	8		
Informed Consent Form signed	X		R										
Screening Number Assigned	X		A										
Inclusion/Exclusion Criteria (8)	X		N										
Demographics	X		D										
Medical and Smoking History	X		O										
Psychiatric Assessment (SCID)	X		M										
Infectious Disease Assessment (7)	X		I										
Pregnancy Test (5)	X	X	Z								X		
Height	X		A										
Weight (3)	X	X	T		X	X	X	X	X	X	X	X	X
Physical Exam (1,8)	X		I	X									X
12-Lead Electrocardiogram (2)	2X		O	X	X	X	X	X	X	X	X	X	X
Urine Drug Screen (5)	X		N	X	As needed	X	As needed	X	As needed	X	As needed	X	As needed
Vital Signs – sitting & standing (3)	X	X		5X	5X	5X	5X	5X	5X	5X	5X	5X	X
Vital Signs Tracking Form													As needed
Clinical Laboratory Tests – blood & urinalysis (4,5)	X												As needed
Addiction Severity Index	X												X
Short Opiate Withdrawal Scale (SOWS-Gossop) (6)		X		X	X	X	X	X	X	X	X	X	X
Objective Opiate Withdrawal Scale (OOWS) (6)	X	X		X	X	X	X	X	X	X	X	X	X
Modified Clinical Global Impression Scale (MCGI) (Subject and Rater) (6)		X		X	X	X	X	X	X	X	X	X	X
VAS-E (6)				X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications (8)	X			X	X	X	X	X	X	X	X	X	X
Tobacco Use Diary				X	X	X	X	X	X	X	X	X	
Adverse Events				X	X	X	X	X	X	X	X	X	X
Admission to the Inpatient Unit		X											
Study Drug Administration:													
Lofexidine/Placebo				X	X	X	X	X					
Placebo									X	X			
Discharge from the Inpatient Unit													X

General Notes:

After signing the informed consent and completing the consent quiz, screening assessments will be performed.

If a subject terminates early from the study, all Day 8 procedures and the Day 7 clinical laboratory tests will be done prior to discharge.

(1) A complete physical examination will be performed during screening. Update Q. 17 on the 2nd page of the physical exam form at baseline. A repeat physical exam will be performed 3-4 hours after randomization on Day 1, and prior to discharge on Day 8 or at early termination.

(2) A 12-lead ECG will be conducted the first day of screening and immediately prior to admission. Four hours after receiving the first dose of study medication on Days 1-7, a 12-lead ECG will also be conducted. A 12-lead ECG will be done prior to discharge on Day 8 or at early termination. If, in the opinion of the investigator, clinically significant changes are noted on the ECG, these measurements should be performed more frequently. Additionally, the next scheduled dose of study medication may be withheld at the discretion of the investigator, or the subject may be discontinued from the study.

(3) Subjects will be weighed each morning prior to breakfast. Vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and body temperature) are to be measured one time during screening, at baseline, within 30 minutes prior to study medication dosing at 0800, 1300, 1800, and 2300 hours on Days 1-7, 3 hours after the study medication dose at 0800 hours on Days 1-7, and prior to discharge on Day 8. For the orthostatic blood pressure readings, subjects will remain seated for 3 minutes prior to a blood pressure reading, and then stand for 1 minute prior to a second blood pressure reading. Height will be measured one time during screening.

(4) Clinical lab tests will be done during screening, on Day 7 or early termination, and as needed at the physician's discretion.

(5) The urine sample collected on the first day of screening will be divided into two aliquots. One sample will go to the local lab for drug testing and urinalysis. For females, the other sample will be used for immediate "dip-stick" analysis of pregnancy. A "dip-stick" pregnancy test will be done during baseline, prior to study drug administration, and also on Day 7.

(6) The SOWS-Gossop, OOWS and MCGI (Subject & Rater) will be completed at baseline. In addition, the OOWS will be completed immediately prior to admission. These measures will also be completed 3.5 hours after the first dose of study medication on Days 1-7, and prior to discharge on Day 8.

(7) A chest x-ray is required only if a PPD is not done, the current PPD is positive, or if a past PPD was positive.

(8) This form should be updated at baseline.

Source: 3002 CSR p.399 and 400

Short Opiate Withdrawal Scale (SOWS) – Gossop

The Applicant selected the 10-item SOWS-Gossop, a patient-reported outcome (PRO) instrument, to evaluate short-acting opioid withdrawal symptom severity with a recall period of the last 24 hours to support the primary efficacy outcome. Each item represents a symptom. Patients evaluate the severity of each symptom by placing a mark next to each item in one of the four columns entitled, "None," "Mild," "Moderate," or "severe." Refer to Table 2 below for a copy of the instrument.

The SOWS-Gossop was scored by summing the 10 individual item scores ranging from 0 to 3 (None = 0, Mild = 1, Moderate = 2, and Severe = 3) with a total possible score range from 0 to 30. A higher score indicates a greater withdrawal symptom severity.

The SOWS-Gossop instrument was self-administered once daily at baseline and throughout the duration of trial, specifically at 3.5 hours after administration of the initial study medication dose of the day.

Table 4 SOWS-Gossop Scoring Method

Condition	Score ^a			
	None	Mild	Moderate	Severe
Feeling sick	0	1	2	3
Stomach cramps	0	1	2	3
Muscle spasms/twitching	0	1	2	3
Feeling of coldness	0	1	2	3
Heart pounding	0	1	2	3
Muscular tension	0	1	2	3
Aches and pains	0	1	2	3
Yawning	0	1	2	3
Runny eyes	0	1	2	3
Insomnia/problems sleeping	0	1	2	3

^a Possible score range = 0 to 30.

The withdrawal symptoms described in literature and not covered by the SOWS-Gossop include anxiety, dysphoria, agitation, sweating, runny nose, goose bumps, vomiting, and diarrhea.

The Applicant submitted a PRO Evidence Dossier to support the validity of the instrument in the context of use in Phase 3 studies of opioid withdrawal management in subjects with opioid use disorder.

Reviewer Comment: The Agency has evaluated the SOWS-Gossop for the current context of use and concludes that it appears to assess some relevant short-acting opioid withdrawal symptoms (e.g., aches and pain, insomnia) while omitting other withdrawal symptoms (e.g., nausea, vomiting, diarrhea, dysphoria, anger and anxiety) based on the qualitative study results submitted by the Applicant. The evidence submitted by the Applicant for Agency evaluation of the PRO instrument's psychometric properties (reliability, construct validity, and ability to detect change) generally appeared supportive. See Dr. Patel's review for details.

Study Endpoints

The Applicant's prespecified primary efficacy endpoints were:

1. The SOWS-Gossop score on day 3 and
2. The time-to-dropout as measured by the number of 6 hour-intervals that a subject completes during the 5-day treatment phase of the study.

The secondary efficacy endpoints were:

1. Comparison of detoxification area under the withdrawal symptom-time curve, where withdrawal symptom is represented by daily mean SOWS-G score, over the full course of

- detoxification (5-day treatment phase and 8-day study phase)
2. Daily mean SOWS-Gossop scores during the treatment phase
 3. Daily mean OOWS-Handelsman scores during the treatment phase
 4. Daily mean VAS-E scores during the treatment phase.
 5. Daily mean MCGI (Subject and Rater) scores during the treatment phase.
 6. The proportion of subjects who are completers (received first day 5 dose and completed first Day 5 SOWS-Gossop assessment)
 7. The proportion of subjects who complete the 8-day study phase (a completer who is discharged in the morning of day 8 after completing the required Day 8 assessments).
 8. The proportion of subjects who complete the 5-day study medication treatment phase (a subject who discharges in the first time quadrant on Day 6 or later).
 9. The proportion and daily mean of subjects requiring any concomitant medication to alleviate opiate withdrawal symptoms during the treatment phase.
 10. The proportion of subjects requiring opioid rescue for relief of opiate withdrawal symptoms during the treatment phase.
 11. The total number and daily mean of withdrawal-related adverse events occurring during the treatment phase.

Instead of using the Applicant's prespecified efficacy endpoints, we looked at the SOWS-Gossop and completion data for the first 5 days of the treatment period for both studies, because it would be useful to see the data over the same time frame. We think that a landmark analysis that captures the symptoms measured on the SOWS-Gossop over several days of the treatment period is more informative than a single measurement on one day of the treatment period, which was the prespecified primary endpoint in Study 3002. We also observed that Day 3, the prespecified time point for analysis per protocol, was not the day of peak withdrawal scores.

Statistical Analysis Plan

The primary analysis population was defined as subjects who received at least one dose of study medication and completed the post-medication SOWS-Gossop score on Day 1. We did not agree on the analysis population since it should not depend on post-medication efficacy assessments. Therefore, all the efficacy analyses for Study 3002 were performed using all randomized subjects that received at least one dose of study medication.

The primary analyses were prespecified as:

1. A comparison of the mean Day 3 SOWS-Gossop scores between the lofexidine and placebo groups using an analysis of covariance (ANCOVA) model adjusted for baseline SOWS-Gossop scores and opioid severity score based on SCID.
2. A log-rank test to compare the risk-adjusted dropout rates between the treatment groups. Kaplan-Meier survival curves were provided for a comparison of the distributions of time-quadrants until dropout between the two treatment groups.

Our first selected primary endpoint, SOWS-Gossop scores from Days 1 to 5, was analyzed using a mixed model for repeated measures (MMRM). The MMRM model included fixed effects for treatment, baseline SOWS-Gossop scores, opioid dependence severity, study day, and treatment-

by-day interaction, as well as a random effect for subjects. Our second primary endpoint of interest was completion status on Day 5. It was compared using a Fisher's exact test.

To account for two primary endpoints, a stepwise Bonferroni-Holm method was used. The first hypothesis was tested at the significance level of 0.025, and tested at 0.05 for the second hypothesis.

To account for missing SOWS-Gossop scores, the applicant used a multiple imputation approach to replace missing data. This method assumed missing at random (MAR), that is conditional on baseline covariates, the missing SOWS-Gossop scores are similar to that of observed values from complete cases in the same treatment group. This approach could potentially attribute a treatment benefit to a subject who discontinued due to lack of efficacy or an adverse event. Therefore, we adopted a conservative approach assuming data were missing not at random (MNAR). Missing SOWS-Gossop scores were imputed using the mean of placebo completers on Day 2. As shown in Figure 1, this was the day where the SOWS-Gossop scores were highest. This approach assigns a bad outcome regardless of treatment and dropout reasons. Imputations were performed 5 times. The results of the MMRM analysis on each of the 5 imputed datasets were then combined to derive the overall results.

Data Quality and Integrity

All documentation including the study protocol, statistical analysis plan, clinical study report, and literature referenced, as well as the SDTM and ADaM datasets were submitted under the network path \\CDSESUB1\evsprod\NDA209229\0002. Datasets were submitted by the applicant to the CDER electronic data room in SAS transport format.

In response to the information request sent on September 18, 2017, the applicant resubmitted datasets, corrected define files, as well as the SAS programs used to generate the efficacy analysis datasets under the network path \\CDSESUB1\evsprod\NDA209229\0006. The datasets were of acceptable quality and were adequately documented to allow for a thorough review of the data.

Subgroup analyses for Study 3002 were not submitted initially and an IR was sent on Oct 30, 2017, requesting subgroup analyses of the primary efficacy endpoints by age, sex, and race be submitted. These were submitted under the network path \\CDSESUB1\evsprod\NDA209229\0010.

6.1.2 Study Results

Patient Disposition

See Study Site Information for enrollment by site and primary investigator. The study report states that 264 subjects out of 448 screened were randomized to study medication and received at least one dose of study medication. However, the exposure dataset only contains 263 unique subjects, suggesting that one of the 264 subjects randomized to the placebo group (the individual

with no data in the exposure the dataset) did not receive any study medication.

Disposition of all randomized subjects in the 8-day study period is shown in Table 5.

Table 5 Disposition Day 8 for Study 3002

	Lofexidine N=134	Placebo N=130
Completed Study (Day 8)	50 (37%)	35 (27%)
Discontinued	84 (63%)	95 (73%)
Lack of efficacy	18 (13%)	37 (28%)
Adverse event	8 (6%)	6 (5%)
Subject request	54 (40%)	45 (35%)
Non-adherent to study procedures	4 (3%)	7 (5%)

Source: 3002 CSR Table 7 and Patient analysis dataset

Among all randomized subjects, more subjects in the placebo group discontinued than in the LFX group, 73% vs 63%. In both treatment groups, the most frequent dropout reason was subject request (not related to withdrawal symptoms). As expected, more subjects dropped out the study, due to lack of efficacy in the placebo group, compared to lofexidine group, 28% vs 13%. There were 5 subjects in each treatment group who discontinued due to adverse event.

Because the SOWS-Gossop scores from Days 1 to 5 were analyzed for clinical interest, disposition at Day 5 (the end of the treatment period) was also evaluated.

Table 6 Disposition Day 5 for Study 3002

	Lofexidine (N=134)	Placebo (N=130)
Completed Treatment Period (Day 5)	66 (49%)	43 (33%)
Discontinued	68 (51%)	87 (67%)
Lack of efficacy	18 (13%)	37 (28%)
Adverse event	7 (5%)	6 (5%)
Subject request	43 (32%)	38 (29%)
Non-adherent to study procedures	0	6 (5%)

Source: 3002 Patients analysis dataset

Approximately half of patients completed the treatment period in the lofexidine group compared to only one third of patients in the placebo group. Most subjects that dropped out of the study in the placebo group had dropped out by Day 5 (an additional 6% of placebo subjects dropped out on Day 6 and 7 based on subject request). In the lofexidine group, 12% (or double the number of placebo subjects) dropped out on Day 6 and 7 (8% due to subject request and 3% due to non-adherence to study protocol or procedures).

Reviewer Comment: The higher incidence of discontinuations in the placebo group due to lack of efficacy is consistent with lofexidine having a treatment effect on withdrawal symptoms. In the post-treatment period, dropout due to patient request and non-adherence to study procedures increased more in the lofexidine group than in the placebo group. This also suggests withdrawal of an effective agent.

Demographic Characteristics

The baseline characteristics for all randomized patients are shown in Table 7. Most of the subjects were male (76%) and currently using tobacco (88%). The mean age of the population was 37 years. There was a slightly greater percentage of white subjects in the placebo group (59%) compared with lofexidine group (47%).

Table 7 Demographics for Study 3002

Characteristic	Placebo (N=130)	Lofexidine (N=134)	Total (N=264)
Sex			
Male	99 (76)	101 (75)	200 (76)
Female	31 (24)	33 (25)	64 (24)
Age (years)			
Mean (SD)	38 (11)	36 (11)	37 (11)
Race			
White	76 (59)	63 (47)	139 (53)
Black or African American	27 (21)	37 (28)	64 (24)
Hispanic	27 (21)	34 (25)	61 (23)
Tobacco Use			
Current	120 (92)	112 (84)	232 (88)
Never or not current	10 (8)	22 (16)	32 (12)

Source: Statistical reviewer

Efficacy Results

First Primary Endpoint

Analysis of the Applicant's first prespecified primary endpoint, SOWS-Gossop scores on Day 3, demonstrated a significant difference between the lofexidine and placebo. Results are shown in Table 8.

Table 8 Comparisons of SOWS-Gossop scores on Day 3 (Study 3002)

	Placebo	Lofexidine	P-value
Mean (SD)	8.58 (5.42)	6.43 (4.72)	
LS Mean Difference (SE)		-2.24 (0.80)	0.009
95% CI		(-3.88, -0.60)	

Source: Statistical reviewer

However, the average SOWS-Gossop scores from Day 1 through Day 5 were considered more relevant and are summarized below in Table 9. The estimated treatment effect on the mean

SOWS-Gossop scores were statistically significantly (-2.33, $p < 0.001$) lower in the lofexidine group compared with placebo group.

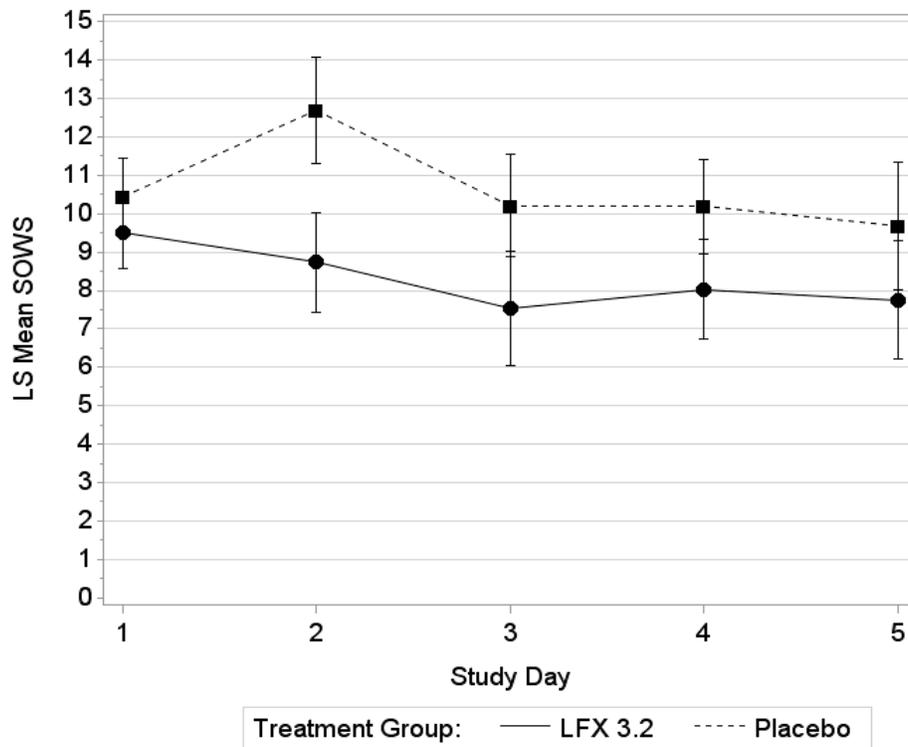
Table 9 Comparisons of SOWS-Gossop scores Days 1-5 (Study 3002)

	Placebo	Lofexidine	P-Value
Overall LS Mean (SE)	10.64 (0.39)	8.31 (0.37)	
95% CI	(9.88, 11.41)	(7.57, 9.04)	
LS Mean Difference (SE)		-2.33 (0.55)	<0.001
95% CI		(-3.42, -1.25)	

Source: Statistical reviewer

The estimated mean SOWS-Gossop scores over the 5-day treatment phase are displayed in Figure 1. There was a clear separation between treatment groups over time. The daily mean scores in the placebo group were higher with the peak separation on Day 2 compared with lofexidine group.

Figure 1 Mean SOWS-Gossop Scores over 5 Days for Study 3002



Source: Statistical reviewer

Second Primary Endpoint

Time to dropout in 6-hour time quadrants and by day are summarized by treatment group in Table 10. By Day 2, approximately 50% of the subjects discontinued from the study.

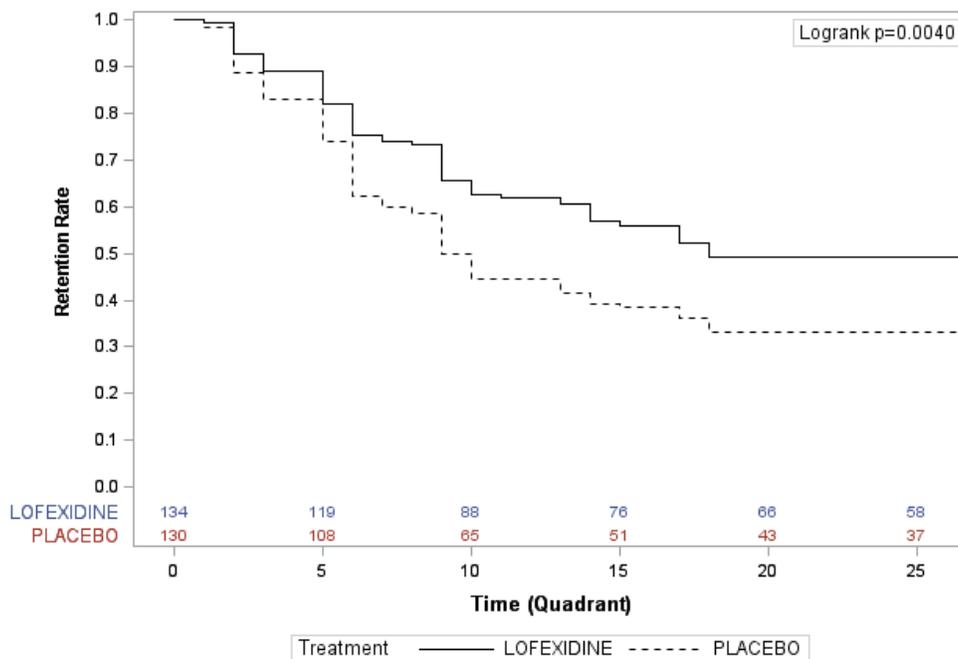
Table 10 Time to dropout for Study 3002

Variable	Treatment	Mean	Median	Min	Max
Quadrant	Lofexidine	8.4	7	1	18
	Placebo	7.6	6	1	18
Day	Lofexidine	2.7	2	1	5
	Placebo	2.5	2	1	5

Source: Statistical reviewer

Kaplan-Meier curves of subject retention are displayed in Figure 2, where the number of subjects at risk by treatment group was marked at the bottom. There was a clear separation between treatment groups starting from Day 2. The log rank test was statistically significant ($p=0.004$) indicating that lofexidine group has a higher retention rate through Day 5 compared with placebo group.

Figure 2 Kaplan-Meier Curves of Subject Retention for Study 3002



Source: Statistical reviewer

Our endpoint, completion status on Day 5, was measured by proportion of subjects who completed the 5-day treatment phase and were discharged in the first time quadrant or later (i.e. minimum quadrant is 21). Results are shown in Table 10. The completion rate during the treatment phase was significantly higher ($p=0.009$) in the lofexidine group (49%) compared to placebo group (33%).

Table 11 Proportion of completers on Day 5 (Study 3002)

	Placebo (N=130)		Lofexidine (N=134)		P-value
	N	%	N	%	
Non-completer	87	67	68	51	0.009
Completer	43	33	66	49	

Source: Statistical reviewer

Missing Data

There were 63% to 68% subjects who dropped out early in the Phase 3 efficacy studies and therefore we explored the impact of missing data during the review.

Unlike chronic diseases, one would expect that subjects having opioid use disorder and dependence to short-acting opioids usually experience withdrawal symptoms at the beginning of the opioid detoxification period.

To better understand the dropout pattern, dropout rates by study day were summarized for both studies in Table 12. Compared to subjects on placebo, fewer subjects on lofexidine dropped out during the 5 days of opioid discontinuation, 51% vs 67%. Among them, subjects tend to drop out early during the double-blind treatment phase, specifically on or prior to Day 2: 27% subjects dropped out from the lofexidine group compared to 42% subjects dropped out from the placebo group. Lack of efficacy, adverse event, and other were the most frequent reasons for dropout. A higher dropout rate due to lack of efficacy was observed in the placebo group (ranging from 9% to 13%) compared to the lofexidine group (ranging from 4% to 7%). This demonstrates that the dropout patterns were similar across studies and not unexpected.

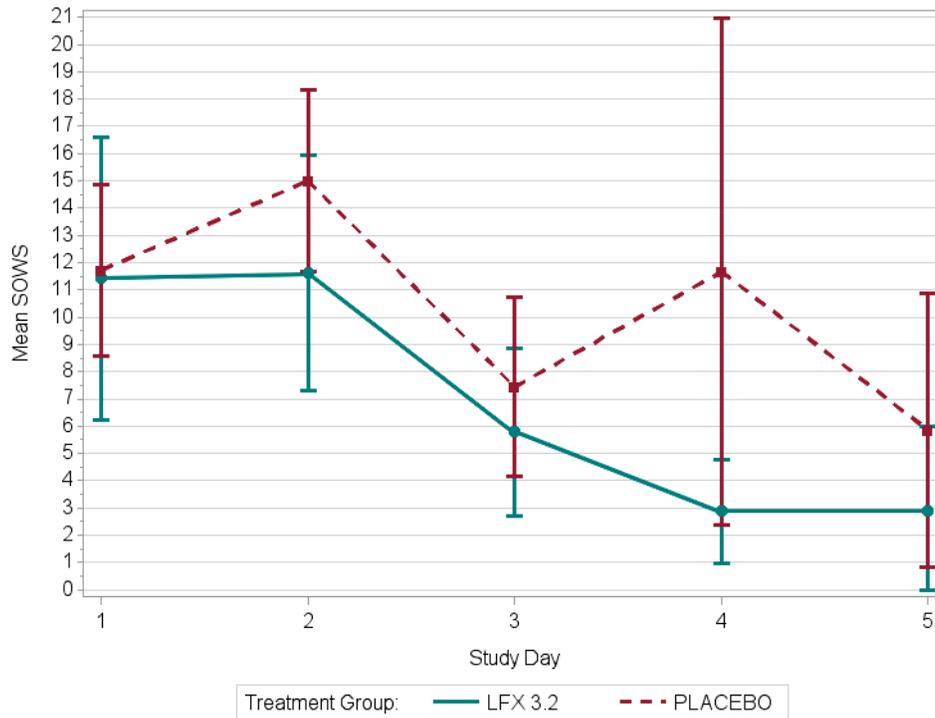
Table 12 Dropout Rates by Day and Reason for Study 3002

Dropout Reason	Placebo		LFX 3.2	
	N	%	N	%
Day 1				
Lack of efficacy	12	9%	6	4%
Other	5	4%	7	5%
Adverse event	2	2%	2	1%
Evidence of contraband drug use	1	1%	0	0%
Lack of compliance	2	2%	0	0%
Subtotal	22	17%	15	11%
Day 2				
Lack of efficacy	17	13%	9	7%
Other	13	10%	12	9%
Lack of compliance	2	2%	0	0%
Subtotal	32	25%	21	16%
Day 3				
Other	10	8%	13	10%
Lack of efficacy	4	3%	1	1%
Adverse event	3	2%	1	1%
Evidence of contraband drug use	1	1%	0	0%
Subtotal	18	14%	15	11%
Day 4				
Other	7	5%	5	4%
Lack of efficacy	1	1%	2	1%
Adverse event	0	0%	1	1%
Subtotal	8	6%	8	6%
Day 5				
Other	5	4%	9	7%
Lack of efficacy	2	2%	0	0%
Subtotal	7	5%	9	7%
Total	87	67%	68	51%

Source: Statistical reviewer

Figure 3 displays the average values of the last observed SOWS-Gossop scores by the day of dropout. Based on the pattern, it seems more convincing that subjects on lofexidine had lower SOWS-Gossop scores after withdrawal from the study than subjects on placebo. Among those completers, consistent results were found across studies that in terms of withdrawal symptoms during the 5-day opioid discontinuation treatment, subjects who were treated with lofexidine had greater improvement on SOWS-Gossop scores compared to those treated with placebo.

Figure 3 Mean Observed SOWS-Gossop Scores of Early Dropout by Day (Study 3002)



Source: Statistical reviewer

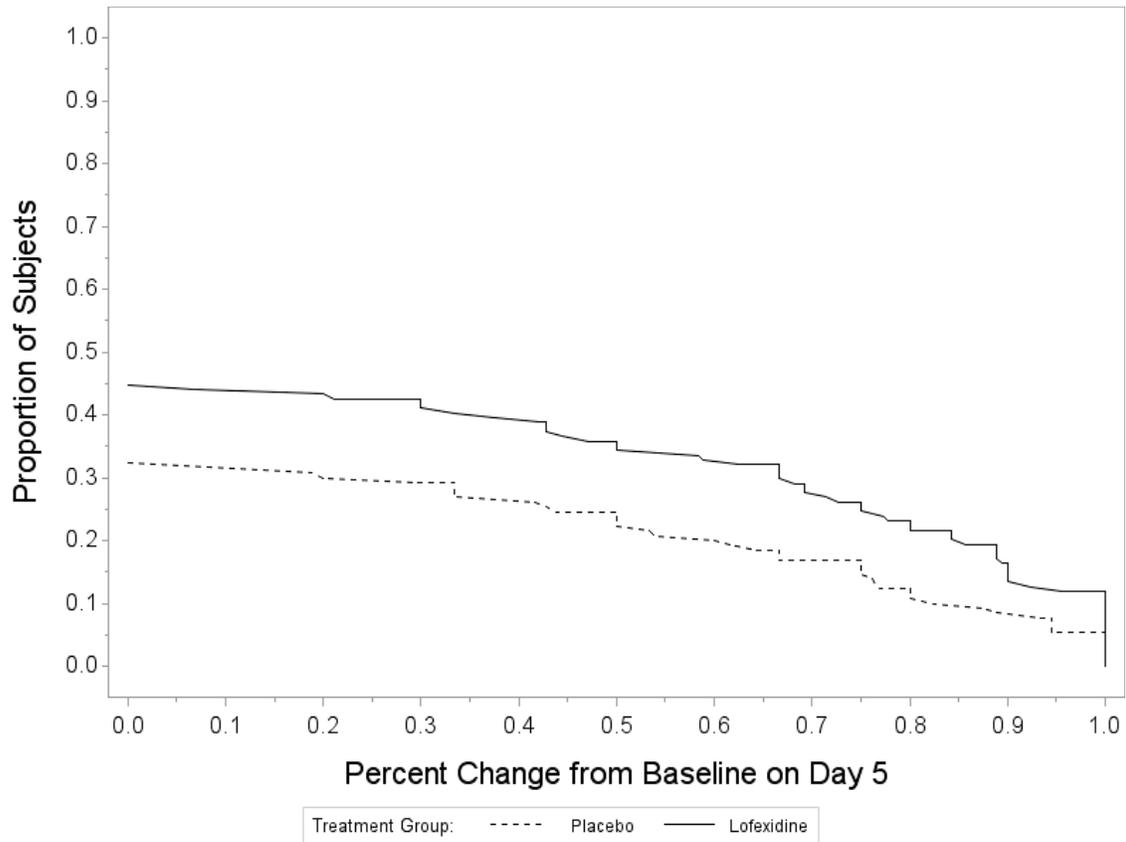
Because there were more completers in the lofexidine group and their SOWS-Gossop scores were lower than placebo, these results represent a drug benefit even with the large amount of missing data. However, to explore the impact of missing data, we conducted several different analyses, including complete case analysis, multiple imputation assuming MNAR, and continuous responder curves. The results from these analyses were consistent and supported the findings of the primary efficacy analyses.

Table 13 Complete Case Analysis for Study 3002

	Placebo	Lofexidine
Overall LS Mean (SE)	8.93 (0.48)	7.02 (0.44)
95% CI	(7.98, 9.87)	(6.15, 7.89)
LS Mean Difference (SE)		-1.91 (0.65)
95% CI		(-3.20, -0.61)
P-value		0.004

Source: Statistical reviewer

Figure 4 Continuous Responder Curve for Study 3002



Source: Statistical reviewer

Concomitant Medication Use

The table shown below lists the permitted concomitant medication use during the study treatment phase. Note that the percentages do not add up to 100 because the medication use is not mutually exclusive (i.e. one subject might have used different concomitant medications or used same medication on different days). For the proportion of subjects by day, the number of subjects stayed in the study each day was used as the denominator. There was a numerically greater percentage of subjects who used concomitant medication in the placebo group compared with the lofexidine group.

Table 14 Proportion of subjects who used concomitant medication for Study 3002

Concomitant Medication	Study Day	Treatment Group		
		LOFEXIDINE	PLACEBO	Total
Overall	n (%)	97 (72)	105 (81)	202 (77)
	Total	134	130	264
Alumina, Magnesia and Simethicone	Overall (n, %)	22 (16)	37 (28)	59 (22)
	1	5 (4)	20 (15)	25
	2	10 (8)	15 (14)	25
	3	5 (5)	10 (13)	15
	4	7 (8)	3 (5)	10
	5	3 (4)	4 (8)	7
Bismuth sulfate	Overall (n, %)	26 (19)	48 (37)	74 (28)
	1	11 (8)	28 (22)	39
	2	13 (11)	22 (20)	35
	3	6 (6)	15 (20)	21
	4	7 (8)	10 (17)	17
	5	3 (4)	4 (8)	7
Acetaminophen	Overall (n, %)	60 (45)	88 (68)	148 (56)
	1	37 (28)	70 (54)	107
	2	29 (24)	51 (47)	80
	3	21 (21)	35 (46)	56
	4	17 (20)	24 (41)	41
	5	12 (16)	15 (30)	27
Zolpidem	Overall (n, %)	73 (54)	81 (62)	154 (58)
	1	53 (40)	66 (51)	119
	2	40 (34)	56 (52)	96
	3	35 (36)	38 (50)	73
	4	30 (36)	35 (60)	65
	5	25 (33)	27 (54)	52

Source: Statistical reviewer

Overall, placebo-treated subjects used more of each concomitant medication than lofexidine-treated subjects. This is supportive of an efficacy finding and does not raise concern that concomitant medication contributed to the observed treatment effect on the SOWS-Gossop scores.

6.2 USWM-LX1-3003-1

6.2.1 Study Design

This study initiated on June 17, 2013 and completed on December 24, 2014. The database was locked on Jan 23, 2015.

Overview and Objective

The primary objective of this study was to investigate the efficacy, safety, and dose-response of lofexidine (2.4 mg/day versus 3.2 mg/day) in reducing withdrawal symptoms and facilitating completion of opioid discontinuation treatment in subjects undergoing withdrawal from short-acting opioids.

Trial Design

This was a Phase 3, multicenter (18 sites in the United States) study which consisted of two parts. Part 1 of the study used an inpatient, randomized, double-blind, and placebo-controlled design from Days 1 to 7. Part 2 of the study used an open-label, variable-dose design for up to an additional 7 days in either an inpatient or outpatient setting depending on the wishes of the site investigator and the subject. The double-blind treatment period of Study 3003-1 was very similar in design to Study 3002, with the main differences being the addition of a 2.4 mg/day lofexidine arm and a longer treatment period, 7 days versus 5 days.

This study intended to randomize a total of 600 subjects to receive lofexidine 2.4 mg/day, lofexidine 3.2 mg/day, or matching placebo in a 3:3:2 ratio for 7 days during Part 1 of the study. This should achieve 90% of power. During Part 2, all subjects who completed Part 1 were eligible to participate in the open-label phase. Participants received open-label, variable dose lofexidine treatment (not to exceed 3.2 mg/day) from Days 8 to 14.

The key inclusion criteria included:

1. At least 18 years of age.
2. Dependent⁹ on heroin, morphine, Vicodin, Lortab, Lorcet, Percocet, Percodan, Tylox, hydrocodone by any route of administration or oxycodone (including oxycodone time-released formulation).
3. Subject report of opioid use for at least 21 of the past 30 days.
4. Score of 2 or greater on the OOWS-Handelsman.
5. Positive urine toxicology screen for opiates and negative for methadone and buprenorphine
6. Female and of childbearing potential must have agreed to use birth control.

⁹ Opioid dependence in accordance with the Mini International Neuropsychiatric Interview (MINI) [Medical Outcomes Systems, 2013; Sheehan et al, 1998].

Subjects were to be excluded from participation for the following:

1. Pregnant or lactating women.
2. Self-reported methadone or buprenorphine use in the last 14 days.
3. Having a psychiatric disorder that the study physician believed would make study participation unsafe or treatment compliance difficult.
4. Addiction to another substance that requires detoxification.
5. Seizures, or anticonvulsant therapy use during the past 5 years.
6. Pancreatic disease such as Type 1 diabetes.
7. Liver disease or AST or ALT levels 5 times the upper limit of normal.
8. Gastrointestinal or renal disease that would affect absorption, metabolism or excretion of the study drug.
9. Clinically significant abnormal ECG such as second or third degree heart block, uncontrolled arrhythmia, or QTc interval > 450 msec for males, and > 470 msec for females.
10. Heart rate less than 55 bpm or symptomatic bradycardia.
11. Systolic blood pressure < 95 mmHg or symptomatic hypotension.
12. Diastolic blood pressure < 65 mmHg.
13. Blood pressure > 155/95 mmHg.
14. History of myocardial infarction.
15. Self-reported AIDS, HIV, active tuberculosis or active syphilis.
16. Clinically significant abnormal lab values.
17. Use of psychotropics, prescription analgesics, anticonvulsants, antihypertensives, antiarrhythmics, antiretrovirals, or cholesterol lowering medication in the past 4 weeks.

As in Study 3002, the concomitant medications allowed in the study were alumina, magnesia, simethicone, bismuth sulfate, acetaminophen, zolpidem.

The schedule of study assessments is reproduced from the study protocol below:

Table 15 Schedule of Assessments Study 3003-1

Activity	Randomized, Double-Blind, Placebo-Controlled (Days 1-7) followed by Open-Label, Continuation Treatment (Days 8-14)					Study Discontinuation/ End of Study*
	Screening	Baseline	Inpatient Treatment	In/Outpatient Treatment		
	Days -6 to -1	Day 1	Days 1-7	Days 8-14		
Informed Consent Signed	X					
Screening Number Assigned	X					
Inclusion/Exclusion Criteria	X	X (b)				
Prior Medication History	X	X (b)				
Demographics	X					
Medical and Smoking History	X					
Mini-International Neuropsychiatric Interview	X					
Infectious Disease Assessments (c)	X					
Pregnancy Test (d)	X	X				X
Height	X					
Weight	X					X
Admission to Inpatient Unit		X				
Randomization		X				
Study Medication Administration			X (QID)	X (variable)		
Medication Compliance			X	X		X
Discharge from Inpatient Unit			Day 7			
Efficacy Assessments						
Short Opiate Withdrawal Scale of Gossop (e)		X	X	X		X
Objective Opiate Withdrawal Scale of Handelsman (e)	X	X (f)	X	X		X
Modified Clinical Global Impression (e)			X	X		X
Visual Analog Scale for Efficacy (e)			X	X		X
Clinical Opiate Withdrawal Scale (e)	X	X	X	X		X
Concomitant Medications Assessment			X	X		X
Assessment of Detoxification Completion			X (g)	X		X
Safety Assessments						
Adverse Events Assessment			X	X		X
Vital Signs (Sitting/Recumbent & Standing BP and pulse, respiration, and temperature)	X	X	X (i)	X (j)		X
12-Lead Electrocardiogram (duplicate)	X (k)		X (l)	Day 8 and 14 (m)		X
Pharmacokinetic Sampling			X (n)			
Pharmacokinetic Sampling			Day 3 and 6 (r)			
Clinical Laboratory Tests (hematology, chemistry, urinalysis)	X		X (o)	X (o)		X
Physical Exam (p)	X	X	X	X		X

Activity	Randomized, Double-Blind, Placebo-Controlled (Days 1-7) followed by Open-Label, Continuation Treatment (Days 8-14)					Study Discontinuation/ End of Study*
	Screening	Baseline	Inpatient Treatment	In/Outpatient Treatment		
	Days -6 to -1	Day 1	Days 1-7	Days 8-14		
C-SSRS Baseline Version		X				
C-SSRS Since Last Visit Version			X (s)	X (t)		X
Urine Drug Screen (q)	X	X	X	X		X
Telephone Follow Up (h)						X

- Abbreviations: BP = blood pressure; C-SSRS = Columbia Suicide Severity Scale; QID = 4 times daily
- * The study discontinuation/end of study assessments/procedures should always be done upon exit from the study.
- (a) The Baseline period is the morning of admission, before randomization.
 - (b) This form is to be updated at Baseline.
 - (c) A chest x-ray is required only if a PPD (purified protein derivative) skin test for tuberculosis is not done, the current PPD is positive, or if a past PPD was positive.
 - (d) The urine sample collected on the first day of screening will be divided into two aliquots. One sample will be sent to the central lab (b) (4) for urinalysis and the other sample will be used for urine drug screening and immediate "dipstick" analysis of pregnancy (females only).
 - (e) During Inpatient Treatment (Days 1-7), efficacy scales will be completed daily: the Short Opiate Withdrawal Scale of Gossop 3.5 hours (±10 minutes) after the first dose of study medication followed by the other efficacy scales shortly thereafter. Efficacy scales will be completed daily before dosing during Days 8-14.
 - (f) The Objective Opiate Withdrawal Scale of Handelsman (OOWS-Handelsman) will be completed at Baseline to determine final eligibility as subjects must have a score ≥2 in order to participate in the study (inclusion criterion #4).
 - (g) To be done at the end of double-blind dosing and before initiating open-label dosing.
 - (h) The follow-up telephone contact will be 30 days after the subject's last dose and will include an evaluation of the subject's current treatment status (e.g., relapse, current psychosocial treatment, successful entry into a methadone, buprenorphine, or naltrexone program) and an adverse event evaluation.
 - (i) Vital signs (resting [sitting/recumbent] and standing blood pressure and pulse, respiration, and temperature) will be measured before every dose and 3.5 hours after study medication administration at 8 AM, 1 PM, and 6 PM (7 times per day).
 - (j) Vital signs (resting [sitting/recumbent] and standing blood pressure, and pulse) will be measured at least once daily before dosing and 3.5 hours after dosing on Days 8-13 and once before any dose on Day 14. Oral temperature and respiration are not required measurements Days 8-14. Note that if subjects are being treated on an outpatient basis and cannot stay in the clinic for measurement of the 3.5-hour post-dose vital signs required on Days 8-13, they will be given a portable digital blood pressure machine for measurement of their vital signs at this required time point. They will also be provided a diary to record the measurements.
 - (k) Baseline 12-lead electrocardiograms (ECGs) will be done on one day during the screening period, time-matched to the post randomization ECG schedule (i.e., pre-1 PM [before 1 PM dose], 4 PM [3 hours post-dose], and 5 PM [4 hours post-dose]).
 - (l) 12-lead ECGs will be done before the first daily dose, pre-1 PM dose, at 4 PM, and at 5 PM on Days 1 and 7, and before the first daily dose only on Days 2 and 4.
 - (m) 12-lead ECGs will be done before the first daily dose and 3.5 hours after first daily dose on Day 8, on Day 14, the ECGs will be done before a dose on that day.
 - (n) A finger prick blood sample will be collected concurrently with each scheduled ECG during Days 1-7.
 - (o) Clinical lab testing will be done as clinically warranted throughout the study and at the end of double-blind dosing and before initiating open-label dosing.
 - (p) A complete physical examination will be performed during screening and the physical exam form will be updated at Baseline. A complete physical examination will be performed on Day 1 (3-4 hours after randomization) and at the end of double-blind dosing and before initiating open-label dosing. During Days 8-14, a complete physical exam will be performed as clinically warranted and at discontinuation from the study.
 - (q) Urine drug screen will be done at least every other day to monitor for contraband (inpatient setting) or illicit (outpatient setting) drug use.
 - (r) A finger prick blood sample will be collected at 9 PM and 10 PM (3 and 4 hours, respectively, after the 6 PM dose).
 - (s) C-SSRS will be completed at 3.5 hours after the first dose (8 AM) on Days 1-7.
 - (t) C-SSRS will be completed once daily on Days 8-14.

Source: Table 1 Study 3003-1 protocol

Study Endpoints

The Applicant's prespecified primary efficacy endpoint was the SOWS-Gossop scores from Days 1 to 7. The prespecified secondary efficacy endpoint was completion status, defined as the proportion of completers where a "completer" was defined as a subject who received at least one dose of study medication on Day 7 and completed the 3.5-hour post-dose SOWS-Gossop assessment on Day 7.

Instead of the Applicant's prespecified efficacy endpoints from Days 1 to 7, SOWS-Gossop and completion data for the first 5 days of the treatment period were considered more clinically relevant and therefore our endpoints of interest.

Statistical Analysis Plan

The applicant defined three analysis populations:

- Intent-to-treat (ITT) population: all randomized subjects.
- Modified Intent-to-treat (mITT) population: all ITT subjects who received at least one dose of study medication.
- Per-protocol (PP) population: all mITT subjects who satisfied the inclusion/exclusion criteria, received the treatment to which they were randomized, and did not have any major protocol deviation within the double-blind phase.

All the efficacy analyses for Study 3003-1 were conducted in the mITT population.

To prevent the skewness in the SOWS-Gossop scores, the primary endpoint of SOWS-Gossop scores from Days 1 to 7 was prespecified to be transformed to the natural logarithm of the original score plus 1, and then analyzed using an MMRM model with fixed effects treatment, baseline log-transformed SOWS-Gossop score, sex, study day, and treatment by day interaction, as well as a random effect for subjects. The Applicant's secondary endpoint of completion status was analyzed using a logistic regression model with terms treatment and sex.

Our selected primary endpoint of SOWS-Gossop scores from Days 1 to 5 was analyzed using the same MMRM model with same covariates. To be consistent with Study 3002, our secondary endpoint of interest completion status on Day 5 was analyzed using Fisher's exact test.

A sequential testing strategy was prespecified to account for multiplicity. The hypotheses were tested in the following order at the level of 0.05:

- 1) Primary endpoint, lofexidine 3.2 mg versus placebo
- 2) Primary endpoint, lofexidine 2.4 mg versus placebo
- 3) Secondary endpoint, lofexidine 3.2 mg versus placebo
- 4) Secondary endpoint, lofexidine 2.4 mg versus placebo

To handle missing SOWS-Gossop scores in the primary analysis, a control-based pattern mixture model with multiple imputation was used assuming that early withdrawals in the lofexidine group followed the trajectory of placebo subjects that remain in the study. This method assumed that the data was MNAR. The imputation model used a sequential regression model including

sex and log-transformed pre-dropout SOWS-Gossop scores. As in Study 3002, we used multiple imputation with placebo mean on Day 2 to impute missing data. The data were imputed 20 times and was then analyzed using the same MMRM model with the same covariates.

Data Quality and Integrity

All documentation including the study protocol, statistical analysis plan, clinical study report, and literature referenced, as well as the SDTM and ADaM datasets were submitted under the network path \\CDSESUB1\evsprod\NDA209229\0002. Datasets were submitted by the applicant to the CDER electronic data room in SAS transport format.

In response to the information request sent on September 18, 2017, the applicant resubmitted datasets, corrected define files, as well as the SAS programs used to generate the efficacy analysis datasets under the network path \\CDSESUB1\evsprod\NDA209229\0006. The datasets were of acceptable quality and were adequately documented to allow for a thorough review of the data.

6.2.2 Study Results

Patient Disposition

See Study Site Information for enrollment by site and primary investigator. Of the 603 subjects randomized, one subject in the lofexidine 2.4 mg group did not receive treatment and therefore excluded from the mITT population. Patient disposition is shown in Table 16. In the mITT population, 378 subjects discontinued the double-blind treatment phase. More subjects discontinued early in the placebo group (109, 72%) than those in the lofexidine groups (135, 59% in 2.4 mg; 134, 60% in 3.2 mg). Overall, the most frequent dropout reason was lack of efficacy followed by withdrew consent. Approximately twice as many subjects dropped out due to lack of efficacy in the placebo group compared to lofexidine groups. A total of 14% subjects in the high dose group dropped out due to adverse event related to study drug, 7% in the low dose group, and 1% in the placebo group. Based on the data submitted by the applicant some of the dropout reasons under “Other” category were not classified correctly (see footnotes). After reclassification, the pattern of dropout reasons did not change; the most common reasons were still lack of efficacy, withdrew consent, and adverse event.

Table 16 Disposition for Study 3003-1

Number of Subjects	Placebo	Lofexidine	
		2.4 mg	3.2 mg
Randomized	151	229	222
Completed DB phase, n (%)	42 (28)	95 (41)	88 (40)
Discontinued DB phase, n (%)	109 (72)	135 (59)	134 (60)
Lack of efficacy ¹	53 (35)	44 (19)	30 (14)
Adverse event related to study drug ²	2 (1)	15 (7)	30 (14)
Adverse event unrelated to study drug ²	0	0	3 (1)
Evidence of contraband drug use	4 (3)	4 (2)	4 (2)
Therapy with exclusionary drug	0	1	1
Lack of compliance ³	5 (4)	7 (3)	3 (1)
Other	45 (30)	64 (28)	63 (28)
Withdrawn consent	18 (12)	30 (13)	36 (16)
Subject request	15 (10)	14 (6)	17 (8)
Lack of efficacy ¹	1 (1)	10 (4)	2 (1)
Withdrawn consent and left against medical advice	5 (4)	5 (2)	3 (1)
Adverse event ²	4 (3)	2 (1)	2 (1)
Completed detox	2 (1)	3 (1)	2 (1)
Lack of compliance ³	0	0	1

¹Categories were combined into Lack of Efficacy

²Categories were combined into Adverse Event

³Categories were combined into Lack of Compliance

Source: 3003-1 CSR Figure 1 and Table 8

Table 17 Reclassified Disposition for Study 3003-1

Number of Subjects	Placebo	Lofexidine	
		2.4 mg	3.2 mg
Randomized	151	229	222
Completed DB phase, n (%)	42 (28)	95 (41)	88 (40)
Discontinued DB phase, n (%)	109 (72)	135 (59)	134 (60)
Lack of efficacy	54 (36)	54 (23)	32 (14)
Adverse event	6 (4)	17 (7)	35 (15)
Evidence of contraband drug use	4 (3)	4 (2)	4 (2)
Therapy with exclusionary drug	0	1	1
Lack of compliance	5 (4)	7 (3)	4 (1)
Other	40 (26)	52 (23)	58 (26)
Withdrawn consent	18 (12)	30 (13)	36 (16)
Subject request	15 (10)	14 (6)	17 (8)
Withdrawn consent and left against medical advice	5 (4)	5 (2)	3 (1)
Completed detox	2 (1)	3 (1)	2 (1)

Source: Statistical reviewer

Demographic Characteristics

Baseline characteristics are shown in Table 18 and were similar across the treatment groups. Most of the subjects were male (71%), white (74%) and the mean age was 35 years. There was a slightly greater percentage of black subjects in the lofexidine groups (24% in 2.4 mg/day, 22% in 3.2 mg/day) compared with placebo group (17%).

Table 18 Demographics for Study 3003-1

Characteristic	Placebo (N=151)	Lofexidine		Total (N=602)
		2.4 mg (N=229)	3.2 mg (N=222)	
Sex				
Male	107 (71)	162 (71)	158 (71)	427 (71)
Female	44 (29)	67 (29)	64 (29)	175 (29)
Age (years)				
Mean years (SD)	36 (12)	35 (11)	35 (11)	35 (11)
Median	32	34	33	33
Min, Max	19, 63	19, 74	19, 68	19, 74
Race				
White	117 (78)	169 (74)	158 (71)	444 (74)
Black or African American	26 (17)	54 (24)	48 (22)	128 (21)
Asian	1 (1)	1	3 (1)	5 (1)
American Indian or Alaska Native	2 (1)	0	2 (1)	4 (1)
Native Hawaiian or Other Pacific Islander	3 (2)	0	2 (1)	5 (1)
Other	2 (1)	5 (2)	9 (4)	16 (3)
Ethnicity				
Hispanic or Latino	22 (15)	33 (14)	28 (13)	83 (14)
Not Hispanic or Latino	129 (85)	196 (86)	194 (87)	519 (86)
Body Weight (kg)				
Mean (SD)	76 (15)	76 (17)	76 (17)	76 (16)
Median	74	74	74	74
Min, max	44, 132	40, 149	44, 147	40, 149

Source: 3003-1 CSR Table 12

Efficacy Results

Primary Endpoint

Analysis of the Applicant's pre-specified primary endpoint, SOWS-Gossop scores from Day 1 through Day 7, demonstrated a significant difference between placebo and both doses of lofexidine. However, there was no significant difference between the two doses of lofexidine. Results are shown in Table 19.

Table 19 Comparisons of SOWS-Gossop scores Days 1-7 (Study 3003-1)

	Placebo	LFX 2.4	LFX 3.2
Overall Geometric Mean	5.23	4.07	3.80
Overall LS Mean	1.83	1.62	1.57
95% CI	(1.64, 2.01)	(1.49, 1.75)	(1.43, 1.70)
LS Mean Difference		-0.21	-0.26
95% CI		(-0.37, -0.04)	(-0.44, -0.09)
P-value ¹		0.017	0.003

¹ P-values were from inference on the log scale.

Source: Statistical reviewer

Our results (Table 20) for SOWS-Gossop scores from Day 1 through Day 5 were consistent with the Applicant's results. The estimated treatment effect on log-transformed SOWS-Gossop scores for each of lofexidine groups compared to placebo group was statistically significant and there was no significant difference between the two doses of lofexidine.

Table 20 Comparisons of SOWS-Gossop scores Days 1-5 (Study 3003-1)

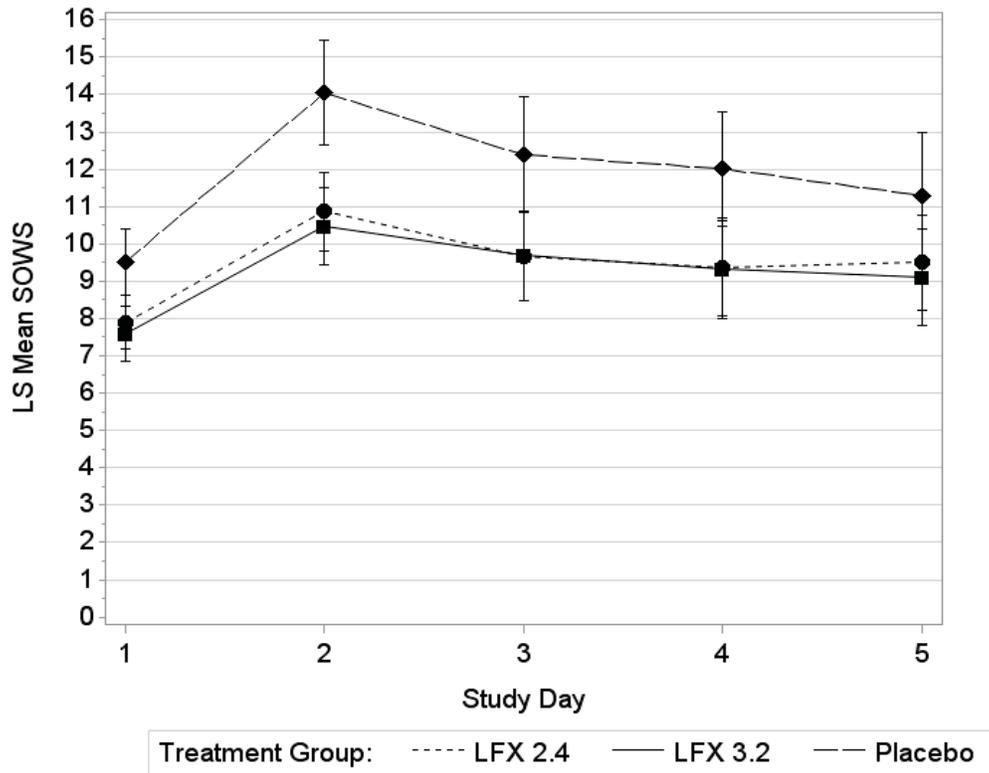
	Placebo	LFX 2.4	LFX 3.2
Overall LS Mean (SE)	2.29 (0.05)	2.02 (0.04)	1.97 (0.04)
95% CI	(2.20, 2.38)	(1.95, 2.10)	(1.89, 2.05)
LS Mean Difference (SE)		-0.26 (0.06)	-0.31 (0.06)
95% CI		(-0.38, -0.15)	(-0.44, -0.20)
P-value ¹		<0.001	<0.001

¹ P-values were from inference on the log scale.

Source: Statistical reviewer

The mean SOWS-Gossop scores and 95% confidence intervals using the untransformed data over the 5-day treatment phase are displayed in Figure 5. Missing data were imputed using a multiple imputation approach with placebo mean on Day 2. As seen in Study 3002, there was a clear separation over time between placebo and each lofexidine group with the peak separation on Day 2. However, the gap between two lofexidine groups was minimal and confidence intervals overlapped.

Figure 5 Mean SOWS-Gossop Scores over 5 Days for Study 3003-1



Source: Statistical reviewer

Secondary Endpoint

Results for the secondary endpoint, completion status on Day 7, are shown in Table 21. Approximately 40% subjects in the lofexidine groups completed the treatment phase compared to 28% in the placebo group. The odds of having subjects completed opioid withdrawal was significantly greater in any of the lofexidine groups (p-value=0.007, LFX 2.4; p-value=0.019, LFX 3.2) compared to the placebo group. The odds ratio in high dose group (OR=1.71) was slightly smaller than the low dose group (OR=1.85) and was not significantly different.

Table 21 Proportion of Completers on Day 7 for Study 3003-1

	Placebo		LFX 2.4		LFX 3.2	
	N	%	N	%	N	%
Non-completer	109	72	134	59	134	60
Completer	42	28	95	41	88	40
OR (95% CI)			1.85 (1.18, 2.88)		1.71 (1.09, 2.67)	
P-value			0.007		0.019	

Source: Statistical reviewer

As shown in Table 22, our endpoint of interest was the proportion of subjects who completed Day 5 during the double-blind treatment phase. There were 32%, 46%, and 47% subjects who completed 5 days of treatment in the placebo, lofexidine 2.4 mg (p-value=0.01), and lofexidine 3.2 mg (p-value=0.007) groups, respectively. There was no significant difference between the two doses of lofexidine.

Table 22 Proportion of Completers on Day 5 for Study 3003-1

	Placebo		LFX 2.4		LFX 3.2	
	N	%	N	%	N	%
Non-completer	102	68	124	54	118	53
Completer	49	32	105	46	104	47
P-value			0.010		0.007	

Source: Statistical reviewer

Missing Data

Dropout rates by study day for Study 3003-1 are summarized in **Table 23**. Compared to subjects on placebo, fewer subjects on lofexidine dropped out during the 5 days of opioid discontinuation: around 54% vs 68%. Among them, subjects tended to drop out early during the double-blind treatment phase, specifically on or prior to Day 2, and more subjects dropped out from the placebo group (53%) compared to subjects in the lofexidine groups (35% in LFX 2.4, 41% in LFX 3.2). Lack of efficacy, adverse event, and other were the most frequent reasons for dropout. A higher dropout rate due to lack of efficacy was observed in the placebo group (ranging from 12% to 19%), compared to the lofexidine groups (ranging from 4% to 10%). This demonstrates that the dropout patterns were similar across studies and not unexpected.

Table 23 Dropout Rates by Day and Reason for Study 3003-1

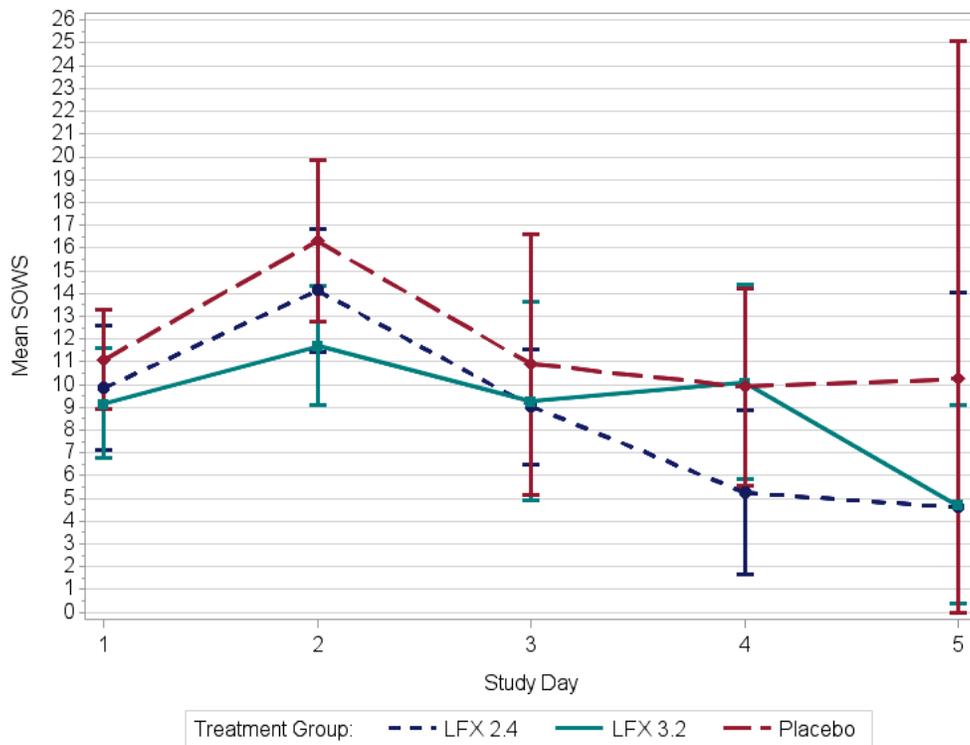
Dropout Reason	Placebo		LFX 2.4		LFX 3.2	
	N	%	N	%	N	%
Day 1						
Lack of efficacy	28	19%	13	6%	9	4%
Adverse event	0	0%	5	2%	12	5%
Other	21	14%	15	7%	23	10%
Lack of compliance	2	1%	1	0%	2	1%
Subject request	19	13%	14	6%	19	9%
Therapy with exclusionary drug	0	0%	0	0%	1	0%
Evidence of contraband drug use	0	0%	0	0%	1	0%
Completed detox	1	1%	0	0%	0	0%
Withdrew Consent	0	0%	0	0%	1	0%
Subtotal	50	33%	33	14%	45	20%
Day 2						
Lack of efficacy	18	12%	23	10%	14	6%
Adverse event	0	0%	5	2%	10	5%
Other	12	8%	20	9%	24	11%
Subject request	11	7%	18	8%	21	9%
Therapy with exclusionary drug	0	0%	1	0%	0	0%
Evidence of contraband drug use	1	1%	1	0%	1	0%
Lack of compliance	0	0%	0	0%	1	0%
Subtotal	30	20	48	21	47	21
Day 3						
Lack of efficacy	4	3%	7	3%	3	1%
Adverse event	0	0%	3	1%	4	2%
Other	8	5%	16	7%	10	5%
Lack of compliance	1	1%	3	1%	0	0%
Subject request	4	3%	12	5%	9	4%
Evidence of contraband drug use	3	2%	1	0%	0	0%
Subtotal	12	8	26	11	16	7
Day 4						
Adverse event	2	1%	2	1%	2	1%
Lack of efficacy	3	2%	1	0%	2	1%
Other	5	3%	13	6%	6	3%
Lack of compliance	2	1%	1	0%	0	0%
Subject request	3	2%	11	5%	5	2%
Evidence of contraband drug use	0	0%	1	0%	1	0%
Subtotal	10	7	16	7	10	5
Day 5						
Subject request	0	0%	1	0%	0	0%
Total	102	68%	123	54%	118	53%

Source: Statistical reviewer

Figure 6 displays the average values of the last observed SOWS-Gossop scores by the day of dropout. Except for Day 4, subjects on lofexidine had lower SOWS-Gossop scores after withdrawal from the study than subjects on placebo. This observation is consistent with the higher incidence of discontinuations categorized as due to lack of efficacy in the placebo group compared to the lofexidine groups and the higher incidence of discontinuations due to lack of efficacy in the beginning of the treatment period observed in all treatment groups. Among those completers, consistent results were found across studies that in terms of withdrawal symptoms during the 5-day opioid discontinuation treatment, subjects who treated with lofexidine had greater improvement on SOWS-Gossop scores compared to those treated with placebo.

Because there were more completers on the lofexidine groups and their SOWS-Gossop scores were lower than placebo, these results represent a drug benefit even with the large amount of missing data. However, we conducted several different analyses to explore the effect of missing data, including complete case analysis, multiple imputation assuming MNAR, and continuous responder curves. The results from these analyses were consistent and supported the findings of the primary efficacy analyses.

Figure 6 Mean Observed SOWS-Gossop Scores of Early Dropout by Day (Study 3003-1)



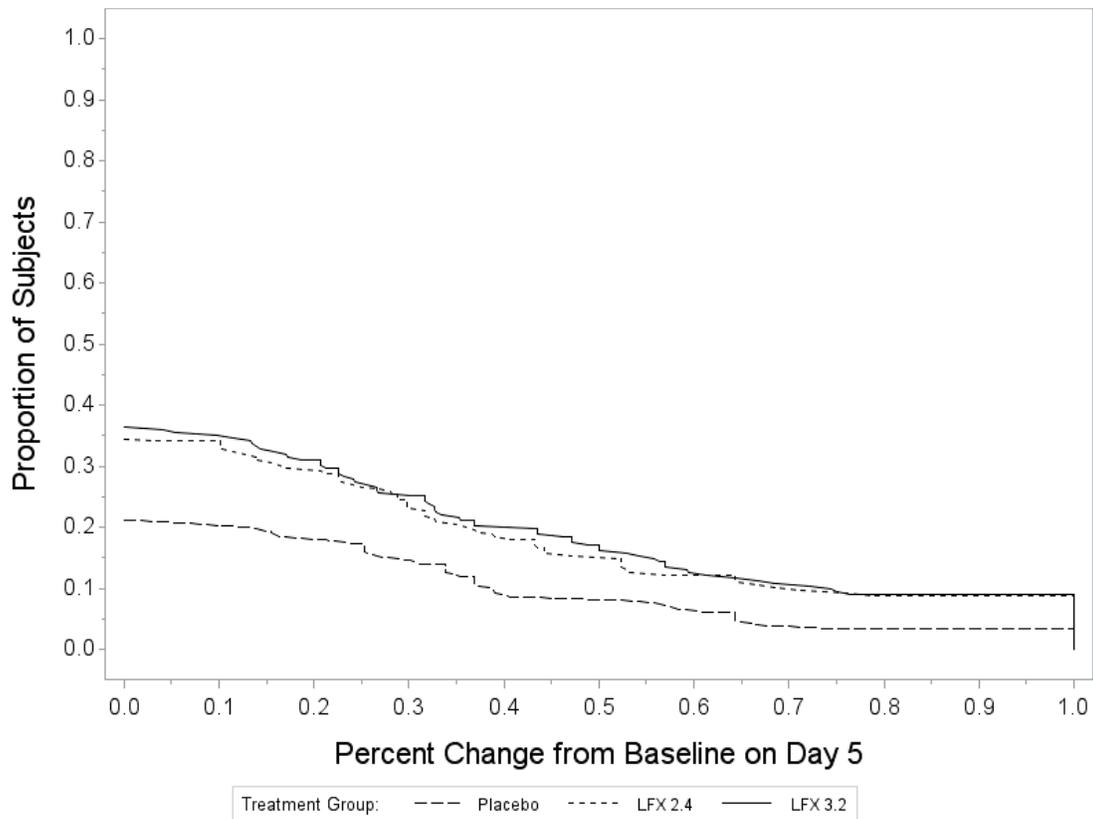
Source: Statistical reviewer

Table 24 Complete Case Analysis for Study 3003-1

	Placebo	LFX 2.4	LFX 3.2
Overall LS Mean (SE)	2.16 (0.07)	1.81 (0.05)	1.73 (0.05)
95% CI	(2.03, 2.29)	(1.72, 1.91)	(1.63, 1.83)
LS Mean Difference (SE)		-0.34 (0.08)	-0.43 (0.08)
95% CI		(-0.50, -0.18)	(-0.59, -0.26)
P-value		<0.001	<0.001

Source: Statistical reviewer

Figure 7 Continuous Responder Curve for Study 3003-1



Source: Statistical reviewer

Concomitant Medication Use

Table 25 lists the permitted concomitant medication use during the study treatment phase. There was a numerically greater percentage of subjects who used concomitant medication in the placebo group compared with the lofexidine groups for acetaminophen and similar use between groups for the other medications, especially in the first days of the treatment period.

Table 25 Proportion of subjects who used concomitant medication in Study 3003-1

Concomitant Medication	Study Day	LFX 2.4 mg	LFX 3.2 mg	Placebo
		(N=229) n / m (%)	(N=220) n / m (%)	(N=151) n / m (%)
APAP	Overall	103 / 229 (45.0)	103 / 222 (46.4)	81 / 151 (53.6)
	Day 1	51 / 229 (22.3)	59 / 222 (26.6)	43 / 151 (28.5)
	Day 2	56 / 202 (27.7)	53 / 186 (28.5)	52 / 106 (49.1)
	Day 3	40 / 153 (26.1)	39 / 133 (29.3)	35 / 71 (49.3)
	Day 4	37 / 123 (30.1)	38 / 117 (32.5)	31 / 60 (51.7)
	Day 5	34 / 106 (32.1)	27 / 107 (25.2)	24 / 50 (48.0)
	Day 6	28 / 99 (28.3)	26 / 96 (27.1)	20 / 45 (44.4)
	Day 7	18 / 98 (18.4)	15 / 92 (16.3)	9 / 42 (21.4)
Alumina, Magnesia and Simethicone	Overall	32 / 229 (14.0)	30 / 222 (13.5)	24 / 151 (15.9)
	Day 1	13 / 229 (5.7)	14 / 222 (6.3)	11 / 151 (7.3)
	Day 2	14 / 202 (6.9)	10 / 186 (5.4)	15 / 106 (14.2)
	Day 3	13 / 153 (8.5)	17 / 133 (12.8)	10 / 71 (14.1)
	Day 4	8 / 123 (6.5)	11 / 117 (9.4)	6 / 60 (10.0)
	Day 5	6 / 106 (5.7)	7 / 107 (6.5)	4 / 50 (8.0)
	Day 6	4 / 99 (4.0)	4 / 96 (4.2)	1 / 45 (2.2)
	Day 7	3 / 98 (3.1)	2 / 92 (2.2)	1 / 42 (2.4)
Bismuth sulfate	Overall	68 / 229 (29.7)	58 / 222 (26.1)	44 / 151 (29.1)
	Day 1	27 / 229 (11.8)	23 / 222 (10.4)	15 / 151 (9.9)
	Day 2	34 / 202 (16.8)	26 / 186 (14.0)	26 / 106 (24.5)
	Day 3	30 / 153 (19.6)	25 / 133 (18.8)	21 / 71 (29.6)
	Day 4	22 / 123 (17.9)	15 / 117 (12.8)	16 / 60 (26.7)
	Day 5	17 / 106 (16.0)	12 / 107 (11.2)	15 / 50 (30.0)
	Day 6	10 / 99 (10.1)	8 / 96 (8.3)	8 / 45 (17.8)
	Day 7	7 / 98 (7.1)	4 / 92 (4.3)	4 / 42 (9.5)
Zolpidem	Overall	122 / 229 (53.3)	118 / 222 (53.2)	67 / 151 (44.4)
	Day 1	75 / 229 (32.8)	67 / 222 (30.2)	46 / 151 (30.5)
	Day 2	76 / 202 (37.6)	68 / 186 (36.6)	41 / 106 (38.7)
	Day 3	71 / 153 (46.4)	72 / 133 (54.1)	39 / 71 (54.9)
	Day 4	58 / 123 (47.2)	62 / 117 (53.0)	35 / 60 (58.3)
	Day 5	50 / 106 (47.2)	59 / 107 (55.1)	31 / 50 (62.0)
	Day 6	42 / 99 (42.4)	54 / 96 (56.3)	25 / 45 (55.6)
	Day 7	25 / 98 (25.5)	26 / 92 (28.3)	13 / 42 (31.0)

Source: Response to Information Request dated 2/9/18

Overall, placebo-treated subjects used more of each concomitant medication than lofexidine-treated subjects. This is supportive of an efficacy finding and does not raise concern that concomitant medication contributed to the observed treatment effect on the SOWS-Gossop scores, and therefore was not considered when evaluating SOWS-Gossop Scores.

The study also evaluated the effect of lofexidine on withdrawal symptoms as measured by a clinician-administered instrument, the Clinical Opioid Withdrawal Scale (COWS). The COWS has not been reviewed to determine whether it has been appropriately developed and validated to support efficacy claims. However, it has become widely-used clinically and is familiar to many clinicians. The findings using the COWS were similar to those using the SOWS-Gossop.

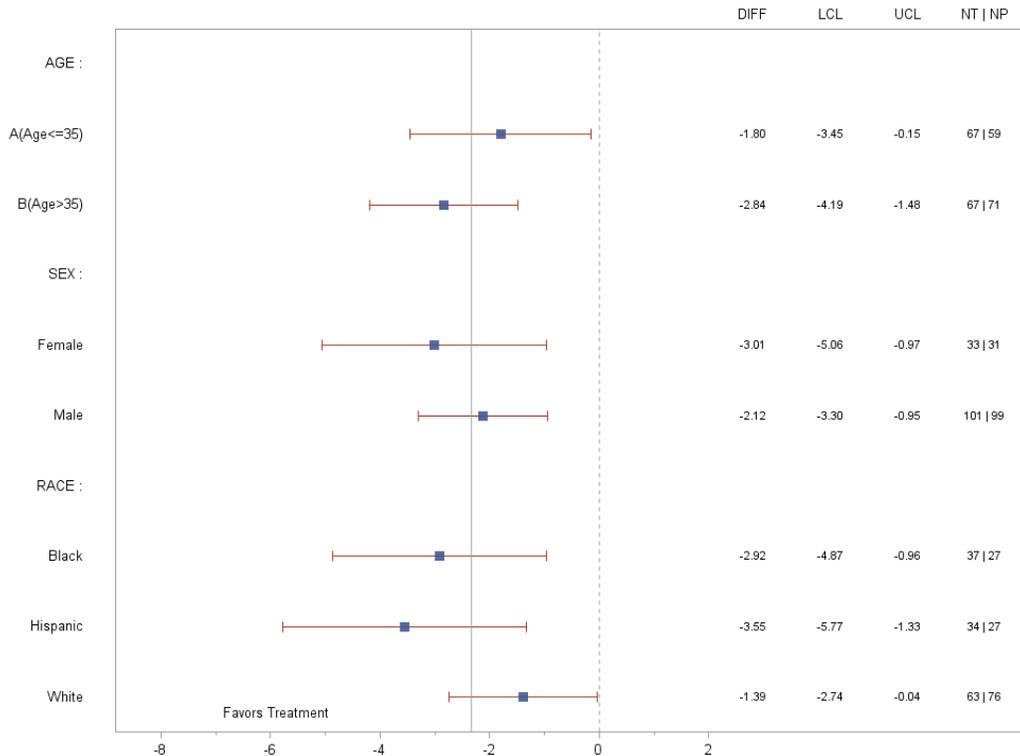
7 Findings in Special/Subgroup Populations

7.1 Sex, Race, and Age for Study 3002

In addition to the subgroup analyses performed by the Applicant for the primary efficacy endpoints, I conducted subgroup analyses for our endpoint of interest, SOWS-Gossop scores from Day 1 to Day 5, by age dichotomized at the cutoff of 35 (≤ 35 years and >35 years), sex (male and female), and race (White, Black, and Hispanic).

The statistical methods were based on those used in our efficacy analysis (Section 6.1.1). Missing data were imputed using a multiple imputation approach with mean of the placebo completers on Day 2. For each subgroup, I present the least square mean difference in SOWS-Gossop scores Days 1-5 comparing lofexidine with placebo and its 95% CI. Results are shown in Figure 8. The mean differences of SOWS-Gossop scores were consistent across all subgroups. There were no statistically significant interactions between treatment and the subgroup of interest. A negative mean difference favoring lofexidine was observed in all subgroups.

Figure 8 Subgroup Analyses for SOWS-Gossop Scores Days 1-5 (Study 3002)



The LS mean difference of lofexidine vs placebo with respect to SOWS-Gossop Scores Days 1-5 was analyzed using MMRM model with treatment, baseline SOWS, opioid dependence severity, study day, the subgroup of interest, treatment-by-subgroup and treatment-by-day interactions.

DIFF: LS mean difference

LCL: lower confidence limit

UCL: upper confidence limit

NT: number of subjects in the active treatment group

NP: number of subjects in the placebo group

Solid vertical line: overall estimated effect size.

Dashed vertical line: no effect.

Source: Statistical reviewer

Subgroup analyses for our endpoint of interest, completion status on Day 5, were performed by the same subgroups list above. Specifically, 2x2 tables stratified by subgroup of interest were created to summarize the completion status for each treatment in each stratum. Compared to placebo, a greater proportion of completers was observed in the lofexidine group across all subgroups.

7.2 Sex, Race, Age, Weight, and Baseline SOWS-Gossop Scores for Study 3003-1

Similarly, I conducted subgroup analyses for our endpoint of interest, SOWS-Gossop scores from Day 1 to Day 5, by age dichotomized at the cutoff of 35 (≤ 35 years and >35 years), sex (male and female), race (White, Black, and Hispanic), baseline SOWS-Gossop scores dichotomized at the median score (≤ 8 and >8), and weight (≤ 65 kg, 66-85 kg, and >85 kg).

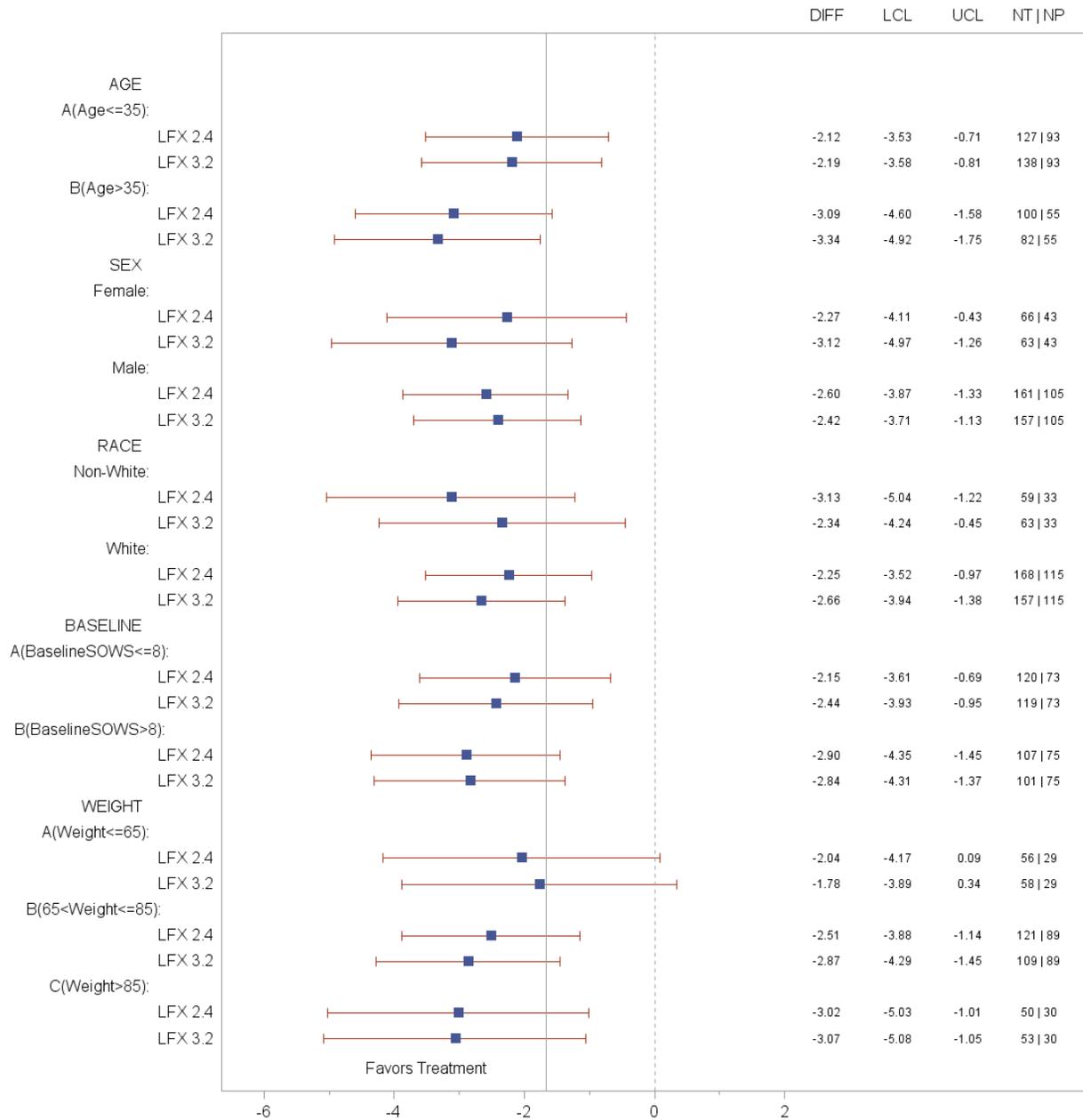
The statistical methods were based on those used in our efficacy analysis (Section 6.2.1). Missing data were imputed using multiple imputation with placebo mean on Day 2. For each subgroup, I present the least square mean difference in SOWS-Gossop scores Days 1-5 comparing each lofexidine dose group with placebo and its 95% confidence interval. Results are shown in Figure 9. The mean differences of SOWS-Gossop scores were consistent across all subgroups. There were no statistically significant interactions between treatment and the subgroup of interest. A negative mean difference favoring lofexidine was observed in all subgroups.

Subgroup analyses for our secondary endpoint of interest, completion status on Day 5, were performed by the same subgroups list above. Of those subgroups of interest, weight and sex subgroups have inconsistent trends in terms of completion status. As shown in Table 47, subjects with low body weight (≤ 65 kg) tend to have worse completion status. The proportion of completers in the lofexidine 3.2 mg group was greater than the placebo group in the heavy weight subgroup (>85 kg).

For sex subgroup, the proportion of completers tends to be greater in the male subgroup in general. However, the proportion of completers for subjects treated with lofexidine 3.2 mg/day was greater than placebo treated subjects in the female.

The clinical impact of these findings is unknown given that the study was not designed to show the treatment difference for each subgroup.

Figure 9 Subgroup Analyses for SOWS-Gossop Scores Days 1-5 (Study 3003-1)



The LS mean difference of lofexidine vs placebo with respect to SOWS-Gossop Scores Days 1-5 was analyzed using MMRM model with treatment, baseline SOWS, sex, study day, the subgroup of interest, treatment-by-subgroup and treatment-by-day interactions.

DIFF: LS mean difference

LCL: lower confidence limit

UCL: upper confidence limit

NT: number of subjects in the active treatment group

NP: number of subjects in the placebo group

Solid vertical line: overall estimated effect size.

Dashed vertical line: no effect.

Source: Statistical reviewer

Table 26 Subgroup Analyses for Completion Status on Day 5 by Weight (Study 3003-1)

Weight	Placebo		LFX 2.4		LFX 3.2	
	N	%	N	%	N	%
≤ 65 kg						
Non-completer	23	74	38	68	39	66
Completer	8	26	18	32	20	34
66 - 85 kg						
Non-completer	63	70	59	48	61	55
Completer	27	30	63	52	49	45
> 85 kg						
Non-completer	16	53	27	53	18	34
Completer	14	47	24	47	35	66

Source: Statistical reviewer

Table 27 Subgroup Analyses for Completion Status on Day 5 by Sex (Study 3003-1)

Sex	Placebo		LFX 2.4		LFX 3.2	
	N	%	N	%	N	%
Male						
Non-completer	67	63	83	51	83	53
Completer	40	37	79	49	75	47
Female						
Non-completer	35	80	41	61	35	55
Completer	9	20	26	39	29	45

Source: Statistical reviewer

8 Review of Safety

Reviewer Comment: In this section, doses are expressed in terms of lofexidine hydrochloride salt

The safety data submitted for lofexidine suggest that it causes clinically significant hypotension, bradycardia, and orthostatic hypotension in a dose-dependent fashion. A small number of subjects experienced syncope and there were frequent dose holds for meeting vital sign or symptomatic hypotension or bradycardia criteria in both dose groups, with the incidence being higher in the 3.2 mg group compared to the 2.4 mg group. Upon cessation of treatment with lofexidine, subjects were observed to experience rebound blood pressure elevations. These observed risks are consistent with the known effects of alpha-2 adrenergic agonists.

8.1 Safety Review Approach

The safety data collected in controlled studies was collected in the same population in all studies. See Table of Clinical Studies for the studies included in the safety database. Cardiovascular effects, effects by sex and effects by dose required particular attention.

8.2 Review of the Safety Database

8.2.1 Overall Exposure

The table below summarizes the exposure in the safety database. There were only 37 subjects exposed to the 2.4 mg dose and 82 subjects exposed to the 3.2 mg dose for 7 to 14 days, which provides sparse information on the safety of the product beyond 7 days of use. The database contains no data on subjects exposed for longer than 14 days. See also Adequacy of the safety database: below.

Table 28 Safety Database Exposure and Duration of Exposure

Safety Database for Lofexidine Individuals exposed to any Lofexidine dose in this development program for the indication under review N=1,276			
Clinical Trial Groups	Lofexidine 2.4 mg/day	Lofexidine 3.2 mg/day	Placebo
Controlled trials	229	465	313
All Phase 3 Studies	229	676	313
Day 1	229	676	312
Day 2	196	566	217
Day 3	148	456	152
Day 5	106	372	99
Day 7	96	258	NA
Day 10	30	58	NA
Day 14	7	24	NA

Table 29 Exposure to Lofexidine by Dose, Controlled Period of Phase 3 Studies

Category ^a	Lofexidine HCl 2.4 mg/day (N = 229)	Lofexidine HCl 3.2 mg/day (N = 390)	All Lofexidine HCl (N = 619)	Placebo (N = 313)	Lofexidine HCl 3.2 mg/day → Placebo ^b (N = 75)
Exposure to study medication (days)					
n	229	390	619	313	75
Mean (SD)	4.4 (2.45)	3.9 (2.22)	4.1 (2.31)	3.5 (2.51)	1.9 (0.34)
Median (min, max)	4.0 (1, 7)	4.0 (1, 7)	4.0 (1, 7)	2.0 (1, 15) ^c	2.0 (1, 2)
Average number of doses per day					
n	229	390	619	313	75
Mean (SD)	3.2 (0.71)	3.2 (0.81)	3.2 (0.77)	2.9 (0.84)	3.6 (0.92)
Median (min, max)	3.4 (1, 4)	3.4 (1, 4)	3.4 (1, 4)	3.0 (1, 4)	4.0 (1, 4)
Average daily dose (mg)					
n	229	390	619	313	75
Mean (SD)	1.94 (0.422)	2.54 (0.644)	2.32 (0.641)	NA	NA
Median (min, max)	2.04 (0.6, 2.4)	2.70 (0.8, 3.2)	2.40 (0.6, 3.2)	NA	NA
Cumulative dose (mg)					
n	229	390	619	313	75
Mean (SD)	9.1 (5.97)	10.9 (7.14)	10.2 (6.77)	NA	NA
Median (min, max)	7.8 (0.6, 16.8)	10.4 (0.8, 22.4)	9.6 (0.6, 22.4)	NA	NA

^a Includes data only from the dosing days when lofexidine or placebo was administered.

^b In Studies LX1-3002 and LX-3001, the study design called for 2 days of placebo treatment for all subjects following the double-blind treatment period.

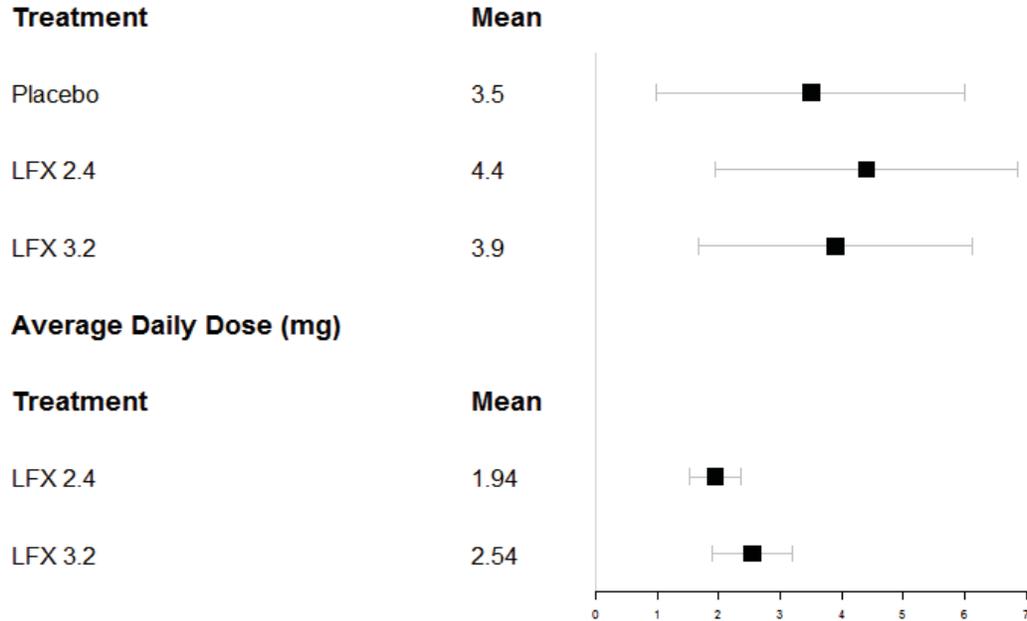
^c Subject (b) (6) had an incorrect ending dose date resulting in a calculated exposure of 15 days rather than the protocol-specified 7-day maximum.

Max = maximum; min = minimum; SD = standard deviation.

Source: Table 23 ISS

Figure 10 Exposure in Controlled Period of Phase 3 Studies

Exposure to Study Drug (days)



Source: Reviewer-generated based on Table 23, ISS

Reviewer Comment: The number of days exposed was highest in the 2.4 mg per day group and lowest in the placebo group, which is consistent with the incidence of dropout being highest in the placebo group. The mean and median average number of doses per day was the same in the 2.4 mg and 3.2 mg groups and thus subjects missed the same number of doses overall in both dose groups. The average mean and median dose for the 3.2 mg group exceeded the mean and median dose for the 2.4 mg group and was greater than 2.4 mg, which is supportive of a proportion of subjects being able to tolerate more than 2.4 mg of lofexidine per day.

8.2.2 Relevant characteristics of the safety population:

The safety population for most of the safety analyses consists of subjects enrolled in the controlled period of the Phase 3-studies. The treatment groups were balanced on sex. There was a slightly higher proportion of black subjects (24%) in the lofexidine group compared to the placebo group (20%) and there was a slightly lower proportion of subjects categorized as “other” in the lofexidine group (9%) compared to the placebo group (11%). The placebo group was older than the lofexidine group, with 51% of subjects being 35 or under compared to 55% in the lofexidine group. There were only 3 subjects (0.3% of the subjects in the population) that were 65 years old or more.

Table 30 Sex, Age, and Race in the Controlled Period of Phase 3 Studies Pooled

Characteristic	Lofexidine HCl 2.4 and 3.2 mg/day (N = 619)	Placebo (N = 313)
Sex, n (%)		
Male	451 (72.9)	233 (74.4)
Female	168 (27.1)	80 (25.6)
Age overall, years		
Number	619	313
Mean (SD)	35.7 (10.76)	37.0 (11.29)
Median (min, max)	34.0 (19, 74)	35.0 (18, 63)
Age group, n (%)		
≤ 35 years	342 (55.3)	160 (51.1)
> 35 years	277 (44.7)	153 (48.9)
Age group, n (%)		
18-49 years	544 (87.9)	254 (81.2)
50-64 years	72 (11.6)	59 (18.8)
65-74 years	3 (0.5)	0
≥ 75 years	0	0
Age group/elderly, n (%)		
< 65 years	616 (99.5)	313 (100.0)
≥ 65 years	3 (0.5)	0
Ethnicity, n (%)		
Hispanic/Latino	101 (16.3)	55 (17.6)
Not Hispanic/Latino	518 (83.7)	258 (82.4)
Race, n (%)		
American Indian or Alaska Native	2 (0.3)	2 (0.6)
Asian	4 (0.6)	1 (0.3)
Black or African American	147 (23.7)	63 (20.1)
Native Hawaiian or other Pacific Islander	2 (0.3)	3 (1.0)
White	411 (66.4)	210 (67.1)
Other	53 (8.6)	34 (10.9)

Source: Table 31 ISS

The treatment groups were balanced on body weight and BMI. In Study 3003-1, which had two dose arms of lofexidine, demographic characteristics were balanced between treatment groups with the exception of race. The 2.4 mg arm had 24% black

and 74% white subjects, the 3.2 mg arm had 22% black and 71% white subjects and the placebo arm had 17% black and 77% white subjects.

8.2.3 Adequacy of the safety database:

The safety database is adequate for the target population for use up to 7 days in duration. The two pivotal Phase 3 studies and open-label safety study that contributed the most data to the safety database were conducted in the U.S. A sufficient number of subjects were exposed to the dose being recommended in the proposed label and the demographic makeup of the population is relevant to the target population. There were only 37 subjects exposed to the 2.4 mg dose and 82 subjects exposed to the 3.2 mg dose for 7 to 14 days, which provides sparse information on the safety of the product beyond 7 days of use. A gap in the database is data on subjects exposed for longer than 14 days. It is plausible that patients with opioid addiction will undergo supervised opioid detoxification multiple times in their lifetime, which could result in a cumulative exposure of well over 14 days. Data beyond 14 days of exposure are limited to 14 subjects exposed to lofexidine in a Phase 2 study for up to 16 weeks.

Clinical setting

The Phase 3 controlled studies were conducted in an inpatient setting. Safety data collected in the outpatient setting in patients came from the seven-day open-label phase of study 3003-1 (N=83) and the in study 3003-2 (N=286), which had three inpatient study days followed by another four inpatient days and seven outpatient days or by 11 outpatient days. In the outpatient setting, subjects had daily vital signs taken before and after the first dose of the day in contrast to having vital signs taken before and after all four doses per day in the studies where there was an inpatient phase in the study design. Subjects who could not remain in the clinic after the dose were given a portable digital blood pressure machine to take the post-dose reading in the outpatient setting.

In the open-label phase of Study 3003-1, investigators decided whether subjects were to be continued as inpatients or transitioned to outpatients. Forty percent of the 83 subjects were transitioned to outpatient care. None remained inpatient due to adverse events; the reasons recorded for keeping patients inpatient were “standard of care” and “PI clinical discretion- not AE”. The mean daily dose was 1.4 mg per day. This lower dose is not unexpected given that these patients had already had a 7-day inpatient opioid-free period and were likely experiencing much less withdrawal driven by the adrenergic system and would be expected to require and tolerate less drug.

In the outpatient phase of Study 3003-2, days 8-14, there were 44 subjects that received at least one dose of lofexidine and the mean average daily dose was 1.5 mg per day.

Because subjects were initiated on lofexidine in these studies in an inpatient setting and had already had several days of therapy, the outpatient experience in these studies is not fully generalizable to patients who are started on lofexidine in the outpatient setting.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1 Issues Regarding Data Integrity and Submission Quality

The application had the following data integrity and quality issues:

- [REDACTED] (b) (4) by the Applicant and the review team because the Contract Research Organization identified data quality issues during routine monitoring of the ongoing study. The Applicant concluded that the [REDACTED] (b) (4) [REDACTED] I concur with this assessment.
- The Office of Computational Science conducted a data fitness assessment and identified missing data values in the datasets as well as missing fields in the datasets that limited the ability of the review team to conduct analyses on the data with the available review tools. The review team issued information requests and the Applicant responded to the extent possible. [REDACTED] (b) (4) [REDACTED]

The Office of Scientific Investigation inspected four clinical sites and the Applicant in support of the NDA. The conclusion from the inspections is that the studies appear to have been conducted adequately and the data appear acceptable to be used to support the application. See Dr. Green's review for further details.

8.3.2 Categorization of Adverse Events

The Applicant's definitions of treatment-emergent adverse events and serious adverse events are acceptable. For the purposes of pooling, the Applicant coded adverse events using Medical Dictionary for Regulatory Activities version 18.0.

8.3.3 Routine Clinical Tests

Clinical laboratory tests

The following table from the Integrated Summary of Safety (ISS) summarizes the timing of laboratory assessments

Table 31 Laboratory Assessments

Study USWM-	Type of Study	Assessments	Timing of Assessments
<i>Phase 3 Studies</i>			
LX1-3003-1	Pivotal placebo-controlled efficacy and safety phase followed by open-label phase	Chemistry, hematology, urinalysis	Screening, end of double-blind dosing/before open-label dosing, end of study
LX1-3002	Pivotal placebo-controlled efficacy and safety	Chemistry, hematology, urinalysis	Screening, as clinically indicated during study, end of study
LX1-3001	Supportive placebo-controlled (b) (4) safety	Chemistry, hematology, urinalysis	Baseline (predose on Day 1), end of study
LX1-3003-2	Open-label safety, no placebo control	Chemistry, hematology, urinalysis	Screening, as clinically indicated during study, end of study
<i>Clinical Pharmacology Studies in Opioid-Dependent Subjects</i>			
LX1-1005-1	ECG, safety, PK with methadone coadministration, no placebo control (pilot)	Chemistry, hematology, urinalysis	Screening, check-in, 7-day follow-up
LX1-1005-2	S ECG, safety, PK with methadone coadministration, placebo control	Chemistry, hematology, urinalysis	Screening; check-in; at methadone re-titration and discharge; and 7-day follow-up
LX1-1006	ECG, safety, PK with buprenorphine coadministration, placebo control	Chemistry, hematology, urinalysis	Screening, check-in, discharge, 7-day follow-up
LX1-1013	Metabolite exposure with buprenorphine coadministration, no placebo control	Chemistry, hematology, urinalysis	Screening and as clinically indicated
<i>Clinical Pharmacology Studies in Healthy Subjects</i>			
LX0-1001	Pilot IV dose-ranging	Chemistry, hematology, urinalysis	Screening only
LX1-1001	PK, BA	Not done	NA
LX1-1002	Ascending single- and multiple-dose PK	Chemistry, hematology, urinalysis	Screening, day before dosing in each study period, end of study
LX1-1003	Mass balance, ADME, BA	Chemistry, hematology, urinalysis	Screening, predose, end of study
LX1-1003-1	Mass balance	Chemistry, hematology, urinalysis	Screening, predose, end of study
LX1-1004	Food effect	Chemistry, hematology, urinalysis	Screening, end of study
LX1-1009	Naltrexone DDI	Chemistry, hematology, urinalysis	Screening, Day -1 (if clinically indicated), end of study
LX1-1010	Paroxetine DDI (CYP2D6 inhibitor)	Chemistry, hematology, urinalysis	Screening, Day -1, Day 2, Day 12, Day 14, end of study

Study USWM-	Type of Study	Assessments	Timing of Assessments
<i>Clinical Pharmacology Studies in Healthy Subjects (continued)</i>			
LX1-1011	Pilot QTc	Chemistry, hematology, urinalysis	Screening, check-in for each study period, 22 hours postdose (Study Period 1), end of study
<i>Clinical Pharmacology Studies in Special Populations</i>			
LX1-1007	Hepatic impairment	Chemistry, hematology, urinalysis	Screening, check-in and 24 hours post lofexidine dosing on Day 1 (chemistry only); end of study
LX1-1008	Renal impairment Reduced design	Chemistry, hematology, urinalysis	Screening, check-in and 24 hours post lofexidine dosing on Day 1 (hematology/chemistry); end of study
LX1-1012	Renal impairment Full design	Chemistry, hematology, urinalysis	Screening, check-in and 24 hours post lofexidine dosing on Day 1 (hematology/chemistry); end of study
<i>Phase 2 Studies</i>			
LX1-2001	3-part, open-label safety (prior sponsor), no placebo control	Chemistry, hematology, urinalysis	Morphine stabilization phase (Days 1 and 8), Day 7 of lofexidine treatment, end of study (in Pilot 2)
LX1-2002	Efficacy of lofexidine and clonidine in naloxone-precipitated withdrawal (investigator-initiated), placebo control at lowest dose	Not done	NA
LX1-2003	Hemodynamic and cognitive effects of coadministration with methadone (investigator-initiated), placebo control for lowest dose	Not done	NA
LX1-2004	Safety and preliminary efficacy post withdrawal with naltrexone (investigator-initiated), placebo control	Chemistry ^a	Screening, monthly during study

ADME = absorption, distribution, metabolism, and excretion; CYP = cytochrome P450; BA = bioavailability; DDI = drug-drug interaction; ECG = electrocardiogram; IV = intravenous(ly); NA = not applicable; PK = pharmacokinetic(s); QTc = heart rate-corrected QT interval

^a Collection of laboratory data is not specified in the study documentation; however, results for elevated liver function tests were reported for 2 subjects. This information is captured in the results section.

Source: Table 5 ISS

There were no signals from the preclinical work or from prior experience with lofexidine that warranted additional laboratory testing beyond the routine testing that the Applicant conducted. The clinical studies were all of short duration and testing at baseline and end-of-study or end of double-blind period was therefore adequate.

8.4 Safety Results

8.4.1 Deaths

There were three deaths in the program. Two deaths occurred before study drug administration. The other death was a 34-year old female who died of an overdose of heroin, cocaine and fentanyl 3 days after completing 7 days of lofexidine 3.2 mg in study 3003-1.

Reviewer Comment: The death is likely a consequence of opioid addiction and unrelated to lofexidine. It does however underscore the importance of continued treatment following detoxification from opioids to avoid relapse.

8.4.2 Serious Adverse Events

The following tables summarize serious adverse events by System Organ Class and Preferred Term.

Table 32 Treatment-emergent SAEs in Controlled Trials (Studies 3001, 3002, and 3003-1)

MedDRA System Organ Class Preferred Term	LFX 2.4 (N=229)		LFX 3.2 (N=390)		ALL LFX (N=619)		Placebo (N=313)	
	No. of Subjects n (%)	No. of Events	No. of Subjects n (%)	No. of Events	No. of Subjects n (%)	No. of Events	No. of Subjects n (%)	No. of Events
Any Serious Treatment Emergent Adverse Event	0	0	14 (3.6)	18	14 (2.3)	18	10 (3.2)	11
Vascular disorders	0	0	6 (1.5)	6	6 (1.0)	6	2 (0.6)	2
Syncope	0	0	3 (0.8)	3	3 (0.5)	3	0	0
Hypotension	0	0	2 (0.5)	2	2 (0.3)	2	1 (0.3)	1
Orthostatic hypotension	0	0	1 (0.3)	1	1 (0.2)	1	0	0
Hypertension	0	0	0	0	0	0	1 (0.3)	1
General disorders and administration site conditions	0	0	5 (1.3)	5	5 (0.8)	5	4 (1.3)	4
Drug withdrawal syndrome	0	0	4 (1.0)	4	4 (0.6)	4	4 (1.3)	4
Chest pain	0	0	1 (0.3)	1	1 (0.2)	1	0	0
Cardiac disorders	0	0	4 (1.0)	4	4 (0.6)	4	1 (0.3)	1
Bradycardia	0	0	3 (0.8)	3	3 (0.5)	3	0	0
Myocardial infarction	0	0	1 (0.3)	1	1 (0.2)	1	0	0
Atrioventricular block second degree	0	0	0	0	0	0	1 (0.3)	1
Injury, poisoning and procedural complications	0	0	2 (0.5)	2	2 (0.3)	2	0	0
Overdose	0	0	1 (0.3)	1	1 (0.2)	1	0	0
Toxicity to various agents	0	0	1 (0.3)	1	1 (0.2)	1	0	0
Psychiatric disorders	0	0	1 (0.3)	1	1 (0.2)	1	1 (0.3)	1
Suicidal ideation	0	0	1 (0.3)	1	1 (0.2)	1	0	0
Withdrawal syndrome	0	0	0	0	0	0	1 (0.3)	1
Gastrointestinal disorders	0	0	0	0	0	0	1 (0.3)	1
Diarrhoea	0	0	0	0	0	0	1 (0.3)	1
Infections and infestations	0	0	0	0	0	0	1 (0.3)	1
Acute hepatitis C	0	0	0	0	0	0	1 (0.3)	1
Investigations	0	0	0	0	0	0	1 (0.3)	1
Electrocardiogram QT prolonged	0	0	0	0	0	0	1 (0.3)	1

Source: ISS, Table 3.13.1

Reviewer Comment: There were no treatment-emergent SAEs in the lofexidine 2.4 mg group compared to 3.6% of subjects in the lofexidine 3.2 mg group and 3.2% of subjects in the placebo group. Syncope, hypotension, and bradycardia occurred more frequently in the lofexidine 3.2 mg group than the other groups. There was also a myocardial infarction, an overdose and a toxicity to various agents SAE in the lofexidine 3.2 mg group. The three subjects who had syncope had a range of timing for the syncope. One subject had it after one dose, one subject had it in the morning following one full day of dosing and one subject had it after four days of intermittent dosing due to doses being held for bradycardia. The hypotension and bradycardia events classified as serious were all from Study 3002 and were deemed serious due to hospitalization for stabilization of vital signs.

The myocardial infarction (MI) occurred in a patient with a 30 pack-year history of cigarette use around 8.5 hours after the last dose of lofexidine and symptoms began an hour after smoking

crack and using IV heroin. Cocaine use could have been a causal factor in the MI. The overdose SAE was a heroin overdose and occurred 24 days after the last dose of study drug. The toxicity to various agents SAE was discussed in the section on deaths above.

Two SAEs occurred in the open-label safety study 3003-2. One was a cerebrovascular accident and one was a manic episode with psychosis. The patient who had a cerebrovascular accident (CVA) had a history of MI, hypertension, hyperlipidemia, TIA and smoked cigarettes. He had a left MCA CVA on day 7 of the study and had received lofexidine that morning. A thrombus was detected in the left ventricle on echocardiogram. He had been taking lisinopril and atorvastatin and he continued to take these during the study. His blood pressure and pulse over the study had decreased slightly overall. None of the orthostatic pulses met abnormal criteria but 40% of the diastolic orthostatic blood pressures had a change of 10 or more mmHg and 36% of the systolic orthostatic blood pressures had a change of 20 or more mmHg, which met criteria for being abnormal.

Reviewer Comment: Based on its effects on the cardiovascular system, lofexidine use cannot be ruled out as a contributing factor to the onset of the CVA in this patient with many comorbidities and risk factors for CVA.

The narrative for the manic episode notes a past history of depressive and manic episodes preceding entry into the study. The narrative also states that the manic episode that occurred during the study began with complaints of insomnia.

8.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

The following table summarizes the discontinuation and dose hold criteria for the Phase 3 studies:

Table 33 Discontinuation and Dose Hold Criteria, Phase 3 Studies

	3001	3002	3003-1
Discontinue Medication	Clinically significant abnormal ECG, persistent symptomatic hypotension, single occurrence of symptomatic bradycardia, persistent hypertension, medical intervention for cardiac event	3001 criteria and More than two doses held in a day or four doses held in study	3001 criteria and Subject misses more than 2 doses in 24 hours Subject misses more than a total of 6 doses Systolic blood pressure <70 mmHg and >20% below screen value; Diastolic blood pressure <40 mmHg and >20% below screen value; Heart rate <40 bpm and >20% below screen value; QTcF >500 msec1 or >25% above screen value for both males and females; Syncope;
Dose Hold	Investigator discretion for symptomatic hypotension or orthostatic SBP 80 mmHg or less	Investigator discretion for orthostatic SBP 90 mmHg or less	Resting SBP < 90 mmHg and > 20% below screening value, resting DBP < 50 mmHg and >20% below screening value, HR <50 bpm and >20% below screening value, symptoms of hypotension or bradycardia, SBP, DBP, or pulse >25% below resting values

Source: Study protocols for 3001, 3002, and 3003-1 and Table 10 ISS

The following table summarizes the discontinuations due to TEAEs in the controlled period of the Phase 3 studies overall by treatment group and those that occurred in at least 1% of one of the treatment groups:

Table 34 Discontinuations Due to TEAEs in $\geq 1\%$ of Lofexidine-treated Subjects in Phase 3 Controlled Studies

MedDRA PT	LFX 2.4 N= 229		LFX 3.2 N=390		Placebo N=313	
	n subjects (%)	n events	n subjects (%)	n events	n subjects (%)	n events
Any TEAE	45 (20%)	65	71 (18%)	115	61 (19%)	154
Hypotension	3 (1%)	3	10 (3%)	11	0	0
Bradycardia	0	0	13 (3%)	13	1 (<1%)	1
Dizziness	8 (3%)	10	7 (2%)	8	1 (<1%)	1
Insomnia	7 (3%)	7	7 (2%)	7	7 (2%)	7
Diarrhea	5 (2%)	5	6 (2%)	6	13 (4%)	13
Orthostatic hypotension	3 (1%)	3	7 (2%)	7	1 (<1%)	1
Pain	3 (1%)	3	6 (2%)	7	10 (3%)	10
Anxiety	4 (2%)	4	3 (1%)	3	10 (3%)	10
Myalgia	5 (2%)	5	3 (1%)	3	4 (1%)	4
Withdrawal Syndrome	2 (1%)	2	3 (1%)	3	5 (2%)	5
Drug Withdrawal Syndrome	2 (1%)	2	4 (1%)	4	4 (1%)	4
Syncope	1 (<1%)	1	4 (1%)	4	0	0
Somnolence	1 (<1%)	1	4 (1%)	4	1 (<1%)	1
Restlessness	1 (<1%)	1	4 (1%)	4	6 (2%)	6
Nausea	5 (2%)	5	1 (<1%)	1	12 (4%)	12
Vomiting	4 (2%)	4	2 (<1%)	2	14 (4%)	14

Source: Table 3.11.1 ISS

The incidence of discontinuations was higher in lofexidine-treated subjects than placebo-treated subjects for hypotension, orthostatic hypotension, bradycardia, dizziness, syncope, and somnolence. There were 13 subjects in the 3.2 mg group (3%) compared to no subjects in the 2.4 mg group that discontinued due to bradycardia. There also appears to be a dose-response relationship for hypotension, orthostatic hypotension, syncope and somnolence between the 3.2 mg and 2.4 mg groups, but not for dizziness. The incidence of discontinuations was higher in placebo-treated subjects for diarrhea, nausea, and vomiting, which are gastrointestinal system-related manifestations of opioid withdrawal. Gastrointestinal system-related discontinuations were also higher in the 2.4 mg group compared to the 3.2 mg group. The incidence of restlessness and pain, which are also adverse events that may be withdrawal-related, was higher in the placebo group.

Reviewer Comment: Of note, diarrhea, nausea, and vomiting, are symptoms of opioid withdrawal that were dropped from the SOWS-Gossop over the development process, and thus were not measured in the primary efficacy outcome instrument, but appear to have caused

discontinuation in a higher proportion of placebo patients, likely because they were having worse opioid withdrawal than the lofexidine patients, which supports the findings of a treatment benefit on the SOWS-Gossop.

The following table summarizes the discontinuations due to AEs in Study 3003-1. This is the only study that had a 2.4 mg and 3.2 mg arm.:

Table 35 Discontinuations Due to AE Study 3003-1

Table 55: Treatment-Emergent Adverse Events That Led to Discontinuation in $\geq 1\%$ of Subjects By Dose

MedDRA Preferred Term	Lofexidine HCl 2.4 mg/day	Lofexidine HCl 3.2 mg/day
Bradycardia	0%	4.5%
Hypotension	1.3%	3.2%
Orthostatic hypotension	1.3%	2.7%
Insomnia	2.2%	3.2%
Somnolence	0.4%	1.8%
Syncope	0.4%	1.4%
Myalgia	2.2%	0.5%
Nausea	2.2%	0.5%
Pain	1.3%	2.3%

MedDRA = Medical Dictionary for Regulatory Activities.

Source: USWM-LX1-3003-1 CSR, Table 41

Source: Table 55 Integrated Summary of Safety

The discontinuations due to adverse events in other studies in the program revealed no new signals or safety concerns. One subject discontinued due to postural hypotension in study 1005-2. In Study 3003-2, an open-label safety study, the majority of discontinuations occurred during days 1-3 and followed a similar pattern to the discontinuations in the controlled Phase 3 studies. One subject discontinued in the outpatient period for syncope, fall, and contusion during the extension of dosing beyond 7 days, on day 11 of dosing.

8.4.4 Significant Adverse Events

TEAEs Leading to Dose Hold

The criteria for holding a dose of lofexidine is summarized in

Table 33 Discontinuation and Dose Hold Criteria, Phase 3 Studies.

There were two AEs that resulted in a dose-hold in study 3001, fifty AEs that resulted in a dose-hold for study 3002 and 255 that resulted in a dose-hold in study 3003-1. The following summarizes the number of doses held by treatment arm and preferred term:

Table 36 TEAEs Leading to Dose Hold, Pooled Phase 3 Controlled Studies

Preferred Term	LFX 2.4 N= 229 n events	LFX 3.2 N=390 n events	Placebo N=313 n events
Hypotension	37	67	1
Orthostatic hypotension	25	52	1
Bradycardia	18	34	2
Dizziness	17	28	0
Fatigue	0	4	0
Hypertension	0	3	0
Fall	0	2	0
Headache	0	2	0
Sedation	0	2	0
Abdominal discomfort	0	1	0
Asthenia	0	1	0
Blood pressure orthostatic abnormal	0	1	0
Constipation	0	1	0
Heart rate abnormal	0	1	0
Sinus bradycardia	0	1	0
Tachycardia	0	1	0
Diarrhoea	0	0	1
Dizziness postural	2	0	0
Somnolence	1	0	0
Syncope	1	0	0

Source: Reviewer-generated from ADAE ISS dataset

The following table summarizes the incidence of a dose being held by preferred term where a subject is only counted once for each preferred term:

Table 37 TEAEs with Incidence > 1% Leading to Dose Hold, Pooled Controlled Phase 3 Studies

Preferred Term	LFX 2.4 N= 229 %	LFX 3.2 N=390 %	Placebo N=313 %
Hypotension	10%	12%	0%
Orthostatic hypotension	9%	8%	0%
Bradycardia	7%	7%	1%
Dizziness	6%	6%	0%

Source: Reviewer-generated from ADAE ISS dataset

The most common reason for a dose being held was hypotension followed by bradycardia and dizziness, and there was a similar incidence of subjects having doses held for hypotension, bradycardia and dizziness in the 2.4 mg and 3.2 mg lofexidine-treated groups.

In Study 3003-1, incidence of subjects that had had doses held by reason for the dose being held are summarized as follows.

Table 38 Study 3003-1 Dose-holds

		Lofexidine 2.4 mg % N=229	Lofexidine 3.2 mg % N=222	Placebo % N=151
	Dose withheld	35	44	7
	Subject refusal	6	5	4
	TEAE	<1	3	0
Protocol- specified	SBP ¹	9	9	0
	HR ²	4	12	2
	Symptomatic hypotension or bradycardia ³	9	13	0
	Orthostasis ⁴	8	14	0

1 recumbent SBP <90 mmHg and >20% below screen value

2 <50 bpm and >20% below screen value

3 lightheadedness, dizziness, syncope

4 >25% below recumbent values

Source: 3003-1 Clinical Study Report Table 31

There was a higher incidence of subjects that had doses held in the 3.2 mg group than the 2.4 mg group, which was driven by the heart rate, symptomatic hypotension or bradycardia and orthostasis criteria.

Severe TEAEs

The following table summarizes the incidence of severe TEAEs in the controlled periods of the Phase 3 studies:

Table 39 Severe TEAEs in Controlled Phase 3 Studies

MedDRA Preferred Term^a	Lofexidine HCl 2.4 and 3.2 mg/day (N = 619) n (%)	Placebo (N = 313) n (%)
Subjects with severe TEAEs	58 (9.4)	52 (16.6)
Insomnia	6 (1.0)	4 (1.3)
Anxiety	9 (1.5)	11 (3.5)
Dizziness	9 (1.5)	0
Vomiting	4 (0.6)	9 (2.9)
Diarrhea	6 (1.0)	2 (0.6)
Nausea	5 (0.8)	4 (1.3)
Abdominal pain	4 (0.6)	4 (1.3)
Drug withdrawal syndrome	4 (0.6)	3 (1.0)
Back pain	1 (0.2)	4 (1.3)
Rhinorrhea	3 (0.5)	6 (1.9)
Abdominal discomfort	2 (0.3)	3 (1.0)
Decreased appetite	2 (0.3)	4 (1.3)
Myalgia	2 (0.3)	3 (1.0)
Pain	2 (0.3)	3 (1.0)
Restlessness	1 (0.2)	3 (1.0)
Feeling of body temperature change	1 (0.2)	3 (1.0)
Arthralgia	0	3 (1.0)

MedDRA = Medical Dictionary of Regulatory Activities; TEAEs = treatment-emergent adverse events.

^a Preferred terms are listed in decreasing order of frequency in the lofexidine HCl group.

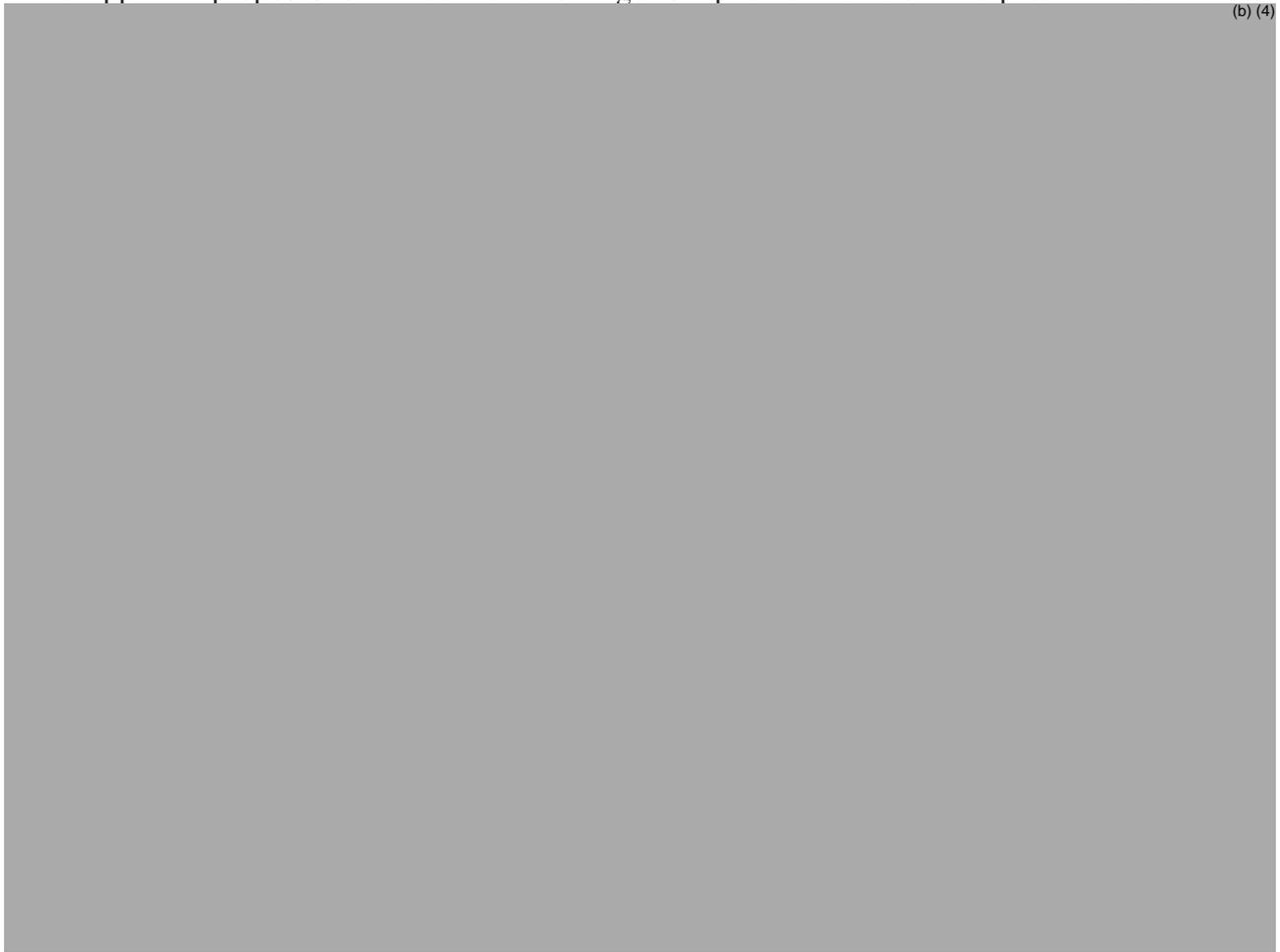
Source: Table 44 ISS

There was a higher incidence of severe TEAEs in the placebo group than the lofexidine group and this is likely a result of symptoms of opioid withdrawal being reported as adverse events and being worse in the placebo group because lofexidine was having a beneficial effect on opioid withdrawal symptoms. The severe TEAEs that had a higher incidence in the lofexidine group were dizziness and diarrhea. The incidence of severe dizziness was higher in the 3.2 mg group compared to the 2.4 mg group (1.8% and 0.9% respectively) and two of the seven subjects in the 3.2 mg group had two severe dizziness TEAEs compared to none in the 2.4 mg group. All the severe diarrhea TEAEs were in the 3.2 mg group (1.5% of subjects).

8.4.5 Treatment Emergent Adverse Events and Adverse Reactions

The Applicant proposes to include the following description of TEAEs in the product label:

(b) (4)



The 2.16 mg and 2.88 mg groups are reported as the 2.4 mg and 3.2 mg groups throughout this review and throughout the rest of the application. Separated by lofexidine dose, the incidence is summarized below:

Table 40 TEAEs Controlled Period Phase 3 Studies

Preferred Term	Lofexidine 2.4 mg N=229 (%)	Lofexidine 3.2 mg N=390 (%)	Placebo N=313 (%)
Insomnia	54	45	37
Hypotension	30	27	1
Orthostatic hypotension	29	25	3
Dizziness	19	23	5
Bradycardia	24	22	4
Somnolence	11	14	5
Dry mouth	10	11	1
Sedation	13	10	3
Constipation	6	6	2
Abdominal discomfort	4	6	4

Source: Reviewer-generated from ISS ADAE dataset

From the pooled data, it appears that the 2.4 mg group had a higher incidence of hypotension, orthostatic hypotension and bradycardia. However, in study 3003-1, the only Phase 3 study that had both the 2.4 mg and 3.2 mg groups, the 3.2 mg group had a higher incidence than the 2.4 mg group for orthostatic hypotension (risk difference of 13%) and bradycardia (risk difference of 8%). The incidence of hypotension in study 3003-1 was equal between the two lofexidine doses. Pooling of the data obscures the clear dose-effects that are illustrated in the table below.

Table 41 Study 3003-1 TEAEs Occurring in $\geq 10\%$ of Subjects in Lofexidine Groups and Higher Incidence in Lofexidine Groups than Placebo

Preferred Term	Lofexidine 2.4 mg (%) N=229	Lofexidine 3.2 mg (%) N=222	Placebo (%) N=151
Insomnia	51	55	48
Orthostatic Hypotension	29	42	5
Bradycardia	24	32	5
Hypotension	30	30	1
Dizziness	19	23	3
Somnolence	11	13	5
Sedation	13	12	5
Dry Mouth	10	10	0

Source: Table 34 3003-1 CSR

The incidence of orthostatic hypotension and bradycardia was higher in the completers compared to the non-completers. The differences between incidence in the 2.4 mg and 3.2 mg groups in bradycardia but not orthostatic hypotension were driven more by non-completers than completers, and this is consistent with there being no subjects in the 2.4 mg group who discontinued due to bradycardia compared with 5% that discontinued in study 3003-1 in the 3.2

mg group due to bradycardia.

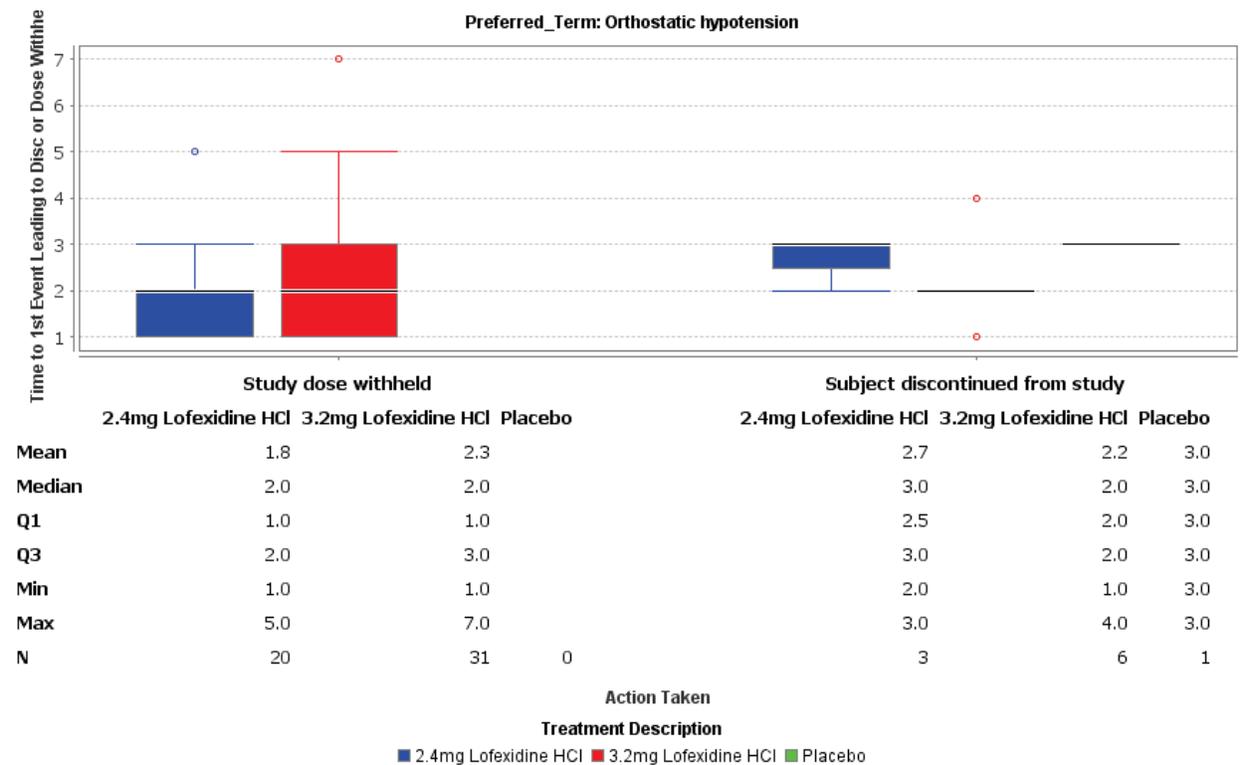
Table 42 Orthostatic Hypotension and Bradycardia in Study 3003-1

Preferred Term	Completers		Non-completers	
	lofexidine 2.4 mg (%) N=91	Lofexidine 3.2 mg (%) N=86	lofexidine 2.4 mg (%) N=138	Lofexidine 3.2 mg (%) N=136
Orthostatic Hypotension	37	50	24	38
Bradycardia	31	36	19	29

Source: Reviewer-generated from ISS AE and ISE SL datasets

The time-to-event for orthostatic hypotension and bradycardia was similar for the 2.4 mg and 3.2 mg groups and the mean and median for both groups was on the second day of the treatment period. The time to having a dose withheld for orthostatic hypotension was on average two days for both dose groups but the average time to having a discontinuation due to orthostatic hypotension was longer for the 2.4 mg group (around 3 days) compared to the 3.2 mg group, as shown in the figure below:

Figure 11 Time to orthostatic hypotension dose hold and discontinuations Study 3003-1

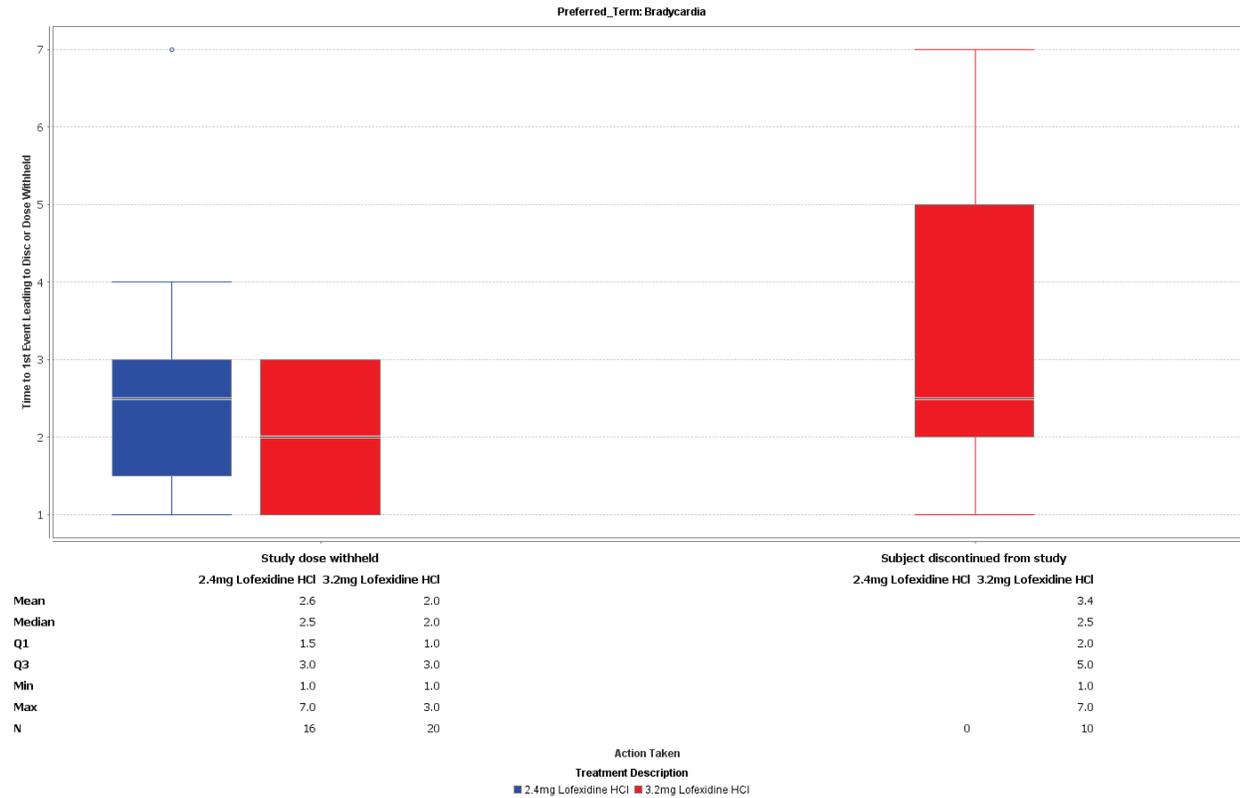


Source: Reviewer generated from study 3003-1 AE dataset

For bradycardia, the mean time to a dose hold was longer for the 2.4 mg group (2.6 days) compared to the 3.2 mg group (2.0 days). The mean time to discontinuation in the 3.2 mg group

for bradycardia was 3.4 days and the median was 2.5 days.

Figure 12 Time to bradycardia dose hold and discontinuations Study 3003-1



Source: Reviewer-generated from study 3003-1 AE dataset

Reviewer Comment: The risk of having dose holds and discontinuations due to orthostatic hypotension and the risk of having dose holds due to bradycardia was concentrated in the first three days of treatment in both groups, while the risk of having a discontinuation in the 3.2 mg group due to bradycardia was more persistent beyond the first three days of treatment.

In addition to the AEs identified as having higher incidence in the larger controlled safety pool, tinnitus, while having an incidence of <5% of subjects, appears to be drug-related based on being observed in 3% of subjects in the 3.2 mg group, 1% of subjects in the 2.4 mg group and <1% in the placebo group with a relative risk between 3.2 mg and placebo of 8. Sixty-two percent of subjects that had tinnitus also had dizziness, 38% had hypotension, 38% had orthostatic hypotension, and 23% had bradycardia. I recommend that tinnitus be included in the description of adverse reactions in the product label.

Syncope occurred in 7 subjects in the lofexidine groups and no subjects in the placebo group in the Phase 3 controlled studies. An additional subject had an episode of presyncope. In open-label study 3003-2 one subject had presyncope and one subject had syncope.

Table 43 TEAEs of Syncope or Presyncope

Preferred Term	lofexidine 2.4 mg n(%) N=229	Lofexidine 3.2 mg n(%) N=390	Placebo n(%) N=151
Syncope	2 (0.9%)	5 (1.3%)	0
Presyncope	0	1 (0.3%)	0

Source: Table 49 ISS

8.4.6 Laboratory Findings

Hematology

There was a higher incidence in shifts to prolonged prothrombin times in lofexidine-treated subjects (9%) than placebo-treated subjects (5%) in the pooled Phase 3 study data as shown below:

Table 44 Prothrombin Time Shifts in Phase 3 Studies Pooled

Parameter/ Baseline	Lofexidine HCl Lofexidine HCl 2.4 and 3.2 mg/day				Placebo			
	Maximum Post-baseline Value				Maximum Post-baseline Value			
	Normal n (%)	1× - < 3× ULN n (%)	3× - < 5× ULN n (%)	5× - < 10× ULN n (%)	Normal n (%)	1× - < 3× ULN n (%)	3× - < 5× ULN n (%)	5× - < 10× ULN n (%)
PT, sec								
Normal	277 (82.7)	31 (9.3)	0	0	120 (86.3)	7 (5.0)	0	0
1× - < 3× ULN	12 (3.6)	15 (4.5)	0	0	7 (5.0)	5 (3.6)	0	0
3× - < 5× ULN	0	0	0	0	0	0	0	0
5× - < 10× ULN	0	0	0	0	0	0	0	0

PT = prothrombin time; ULN = upper limit of normal

Source: Table 63 ISS

Prothrombin time is a measure of extrinsic pathway of coagulation. Among other causes, increases in prothrombin time can be a result of poor clotting factor synthesis by the liver and deficiency or presence of an inhibitor to clotting factors.

There were no other clinically notable hematology findings.

Chemistry

Liver Tests

(b) (4) the tables below summarize pooled data from studies 3002 and 3003-1 and individual

(b) (4)

study results from studies 3002 and 3003-1 (b) (4)

In study 3003-1, there was a higher incidence of elevated post-baseline ALT and AST in the lofexidine-treated subjects than placebo-treated subjects, but this trend was not observed in study 3002. There were very few elevated ALP and total bilirubin values (the only elevated total bilirubin was in the placebo group) in both studies and no differences between groups. There was a high rate of early termination in these studies and in spite of the plan to collect early termination labs, only about half to two-thirds of the subjects had post-baseline lab results in the placebo groups and about two-thirds to three-quarters of subjects had post-baseline lab results in the lofexidine groups.

Table 45 Study 3003-1 Highest Post-Baseline Liver Laboratory Values per Subject

Liver Lab Test	Lofexidine HCl 2.4 mg N = 229			Lofexidine HCl 3.2mg N = 222			Placebo N = 151			Placebo -> Lofexidine HCl ^a N = 19		
	Event Count	Subject Count	n/N (% of Subjects)	Event Count	Subject Count	n/N (% of Subjects)	Event Count	Subject Count	n/N (% of Subjects)	Event Count	Subject Count	n/N (% of Subjects)
ALT ≥ ULN												
2x ULN	9	9	9 / 145 (6.2)	5	5	5 / 156 (3.2)	1	1	1 / 74 (1.4)	0	0	0 / 13
3x ULN	6	6	6 / 145 (4.1)	5	5	5 / 156 (3.2)	1	1	1 / 74 (1.4)	0	0	0 / 13
5x ULN	1	1	1 / 145 (0.7)	2	2	2 / 156 (1.3)	0	0	0 / 74	0	0	0 / 13
10x ULN	0	0	0 / 145	1	1	1 / 156 (0.6)	0	0	0 / 74	0	0	0 / 13
20x ULN	0	0	0 / 145	0	0	0 / 156	1	1	1 / 74 (1.4)	0	0	0 / 13
AST ≥ ULN												
2x ULN	1	1	1 / 144 (0.7)	3	3	3 / 156 (1.9)	1	1	1 / 74 (1.4)	0	0	0 / 13
3x ULN	1	1	1 / 144 (0.7)	4	4	4 / 156 (2.6)	0	0	0 / 74	0	0	0 / 13
5x ULN	1	1	1 / 144 (0.7)	1	1	1 / 156 (0.6)	0	0	0 / 74	0	0	0 / 13
10x ULN	0	0	0 / 144	0	0	0 / 156	0	0	0 / 74	0	0	0 / 13
20x ULN	0	0	0 / 144	0	0	0 / 156	1	1	1 / 74 (1.4)	0	0	0 / 13

Source: Table 8 12/7/17 Response to IR

Table 46 Studies 3002 and 3003-1 Highest Post-Baseline Liver Laboratory Values per Subject

Liver Lab Test	Lofexidine HCl 2.4 mg N = 229			Lofexidine HCl 3.2mg N = 356			Placebo N = 280			Placebo -> Lofexidine HCl ^a N = 19		
	Event Count	Subject Count	n/N (% of Subjects)	Event Count	Subject Count	n/N (% of Subjects)	Event Count	Subject Count	n/N (% of Subjects)	Event Count	Subject Count	n/N (% of Subjects)
ALT ≥ ULN												
2x ULN	9	9	9 / 145 (6.2)	8	8	8 / 260 (3.1)	5	5	5 / 159 (3.1)	0	0	0 / 13
3x ULN	6	6	6 / 145 (4.1)	7	7	7 / 260 (2.7)	3	3	3 / 159 (1.9)	0	0	0 / 13
5x ULN	1	1	1 / 145 (0.7)	3	3	3 / 260 (1.2)	0	0	0 / 159	0	0	0 / 13
10x ULN	0	0	0 / 145	1	1	1 / 260 (0.4)	0	0	0 / 159	0	0	0 / 13
20x ULN	0	0	0 / 145	0	0	0 / 260	1	1	1 / 159 (0.6)	0	0	0 / 13
AST ≥ ULN												
2x ULN	1	1	1 / 144 (0.7)	7	7	7 / 260 (2.7)	4	4	4 / 159 (2.5)	0	0	0 / 13
3x ULN	1	1	1 / 144 (0.7)	4	4	4 / 260 (1.5)	1	1	1 / 159 (0.6)	0	0	0 / 13
5x ULN	1	1	1 / 144 (0.7)	3	3	3 / 260 (1.2)	0	0	0 / 159	0	0	0 / 13
10x ULN	0	0	0 / 144	0	0	0 / 260	0	0	0 / 159	0	0	0 / 13
20x ULN	0	0	0 / 144	0	0	0 / 260	1	1	1 / 159 (0.6)	0	0	0 / 13

Source: Table 12 12/7/17 Response to IR

Table 47 Study 3002 Highest Post-Baseline Liver Laboratory Values per Subject

Liver Lab Test	Lofexidine HCl 3.2mg N = 134			Placebo N = 129		
	Event Count	Subject Count	n/N (% of Subjects)	Event Count	Subject Count	n/N (% of Subjects)
ALT ≥ ULN						
2x ULN	3	3	3 / 104 (2.9)	4	4	4 / 85 (4.7)
3x ULN	2	2	2 / 104 (1.9)	2	2	2 / 85 (2.4)
5x ULN	1	1	1 / 104 (1.0)	0	0	0 / 85
10x ULN	0	0	0 / 104	0	0	0 / 85
20x ULN	0	0	0 / 104	0	0	0 / 85
AST ≥ ULN						
2x ULN	4	4	4 / 104 (3.9)	3	3	3 / 85 (3.5)
3x ULN	0	0	0 / 104	1	1	1 / 85 (1.2)
5x ULN	2	2	2 / 104 (1.9)	0	0	0 / 85
10x ULN	0	0	0 / 104	0	0	0 / 85
20x ULN	0	0	0 / 104	0	0	0 / 85

Source: Table 10 12/7/17 Response to IR

There was a slightly higher incidence of lofexidine-treated subjects that received 3.2 mg than lofexidine-treated subjects that received 2.4 mg and placebo-treated subjects who had a treatment-emergent LFT (ALT, AST or GGT) result that exceeded five times the upper limit of normal or was reported as a treatment-emergent adverse event as shown in the table below:

Table 48 LFTs >5x ULN or LFT TEAE Phase 3 Controlled Studies Pooled

	Lofexidine 2.4 mg N=229 n(%)	Lofexidine 3.2 mg N=390 n(%)	Placebo N=313 n(%)
LFT > 5x ULN or TEAE	2 (1%)	7 (2%)	4 (1%)
Hepatitis screening results negative	1	2	1

Source: Table 68 ISS

There were also four subjects who had a TEAE or a result greater than five times the upper limit of normal in open-label study 3003-2 and one was negative for hepatitis serologies.

There were no cases in lofexidine-treated subjects that met the criteria for drug-induced liver injury as outlined in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation identified in the development program.

Reviewer Comment: There is a suggestion that lofexidine is having an effect on the liver based on the prothrombin time data and the ALT and AST data from study 3003-1, but it does not appear to be clinically significant at either dose tested. In addition to the changes in values being of small magnitude, there was a high rate of missing data in the laboratory data and there was more missing data in the placebo groups, which limits the confidence with which one can draw conclusions from the available data.

There were no other clinically notable chemistry findings.

8.4.7 Vital Signs

Consistent with the findings in the adverse event data, the incidence of potentially clinically significant low blood pressure, orthostatic hypotension and lower pulse values were higher in the lofexidine-treated subjects compared to placebo-treated subjects. The mean changes in lofexidine-treated subjects in systolic blood pressure were in the range of a decrease of 10 mm Hg resting and a decrease of 16 mm Hg standing. The mean changes in heart rate in lofexidine-treated subjects were a decrease of 5 beats per minute resting and an increase of 4 beats per minute standing.

In the controlled period of Phase 3 studies, the proportion of subjects who had a resting but not a standing value for BP at any given assessment time point was greater in lofexidine-treated subjects compared with placebo-treated subjects. Review of line listings of comments revealed occasions documented when the patient was “unable to stand” for the standing assessment, suggesting these missing values represent extreme cases of orthostasis. Approximately 7% of 871 lofexidine-treated subjects and 5% of 280 placebo-treated subjects had missing values for standing BP with non-missing sitting BP. However, in study 3003-1, the incidence of subjects with missing standing BP when resting BP was collected was the same between treatment groups (3.1%, 3.2% and 3.4% in the 2.4 mg/day, 3.2 mg/day and placebo groups respectively) Table 49 Potentially Clinically Significant Low Post-Baseline Systolic and Diastolic Blood Pressure Study 3003-1.

In study 3003-1, there was a higher incidence of potentially clinically significant blood pressure decreases from baseline in the 3.2 mg group (54%) than the 2.4 mg group (45%) and placebo group (7%) as shown in the table below:

Table 49 Potentially Clinically Significant Low Post-Baseline Systolic and Diastolic Blood Pressure Study 3003-1

	Lofexidine HCl		Placebo (N = 151) n (%)
	2.4 mg/day (N = 229)	3.2 mg/day (N = 222)	
	n (%)	n (%)	
N at risk	227	221	148
Decreases	102 (44.9)	120 (54.3)	10 (6.8)
Resting SBP \leq 90 mmHg and a decrease \geq 20 mmHg from screening	47 (20.7)	51 (23.1)	1 (0.7)
Standing SBP \leq 90 mmHg and a decrease \geq 20 mmHg from screening	82 (36.1)	110 (49.8)	3 (2.0)
Resting DBP \leq 50 mmHg and a decrease \geq 15 mmHg from screening	23 (10.1)	23 (10.4)	1 (0.7)
Standing DBP \leq 50 mmHg and a decrease \geq 15 mmHg from screening	43 (18.9)	53 (24.0)	2 (1.4)
Missing standing BP when resting BP was collected	7 (3.1)	7 (3.2)	5 (3.4)

Source: Table 95 ISS

The mean decrease in resting pulse was similar in the lofexidine 3.2 mg group compared to the lofexidine 2.4 mg group in study 3003-1.

In the controlled period of all Phase 3 studies, the incidence of subjects that had clinically significant (criteria specified in table below) post-baseline vital sign values was higher in the 3.2 mg group compared to the 2.4 mg group.

Table 50 Clinically Significant post-baseline vital signs

	Lofexidine 2.4 mg % N = 229	Lofexidine 3.2 mg % N = 390	Placebo % N = 313
Systolic BP < 70 mm Hg and > 20% below baseline	2	8	0
Diastolic BP < 40 mmHg and > 20% below baseline	1	3	1
Pulse rate < 40 bpm and > 20% below baseline	0	<1	0

Source: Table 5.4.1 Integrated Summary of Safety

In the open-label outpatient study setting, most subjects had blood pressure data available for analysis. In study 3003-1, 52/64 subjects in the open-label period had data at the study discontinuation visit. The changes in blood pressure observed were less than what was observed in the controlled periods of the studies (mean change from screening sitting SBP of 2 mm Hg). The sitting heart rate mean change from screening to discontinuation went up by 9 bpm.

The potential for rebound hypertension was examined by evaluating the blood pressure data at the end of treatment and the data for the two days of placebo treatment after discontinuing lofexidine in studies 3002 and 3001 (study 3003-1 did not have a “rebound” period in the study design and thus no data is available for the 2.4 mg per day dose).

Table 51 Elevated Blood Pressure During the Potential Rebound Period in Pooled Studies 3002 and 3001

	Lofexidine HCl 3.2 mg/day (N = 168)		Placebo (N = 162)	
	N at risk	n (%)	N at risk	n (%)
SBP				
≥ 140 mmHg and ≥ 20 mmHg increase from baseline				
Rebound day 1	76	12 (15.8)	48	7 (14.6)
Rebound day 2	68	29 (42.6)	42	6 (14.3)
Rebound day 3	57	11 (19.3)	40	5 (12.5)
≥ 150 mmHg and ≥ 20 mmHg increase from baseline				
Rebound day 1	76	10 (13.2)	48	4 (8.3)
Rebound day 2	68	23 (33.8)	42	5 (11.9)
Rebound day 3	57	7 (12.3)	40	1 (2.5)
≥ 160 mmHg and ≥ 20 mmHg increase from baseline				
Rebound day 1	76	7 (9.2)	48	1 (2.1)
Rebound day 2	68	15 (22.1)	42	1 (2.4)
Rebound day 3	57	4 (7.0)	40	1 (2.5)
≥ 170 mmHg and ≥ 20 mmHg increase from baseline				
Rebound day 1	76	3 (1.3)	48	0
Rebound day 2	68	7 (10.3)	42	0
Rebound day 3	57	3 (5.3)	40	0
DBP				
≥ 90 mmHg and ≥ 15 mmHg increase from baseline				
Rebound day 1	76	7 (9.2)	48	12 (25.0)
Rebound day 2	68	20 (29.4)	0	7 (16.7)
Rebound day 3	57	8 (14.0)	40	6 (15.0)
≥ 100 mmHg and ≥ 15 mmHg increase from baseline				
Rebound day 1	76	2 (2.6)	48	4 (8.3)
Rebound day 2	68	9 (13.2)	0	4 (9.5)
Rebound day 3	57	1 (1.8)	40	0

DBP = diastolic blood pressure; SBP = systolic blood pressure.

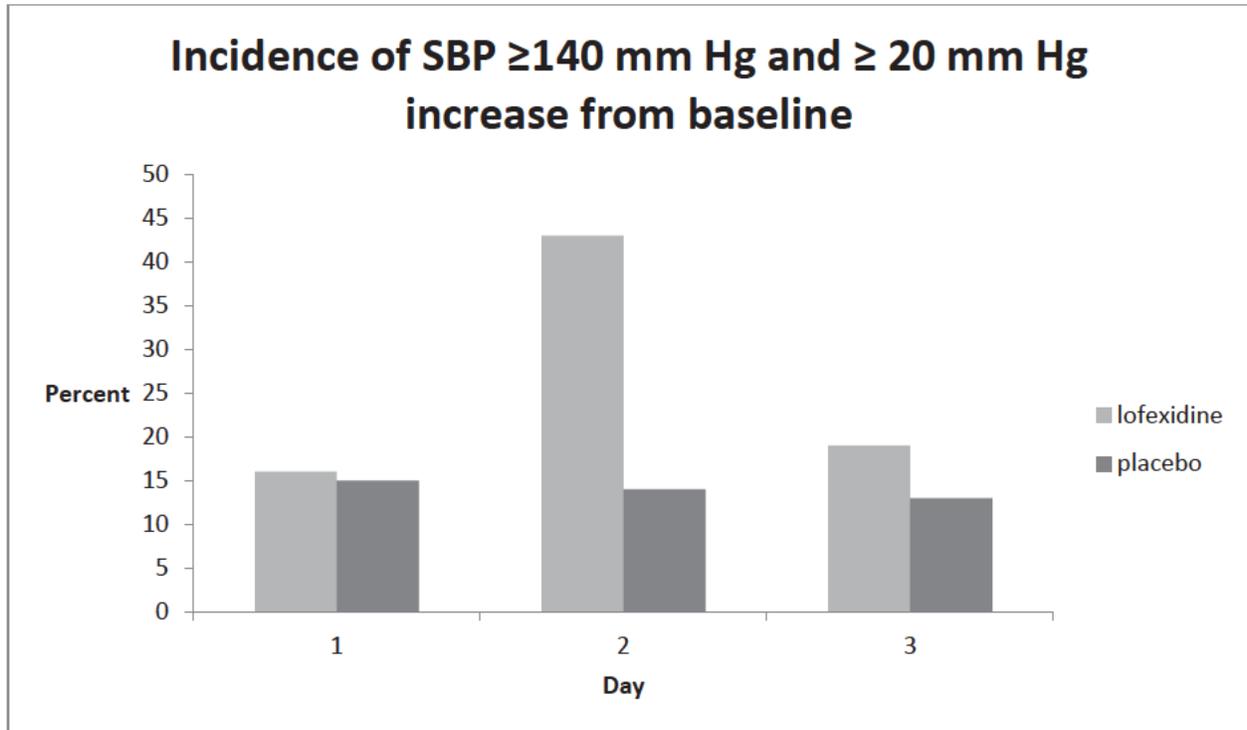
Potential rebound period = 1-3 days after discontinuation of lofexidine.

Source: Table 99 ISS

There were a substantial proportion of subjects in the lofexidine group that had rebound hypertension. Most of the hypertension occurred on day 2 after stopping lofexidine as shown in

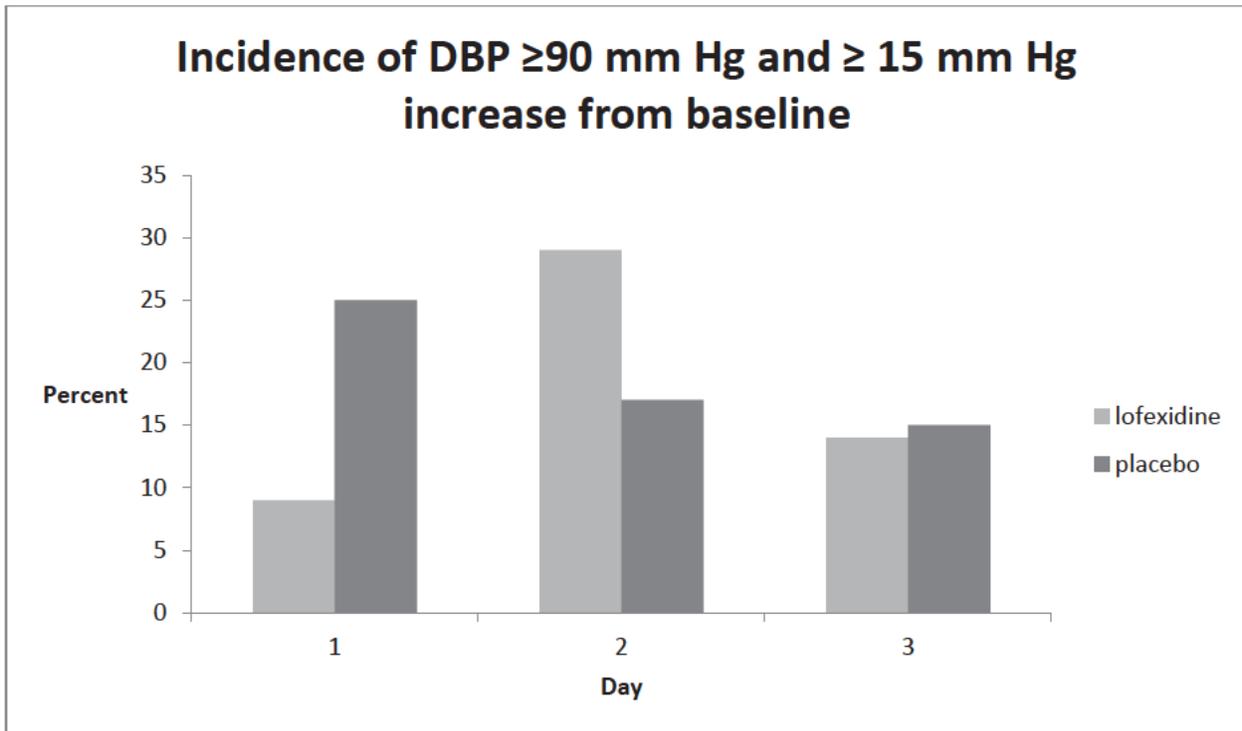
the graphs below.

Figure 13 Incidence of SBP ≥ 140 mm Hg and ≥ 20 mm Hg increase from baseline, Studies 3001 and 3002



Source: Table 99 ISS

Figure 14 Incidence of DBP ≥ 90 mm Hg and ≥ 15 mm Hg increase from baseline, Studies 3001 and 3002



Source: Table 99 ISS

Four subjects had hypertension accompanied by a TEAE potentially related to hypertensive symptoms (agitation, anxiety, nervousness, chest pain, chest discomfort, epistaxis, fatigue, flushing, feeling hot, headache, hypertension, hypertensive encephalopathy, dizziness, nausea, pallor, hyperhidrosis, dyspnoea, cerebrovascular accident, syncope, tachycardia, tremor, or visual impairment) in the lofexidine groups compared to no subjects in the placebo groups. Two of the subjects were in study 3001 and two of the subjects were in study 3002.

The approach to stopping lofexidine treatment differed between study 3001 and 3002. In study 3001, subjects were decreased from 3.2 mg per day to 1.6 mg per day for one day prior to cessation. In study 3002, subjects were receiving 3.2 mg per day and there was no dose taper prior to cessation. The table below compares the available data from the two approaches.

Table 52 Elevated Blood Pressure During the Potential Rebound Period in Individual Studies 3002 and 3001

	Study 3001		Study 3002	
	Lofexidine HCl 3.2 mg/day (N = 34)		Lofexidine HCl 3.2 mg/day (N = 134)	
	N at risk	n (%)	N at risk	n (%)
SBP				
≥ 140 mmHg and ≥ 20 mmHg increase from baseline				
Rebound day 1	10	3 (30.0)	66	9 (13.6)
Rebound day 2	10	6 (60.0)	58	23 (39.7)
Rebound day 3	7	1 (14.3)	50	10 (20.0)
≥ 150 mmHg and ≥ 20 mmHg increase from baseline				
Rebound day 1	10	2 (20.0)	66	8 (12.1)
Rebound day 2	10	5 (50.0)	58	18 (31.0)
Rebound day 3	7	0	50	7 (14.0)
≥ 160 mmHg and ≥ 20 mmHg increase from baseline				
Rebound day 1	10	2 (20.0)	66	5 (7.6)
Rebound day 2	10	3 (30.0)	58	12 (20.7)
Rebound day 3	7	0	50	4 (8.0)
≥ 170 mmHg and ≥ 20 mmHg increase from baseline				
Rebound day 1	10	0	66	1 (1.5)
Rebound day 2	10	2 (20.)	58	5 (8.6)
Rebound day 3	7	0	50	3 (6.0)
DBP				
≥ 90 mmHg and ≥ 15 mmHg increase from baseline				
Rebound day 1	10	1 (10.0)	66	6 (9.1)
Rebound day 2	10	5 (50.0)	58	15 (25.9)
Rebound day 3	7	1 (14.3)	50	7 (14.0)
≥ 100 mmHg and ≥ 15 mmHg increase from baseline				
Rebound day 1	10	0	66	2 (3.0)
Rebound day 2	10	3 (30.0)	58	6 (10.3)
Rebound day 3	7	0	50	1 (2.0)

Source: Response to IR 12/5/17, Tables 1 and 3

Only a third of lofexidine-treated subjects had data in study 3001 and only half of lofexidine-treated subjects had data in study 3002. From the subjects that had blood pressure data, there was a higher incidence of blood pressure elevations in study 3001, and the magnitude of blood pressure elevation was also higher in study 3001. Day 2 after lofexidine cessation was

consistently the day where the most blood pressure elevation was observed.

Reviewer Comment: Based on the available data, rebound hypertension can be expected after lofexidine cessation, the most rebound can be expected to occur on day 2 after cessation, and a decrease of dose by 50% by one day did not appear to mitigate the risk of rebound hypertension.

8.4.8 Electrocardiograms (ECGs)

There were no clinically important findings on ECG apart from decreases in heart rate and changes in QT interval. These issues are discussed in the Vital Signs and QT sections of the safety review.

8.4.9 QT

Refer to the QT-IRT consult response for a detailed review of the cardiac electrophysiology data. Lofexidine has been observed to prolong the QTc interval and decrease heart rate. Bradycardia is a risk factor for torsade de pointes in the presence of QTc prolongation. The QTcF interval appears to be prolonged by around 13 ms based on the results of a pilot QTc study in healthy subjects. However, the measurements of QTcF interval are confounded by the decrease in heart rate. In a study of lofexidine coadministered with methadone in patients that were tolerating a stable dose of methadone with a normal QTc interval at baseline, a further increase in QTcF was observed. The observed increase in QTc interval in the studies conducted by the Applicant does not suggest that the effect is clinically significant and did not appear to be dose-related. However, there is a publication in the literature that reports that three subjects had clinically significant QT prolongation while receiving concurrent lofexidine and methadone. In addition, there is one postmarketing case of torsade de pointes in a patient that was receiving lofexidine. Overall, the concern for QT prolongation with lofexidine appears to be mainly limited to settings in which it would be co-administered with other medicinal products that lead to QTc prolongation (e.g. methadone).

8.4.10 Immunogenicity

Immunogenicity assessments were not part of the clinical development program for this small molecule and there are no immunogenicity safety issues discussed in this review.

8.5 Analysis of Submission-Specific Safety Issues

8.5.1 Outpatient Treatment

Because much of the safety data in the application was collected in the inpatient setting, the frequency of vital sign monitoring and study staff assessments exceeded that which can be expected in clinical practice, especially in the outpatient setting. The outpatient setting may be deemed inappropriate to manage acute opioid withdrawal in opioid use disorder for other clinical reasons pertaining to the difficulties in achieving favorable addiction treatment outcomes in this

setting. However, there may be situations where prescribers have a need to manage patients in the outpatient treatment setting and considering the safety experience in the development program in the outpatient setting is warranted.

In the open-label outpatient periods of studies 3003-1 and 3003-2 there were no cardiovascular serious adverse events. There was one discontinuation in the outpatient setting and it was due to a fall in the setting of syncope that occurred during the in a subject who had a history of syncopal episodes that led to discontinuation. That subject had multiple recorded heart rates in the range of 41-49 on the first seven days of treatment, hypotension and orthostatic hypotension and met dose hold criteria many times in the first four days of dosing. His dose was reduced to 2.4 mg per day on Day 3 and reduced to 1.6 mg per day on day 8. He was still taking 1.6 mg per day on day 11 when the syncopal event occurred. He recovered from the event with no sequelae. Upon review of the case as a whole, it appears to have been inadvisable to continue this patient on lofexidine for so many days beyond initial opioid discontinuation given the many low vital sign readings that he experienced leading up to the syncopal episode. The product label should warn against such an approach.

Adverse events reported were lower in the outpatients compared to the inpatients from days 4-7 as shown below:

Table 53 Adverse Events in Inpatients and Outpatients in Study 3003-2

MedDRA Preferred Term ^a	Days 1-7 (N = 286) n (%)	Inpatient Days 1-3 (N = 286) n (%)	Inpatient Days 4-7 (N = 144) n (%)	Outpatient Days 4-7 (N = 74) n (%)	Outpatient Days 8-14 (N = 54) n (%)
Subjects with any treatment-related TEAEs	198	180	70	21	9
Orthostatic hypotension	90 (31.5)	65 (22.7)	39 (27.1)	9 (12.2)	5 (9.3)
Hypotension	81 (28.3)	67 (23.4)	30 (20.8)	2 (2.7)	1 (1.9)
Bradycardia	72 (25.2)	68 (23.8)	25 (17.4)	6 (8.1)	1 (1.9)
Dizziness	45 (15.7)	38 (13.3)	5 (3.5)	5 (6.8)	0 (0.0)
Sedation	45 (15.7)	45 (15.7)	0 (0.0)	1 (1.4)	0 (0.0)
Dry mouth	21 (7.3)	21 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	19 (6.6)	19 (6.6)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	16 (5.6)	15 (5.2)	0 (0.0)	1 (1.4)	0 (0.0)

MedDRA = Medical Dictionary for Regulatory Activities; TEAEs = treatment-emergent adverse events

^a Preferred terms are listed in decreasing order of frequency in the “Days 1-7” column.

Source: Table 26 CSR Study 3003-2

In part this is likely due to the more frequent vital signs taken in the inpatient setting and the protocol-based requirement to classify certain vital sign parameters as adverse events. However, more dizziness and sedation was reported in the outpatient patients, which could be related to less opportunities for clinical intervention to manage low vital signs in the outpatient setting and possibly patients becoming more symptomatic.

The data do not reveal undue risk to subjects that were managed as outpatients.

8.6 Safety Analyses by Demographic Subgroups

Treatment-Emergent Adverse Events

There were a few notable differences in TEAEs between subgroups of lofexidine-treated subjects in the Phase 3 studies.

Females (n = 168) compared with males (n = 451) had an increased incidence (2% or greater difference) of the following TEAEs:

- Hypotension: 36.3% vs. 25.5%
- Bradycardia: 25.0% vs. 21.5%
- Dizziness: 26.8% vs. 20.6%
- Somnolence: 16.7% vs. 11.8%
- Nausea: 28.6% vs. 17.1%
- Headache: 26.2% vs. 16.2%

Females also had twice the incidence of syncope (1.8% of females compared to 0.9% of males).

In Study 3003-1, the incidence of dose holds or discontinuations for bradycardia or orthostatic hypotension was similar between males and females in the 2.4 mg group, but in the 3.2 mg group the incidence was higher in females with a of 13%.

Table 54 Subjects in Study 3003-1 with a dose hold or discontinuation for bradycardia or orthostatic hypotension by sex

	Lofexidine 2.4 mg	Lofexidine 3.2 mg
Male	22/162 (14%)	29/158 (18%)
Female	9/67 (13%)	20/64 (31%)

Source: Reviewer generated from study 3003-1 AE and DM datasets

The Applicant concluded that these differences appear to be related to lower body weight in females compared to males based on the results of a PK analysis of opioid-dependent subjects in the double-blind portion of Study 3003-1. However, when comparing the incidence of these same events by weight category, as shown below the differences in weight category clearly do not explain the differences observed by sex in the 3.2 mg group:

Table 55 Subjects in Study 3003-1 with a dose hold or discontinuation for bradycardia or orthostatic hypotension by body weight

	Lofexidine 2.4 mg	Lofexidine 3.2 mg
>85 kg	7/51 (14%)	11/53 (21%)
65-85	16/123 (13%)	25/112 (22%)
<65	8/55 (15%)	13/57 (23%)

Source: Reviewer generated from study 3003-1 AE and DM datasets

There was a slightly higher incidence of subjects with held doses or discontinuations for bradycardia or orthostatic hypotension in the lower weight patients compared to higher weight patients in both the 2.4 mg and 3.2 mg treatment groups but these differences were much smaller than the differences observed by sex in the 3.2 mg group.

The incidence of serious cardiovascular adverse events (SAEs) was also higher in females than males in the controlled period of the Phase 3 studies. There were seven cardiovascular SAEs in these studies in the 3.2 mg group: four were in females (4/101 or 4% incidence) and three were in males (3/289 or 1% incidence).

Headache and sedation were more common in black subjects (n = 147) than in white subjects (n = 411):

- Headache: 25.9% vs. 16.5%
- Sedation: 21.1% vs. 8.3%

However, somnolence was more common in white subjects than black subjects 14% vs. 10% and pain in general was more common in white subjects than black subjects and there did not appear to be a trend in TEAEs suggestive of a differential safety experience between subgroups by race. There was a small proportion of subjects in the studies that were in a subgroup by race other than black or white subjects and the summary statistics did not reveal notable differences in the incidence of TEAEs.

There were no notable differences in TEAEs by age group or BMI category.

Vital Signs

Decreases in blood pressure were of similar magnitude in male and female lofexidine-treated subjects. Resting pulse decreases were of larger magnitude in female lofexidine-treated subjects (mean decrease of ≤ 9 bpm) than males (mean decrease of ≤ 5 bpm). Standing pulse increases were observed consistently in placebo-treated males and females and these increases were larger in magnitude than lofexidine-treated males and females.

As shown in the table below, there was a higher incidence of clinically significant low blood pressures in females compared to males:

Table 56 Subjects With Clinically Significant Post-Baseline Vital Sign Values by Sex, Controlled Period of Phase 3 Studies Pooled

	Lofexidine HCl 2.4 and 3.2 mg/day		Placebo	
	Male (N = 451)	Female (N = 168)	Male (N = 233)	Female (N = 168)
SBP < 70 mmHg and > 20% below baseline	20 (4.4)	16 (9.5)	0	0
DBP < 40 mmHg and > 20% below baseline	9 (2.0)	7 (4.2)	2 (0.9)	0
Pulse < 40 bpm and > 20% below baseline	1 (0.2)	0	0	0

DBP = diastolic blood pressure; SBP = systolic blood pressure.

Source: ISS Table 106

Consistent with these findings, in study 3003-1, slightly over a third of the subjects who discontinued due to bradycardia or had doses held for bradycardia were women, while the study population was 29% women

The vital sign data was summarized by age in two subgroups: age 35 and younger and age > 35 years.

In the placebo group the older subgroup had larger increases in resting and standing SBP than the younger subgroup. There were otherwise no consistent differences in BP by age.

The younger group had a higher incidence of increased standing pulse than the older age group.

There were no noteworthy differences in vital signs by racial subgroup with the exception of systolic blood pressure, where 6% of white, 3% of black and 10% of subjects categorized as other had SBP a postbaseline value that was <70 bpm and >20% below baseline.

8.7 Specific Safety Studies/Clinical Trials

This section is not applicable.

8.8 Additional Safety Explorations

8.8.1 Human Carcinogenicity or Tumor Development

There were no signals for carcinogenicity in the animal data, although it must be noted that the carcinogenicity studies were not conducted according to currently-accepted methods. Long-term safety data in the clinical program was limited to fourteen subjects that received lofexidine for up to sixteen weeks in a Phase 2 study and while the small number of subjects exposed revealed no safety signals, such a small sample would be highly unlikely to detect a signal for carcinogenicity risk. The Applicant reports that studies conducted by prior sponsors in support of a hypertension indication revealed no additional safety signals beyond those identified in the current development program.

8.8.2 Human Reproduction and Pregnancy

No pregnancies were reported in the clinical studies conducted for lofexidine. There has been one postmarketing case of pregnancy reported but a follow-up report stated that this was an error and the patient wasn't exposed to lofexidine. The nonclinical studies revealed no teratogenic effects but high doses caused a reduction in fetal weight and increased abortions. The chemical characteristics of lofexidine make it likely that it crosses the placenta and could be excreted in breast milk.

8.8.3 Pediatrics and Assessment of Effects on Growth

There is no information about the effects of lofexidine in the pediatric population.

8.8.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

See Vital Signs section regarding rebound effects on blood pressure. The Controlled Substance Staff concluded in their consult review that lofexidine does not warrant placement in any schedule of the Controlled Substance Act. The review also concludes that withdrawal symptoms of lofexidine are diarrhea, insomnia, anxiety, chills, hypertension, hyperhidrosis and extremity pain based on these adverse events being observed more frequently in subjects that had received lofexidine compared to placebo in the single-blind placebo washout period from studies 3001 and 3002. The review also recommends that the label should include a recommendation for tapering lofexidine over 2 to 4 days at the end of treatment. See the consult review by Dr. Bansil for details.

8.9 Safety in the Postmarket Setting

8.9.1 Safety Concerns Identified Through Postmarket Experience

Lofexidine has been approved for marketing in the United Kingdom since 1990 to relieve symptoms in patients undergoing opioid detoxification. The recommended dose range is up to 2.4 mg per day in divided doses with a maximum single dose of 0.8 mg. The product label recommends individual titration according to the patient's response and a treatment duration of seven to ten days. The Applicant estimates 302,932 packs of 0.2 mg 60 tablets (a pack would provide 2.4 mg lofexidine per day for five days) over the period of 1997 to 2016.

The data on postmarket experience, submitted by the Applicant, comes from foreign spontaneous reports. According to the Applicant, the most frequently reported postmarketing AE has been hypotension. There has been one report of QT prolongation, bradycardia (40-44 bpm), and torsade de pointes in a 26-year-old man that received 0.2 mg lofexidine and that resulted in cardiac arrest with successful resuscitation and full recovery. There has been one death reported and recorded as being a result of dehydration from vomiting and diarrhea in the setting of heroin withdrawal.

8.9.2 Expectations on Safety in the Postmarket Setting

The Phase 3 studies, which formed the bulk of the safety database contributing to the safety evaluation, consisted of subjects who were in withdrawal from short-acting opioids and had an addiction to opioids. These subjects were on average in their mid-30s and, other than viral hepatitis infections, did not have many medical comorbidities. This product has the potential to

be used in the setting of managing opioid withdrawal symptoms in other clinical settings, such as patients with iatrogenic physical dependence to opioids due to prolonged treatment for painful conditions or in managing opioid withdrawal symptoms associated with cessation of long-acting opioids. In these settings, opioid withdrawal symptoms may be somewhat attenuated compared to the abrupt discontinuation of short-acting opioids studied in the clinical program and patients could be more sensitive to the sympathetic adrenergic effects of lofexidine and potentially more vulnerable to significant decreases in blood pressure and heart rate. Additionally, this off-label use could result in patients with more medical comorbidities, such as cardiovascular comorbidities, receiving lofexidine. Therefore, the warnings regarding cardiovascular effects of the drug should clearly state the risks and advise prescribers that the risk has not been assessed in subjects with cardiovascular comorbidities. The prolonged withdrawal symptoms associated with long-acting opioids could result in lofexidine use for longer periods. There is data for up to 14 days of use in a small number of subjects and additional risk with longer use has not been identified thus far.

8.9.3 Additional Safety Issues from Other Disciplines

There were findings in the nonclinical studies of corneal erosion and ulceration in female rats in the GLP repeat-dose toxicology study and a NOAEL was not established. These findings may be a result of decreased lacrimation in the rats. In the clinical data, there were no similar findings of corneal erosion or ulceration reported. No dedicated eye exams were part of the routine testing in the clinical studies. In the adverse event data, eye disorder adverse events were more common in the placebo group, which was driven by more reports of increased lacrimation, which is a symptom of opioid withdrawal. Dry eye was reported with higher incidence in the lofexidine groups, but was rare.

Table 57 Eye Disorders Adverse Events in Controlled Period of Phase 3 Studies

MedDRA System Organ Class Preferred Term	LFX 2.4 (N=229)		LFX 3.2 (N=390)		ALL LFX (N=619)		Placebo (N=313)	
	No. of Subjects n (%)	No. of Events						
Eye disorders	9 (3.9)	13	27 (6.9)	30	36 (5.8)	43	33 (10.5)	40
Lacrimation increased	7 (3.1)	9	16 (4.1)	18	23 (3.7)	27	29 (9.3)	31
Mydriasis	1 (0.4)	1	4 (1.0)	4	5 (0.8)	5	5 (1.6)	5
Dry eye	1 (0.4)	1	2 (0.5)	2	3 (0.5)	3	0	0
Vision blurred	0	0	3 (0.8)	3	3 (0.5)	3	2 (0.6)	2
Eye irritation	2 (0.9)	2	0	0	2 (0.3)	2	0	0
Diplopia	0	0	1 (0.3)	1	1 (0.2)	1	1 (0.3)	1
Photopsia	0	0	1 (0.3)	1	1 (0.2)	1	0	0
Vitreous floaters	0	0	1 (0.3)	1	1 (0.2)	1	0	0
Eye pain	0	0	0	0	0	0	1 (0.3)	1

Source: Table 3.2.1 ISS

8.10 Integrated Assessment of Safety

The main risks of lofexidine are hypotension, bradycardia, orthostatic hypotension, dizziness, syncope, rebound hypertension and QT prolongation. There were clinically important differences in the incidence and clinical significance of bradycardia and orthostatic hypotension

between the 2.4 mg per day dose and the 3.2 mg per day dose. There are no data comparing rebound hypertension with the 2.4 mg per day dose and the 3.2 mg per day dose. Vital sign and ECG monitoring is warranted in patients at increased risk for clinically significant bradycardia, hypotension, rebound hypertension and QT prolongation. Use should be avoided in patients with comorbidities or concomitant medications where the cardiovascular and cardiac electrophysiological effects of lofexidine would place the patient at undue risk.

Opioid overdose risk increases following completion of opioid discontinuation. Labeling should include a warning of this risk and a recommendation for patient counseling and emphasis on continued engagement in treatment in patients with OUD.

None of the submitted data include direct comparisons of lofexidine to the other current treatment options.

9 Advisory Committee Meeting and Other External Consultations

A meeting of the Psychopharmacologic Drugs Advisory Committee was held on March 27, 2018 to discuss this application. Eleven out of 12 members voted YES for approval of this product. Among the members who voted YES, a majority voted for the indication of “mitigation of symptoms associated with abrupt opioid withdrawal” but not the “facilitation of completion of abrupt opioid discontinuation treatment in patients with opioid use disorders.” Objections to the wording focused on the word “completion.” Some members opined that to conclude that a subject had completed opioid discontinuation they should have no remaining symptoms of opioid withdrawal, and the studies as designed did not evaluate this clinical outcome. Some members stated that they did not know what the threshold score would be to conclude that the patient was no longer experiencing withdrawal. One member also noted that opioid withdrawal can go well beyond the 5 or 7-day treatment period studied in the pivotal trials.

The committee members concluded that there is no significant improvement in efficacy from 2.4 mg to 3.2 mg dose, but the incidence of side effects such as bradycardia and hypotension is higher for the 3.2 mg/day dose. It was agreed that 2.4 mg/day should be approved, and some members recommended 3.2 mg/day dose if the 2.4 mg/day dose is not working.

The members did not express concern over the small number of subjects that had been exposed beyond seven days of treatment. Issues that the members recommended studying in the postmarket setting included further evaluation of the potential for rebound hypertension.

10 Labeling Recommendations

10.1 Prescription Drug Labeling

- Throughout the label, the product is described in terms of the lofexidine content, rather

than the lofexidine hydrochloride content. Therefore, the tablet size referred to as 0.2 mg in the studies is described in the label as 0.18 mg; the 3.2 mg/day dose is referred to as 2.88 mg/day and the 2.4 mg/day dose is referred to as 2.16 mg/day

- Indications and Usage: An indication for mitigation of symptoms, “facilitating” but not “facilitating *completion of*” opioid discontinuation treatment is appropriate for the indications and usage section; see Advisory Committee Meeting and Other External Consultations. The language should also be modified to clarify that the product is approved only for treating withdrawal in the setting of *abrupt* discontinuation of opioids.
- Dosage and Administration:
 - The 2.16 mg (2.4 mg as salt) per day dose showed similar efficacy and a better safety profile than the 2.88 (3.2 mg as salt) per day dose and is the most appropriate dose to recommend as a starting target dose for prescribers to balance giving patients adequate relief as quickly as possible after starting therapy and minimizing serious risks. This section should recommend that dose adjustment should be made based on symptoms and adverse effects.
 - Based on the observed withdrawal effects including blood pressure elevations in the clinical program, the lack of evaluation of a taper longer than one day in the clinical program, and the recommendation for a 2 to 4 day taper in the clonidine label, a 2 to 4 day taper recommendation has been added with the expectation that it could mitigate some of the withdrawal symptoms observed in the clinical program.
- Warnings and Precautions: This section should contain a description of and include instructions to prevent and treat the following serious risks
 - Hypotension, Bradycardia, and Syncope
 - QT prolongation
 - CNS depression with concomitant use of sedating drugs
 - Withdrawal (including marked blood pressure increases)
 - Risk of opioid overdose after opioid discontinuation in patients with opioid use disorder

All of these serious risks were observed in the development program and are covered in the safety review. The labeling should advise that patients managed in the outpatient setting will need to be capable of, and instructed on, monitoring themselves for hypotension and bradycardia (b) (4) etc.

- Adverse Reactions: The following modifications were made
 - Presenting common adverse events by assigned daily dose to show the differences between lofexidine and placebo and between different lofexidine doses
 - Adding information about blood pressure elevations and other withdrawal symptoms after cessation
 - Describing the higher incidence of clinically significant cardiovascular adverse events in females than males
 - Adding postmarketing reports of QT prolongation to the postmarketing experience section
- Drug Interactions: only clinically significant drug interactions are to be described and this section was modified to (b) (4)

(b) (4)

- Clinical Studies:
 - Study 3002: The mean SOWS-Gossop scores over the entire 5-day treatment period should be presented in graphical form to give the prescriber an understanding of the treatment effect on patient-reported symptoms over the 5-day period studied. The completion rate over the treatment period should be included to illustrate subject retention in the study.
 - Study 3003-1: The mean SOWS-Gossop scores and completion rate over the entire 7-day treatment period should be presented for the same reasons as study 3002.
 -  (b) (4)
- Patient Counseling Information: This section was modified to align with the Warnings and Precautions section

11 Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation and mitigation strategies are recommended for this product.

12 Postmarketing Requirements and Commitments

Pediatrics

Under the Pediatric Research and Equity Act (PREA), the Applicant of this NDA is required to conduct pediatric studies for lofexidine for the approved indication. The indication approved will be for the mitigation of symptoms associated with *abrupt* opioid withdrawal. The pediatric plan agreed upon by the Division, the Pediatric Review Committee (PeRC), and the Applicant had anticipated an indication not limited to abrupt withdrawal. Although opioid withdrawal in situations of both abrupt withdrawal and gradual opioid taper occurs in patients of all ages, abrupt discontinuation of opioids is not customarily carried out in pediatric patients with iatrogenic opioid dependence. Neonates exposed to opioids in utero do experience abrupt discontinuation of opioid exposure, and abrupt discontinuation may be appropriate in adolescents with OUD. The table below shows the originally agreed-upon studies in the pediatric program.

All studies are deferred because studies in adults are completed and the NDA is currently under review. The milestone dates for final protocol submission, study completion, and final report are

pending final agreement.

Table 58 Pediatric Study Timeline

	Protocol Submission	Study Initiation	Final Report Submission
Study	Estimated Dates No Later Than (Month/Year):		

(b) (4)

FDAAA required safety study

It is anticipated that patients will be exposed to lofexidine for longer than 14 days both in the setting of opioid taper and cumulatively over multiple courses of treatment for opioid withdrawal. The safety data are based on less than 50 subjects beyond 10 days of treatment and, do not extend beyond 14 days, and there are several signals for a serious risk associated with lofexidine that warrant further evaluation in the postmarket setting. The most feasible clinical setting with which to gather data on lofexidine use beyond 14 days of exposure is in the setting of analgesic taper. Lofexidine has not been studied for efficacy in patients undergoing a taper from opioids, but due to the unmet need for a drug that mitigates withdrawal symptoms in this clinical setting, it is expected that lofexidine will be used this way off-label and a controlled study is needed to assess the benefit and risk of lofexidine in this clinical setting. It is not known whether lofexidine would have benefit in the setting of gradual taper, because withdrawal symptoms can often be managed by slowing the taper. Therefore, it is important to establish the potential benefit of longer-term use and confirm that the benefits outweigh the risks.

In the program, there was one stroke that occurred after stopping lofexidine and there was clear rebound hypertension observed. The potential for rebound hypertension should be assessed after more prolonged use to better characterize this risk. In addition, there was a higher incidence of treatment-emergent liver enzyme elevations observed in lofexidine-treated subjects and the effects on liver enzymes should be evaluated with a longer duration of use and in a larger number of subjects to further evaluate this signal, which could be indicative of the potential for lofexidine to cause drug-induced liver injury. This drug will address an unmet medical need and

therefore the additional data needed to evaluate the safety of lofexidine is appropriate for a postmarket rather than pre-approval requirement.

PK, safety, and efficacy studies in children with iatrogenic opioid dependence undergoing gradual taper will also be required. These will be divided into age cohorts as described above under PREA requirements, in part because children under 6 will require a pediatric formulation. This formulation will be needed as well for the PREA-required NOWS study.

Non-clinical Post-marketing Studies

1. Conduct an in vivo comet assay testing lofexidine in the liver and stomach.
2. Conduct a pharmacokinetic study in the rat to characterize the plasma levels of lofexidine and the lofexidine metabolites LADP (N-(2-aminoethyl)-2-(2,6-dichlorophenoxy)propenamide), LDPA (2-(2,6-dichlorophenoxy)propionic acid), and 2,6-DCP (2,6-dichlorophenol) using a validated assay.
3. Conduct a juvenile animal study in rats from PND 36 to PND 90 to support pediatric drug development in children aged 12 to 17 years. The study will evaluate the effect of the drug on growth and development, reproductive (b) (4) bone development, and the central nervous system.
4. Conduct a juvenile animal study in rats from PND 7 to 90 to support pediatric drug development in children and neonates. The study will evaluate the effect of the drug on growth and development, reproductive (b) (4), bone development, and the central nervous system.
5. Conduct a juvenile toxicology in rats to evaluate the impact of lofexidine on early neuronal development during peak synaptogenesis to support pediatric studies in neonates and children under the age of 3.
6. Conduct a fertility and early embryonic development study in rats testing lofexidine administration to males and include histopathology of the testes and sperm assessments (count, motility, and morphology).
7. Conduct a 90-day GLP repeat-dose toxicology study in the rat testing lofexidine HCl to establish a NOAEL to support clinical studies that are longer than 14-days in duration. To avoid the potential confounding impact of C_{max} -induced fluctuations in physiology, which could impact the NOAEL, dose the animals several times a day, as feasible, to mimic the clinical setting.

Post-marketing CMC commitment:

USWM will monitor for reports of product quality issues (b) (4)

13 Appendices

13.1 References

- Akhurst, J. (1999). The Use of Lofexidine by Drug Dependency Units in the United Kingdom. *European Addiction Research*, pp. 43-49.
- Carnwath T, H. J. (1998). Randomised double-blind comparison of lofexidine and clonidine in the out-patient treatment of opiate withdrawal. *Drug and Alcohol Dependence*, pp. 251-254.
- Kahn A, M. J. (1997). Double-blind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital. *Drug and Alcohol Dependence*, pp. 57-61.
- Lin S, S. J. (1997). Double-blind randomised controlled trial of lofexidine versus clonidine in the treatment of heroin withdrawal. *Drug and Alcohol Dependence*, pp. 127-133.
- Schmittner J, S. J. (2009, May 29). Electrocardiographic effects of lofexidine and methadone coadministration: secondary findings from a safety study. *Pharmacotherapy*, pp. 495-502.

13.2 Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators. No relationships were disclosed.

Covered Clinical Study (Name and/or Number): 1005-2, 1006, 3002, 3003-1, 3003-2

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 494		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S		

Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

13.3 Study Site Information

Table 59 Study 3002 Enrollment by Study Site

Primary Investigator Last Name	Primary Investigator First Name	Site ID	Number Enrolled in lofexidine 3.2 mg group	Number Enrolled in placebo group
Stine	Susan	200	4	3
Walsh	Sharon	235	10	10
Riesenberg	Robert	237	15	12
Lowy	Adam	238		(b) (6)
Martin	Peter	239	10	4
Pearlman	Richard	240	17	17
Longo	Lance	241	3	9
Mascarenhas	Alipio	242	8	6
Lerman	Mark	244	7	4
Roache	John	245	19	21
Willner	Mark	265	18	19
Yadalam	Kashinath	266	12	15
Swift	Robert	650		(b) (6)
Stock	Christopher	660	7	5
Saxon	Andrew	663	3	4

Table 60 Study 3003-1 Enrollment by Study Site

Primary Investigator Last Name	Primary Investigator First Name	Site ID	Number Enrolled in lofexidine 2.4 mg group	Number Enrolled in lofexidine 3.2 mg group	Number Enrolled in placebo group
Riesenberg	Robert	1	29	22	18
Molpus	Robert	2	24	36	18
Cantu	Julius	3			(b) (6)
Bari	Mohammed	4	19	17	10
Fishman	Marc	6	15	11	13
Yadalam	Kashinath	7	5	6	3
Kjome	Kimberly	8	14	13	10
Guzzetta	Richard	9	4	7	8
Andersen	Jason	12	26	29	10
Alam	Danesh	13	29	18	18
Webster	Lynn	14			(b) (6)

Aziz	Mohamed	15	9	13	7
D'Souza	Bernadette	16	21	12	9
Mofsen	Ricky	17	11	11	8
Mehra	Vishaal	18	19	23	15
Kwentus	Joseph	19	4	3	2

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/s/

PAMELA J HORN
05/15/2018

DAVID M PETULLO on behalf of YI N REN
05/15/2018
I concur.

DAVID M PETULLO
05/15/2018
I concur.

CELIA J WINCHELL
05/15/2018

SHARON H HERTZ
05/15/2018

MARY T THANH HAI
05/15/2018

Tertiary Pharmacology/Toxicology Review

From: Timothy J. McGovern, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO

NDA: 209229

Agency receipt date: September 26, 2017

Drug: (Lofexidine HCl, LUCEMYRA)

Sponsor: US WorldMeds, LLC

Indication: Mitigation of symptoms associated with opioid withdrawal; Facilitation of completion of opioid discontinuation treatment

Reviewing Division: Division of Anesthesia, Analgesia, and Addiction Products

The pharmacology/toxicology reviewer, team leader and supervisor concluded that the nonclinical data support approval of lofexidine for the indication listed above.

Lofexidine is a central alpha-2 adrenergic agonist that has pharmacological properties similar to clonidine. The recommended pharmacologic class for lofexidine is [REDACTED] (b) (4). It is proposed to administer three to four 0.18 mg tablets orally four times per day (16 tablets/day; 2.88 mg/day). While lofexidine is not approved in the US, it has been marketed in the UK since 1992.

The nonclinical program consists of ADME, pharmacology, repeat-dose toxicity studies, genetic toxicology, carcinogenicity, and reproductive and developmental toxicology studies. Many of the studies were conducted prior to GLP regulations but were considered suitable to support the current safety assessment of lofexidine. The general toxicity studies were conducted in rats and dogs and the primary target organs were identified as the CNS, the cardiovascular system, and the hepatic and renal systems. The NOAELs in rat and dog studies were associated with systemic exposure levels of < 1 and 2-fold, respectively.

A genetic toxicology battery of assays was conducted and one assay, an in vitro mouse lymphoma assay produced positive results. The sponsor is conducting a follow up Comet assay to further evaluate the genotoxic potential of lofexidine that is planned to be submitted post-approval. Carcinogenicity studies were conducted in rats and mice. However, the studies were deemed inadequate to provide a suitable evaluation of carcinogenic potential [REDACTED] (b) (4). Given the proposed use of the product, carcinogenicity studies are not required to support approval.

A battery of reproductive and developmental toxicity studies included non-GLP fertility studies in rats and rabbits, non-GLP embryofetal development studies in rats and rabbits, a GLP pre- and post-natal development study in rats, and a GLP toxicokinetic study in rabbits. No effects on fertility were observed but inadequate evaluations of effects in male rats were conducted. Embryo-fetal toxicity was observed in the rabbit embryo-fetal development study and increased pup mortality, developmental delays and fertility

impairments of the F₁ offspring were observed in the pre- and post-natal development study at doses associated with maternal toxicity. The NOAELs for all of the studies were associated with systemic exposure margins of < 1 when compared to anticipated clinical exposures. These findings will be described in the product label.

Conclusion:

I agree with the Division pharmacology/toxicology conclusion that lofexidine can be approved from the nonclinical perspective. The conclusion considers the proposed indication and the significant human experience to date since the nonclinical program identified several potential toxicities that occurred at exposure levels similar to or below anticipated clinical exposures.

The review team recommends a series of postmarketing requirements including an in vivo Comet assay, a pharmacokinetic study in rats to characterize plasma levels of lofexidine and metabolites in a validated assay, a series of juvenile studies in rats, a fertility and early embryonic development study in rats, and a 90-day GLP rat toxicity study. The proposed postmarketing requirements are supported based upon identified concerns with the available nonclinical data, previous agreements with the sponsor, and related clinical postmarketing requirements.

I have reviewed the proposed wording for the nonclinical sections of the product label and agree with the Division recommendations.

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/s/

TIMOTHY J MCGOVERN
05/14/2018

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 209229
Supporting document/s: 2, 5, 15, 17, & 27
Applicant's letter date: 7/28/2017, 9/26/2017, 12/19/2017, 1/19/2018, & 4/10/2018
CDER stamp date: 7/28/2017, 9/26/2017, 12/19/2017, 1/19/2018, & 4/10/2018
Product: LUCEMYRA (Lofexidine HCl)
Indication: Mitigation of symptoms associated with opioid withdrawal; Facilitation of completion of opioid discontinuation treatment
Applicant: US WorldMeds, LLC
Review Division: Division of Anesthesia, Analgesia, and Addiction
Reviewer: Kevin Snyder, PhD
Team Leader: Newton Woo, PhD
Supervisor: Daniel Mellon, PhD
Division Director: Sharon Hertz, MD
Project Manager: Kim Compton, RPh

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1 Executive Summary

1.1 Introduction

US WorldMeds, LLC submitted NDA 209229 to support marketing approval of LUCEMYRA (lofexidine HCl), a central alpha-2 adrenergic agonist, for the mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment. The proposed dosing regimen is for patients to take three or four 0.18 mg tablets orally four times daily for seven days, yielding a maximum daily dose of 2.88 mg/day (16 tablets/day, dose expressed as the base). Lofexidine is not approved in the U.S. for any indication. However, the drug has been marketed in the U.K. for the treatment of opioid withdrawal since 1992. Lofexidine was originally investigated as a potential drug to treat hypertension. As such, many of the nonclinical studies in support of earlier human drug development were completed prior to Good Laboratory Practices. The development program for the opioid related indications was initiated under IND 47857 in 1995. The Applicant has obtained these pre-GLP nonclinical studies to support this development program. Although the existing toxicity studies were pre-GLP, based on the previous human experience, these studies plus the human data were deemed adequate to permit clinical trials. NDA 209229 was submitted as a 505(b)(1) application.

1.2 Brief Discussion of Nonclinical Findings

LUCEMYRA is a round, convex-shaped peach colored film-coated tablet containing 0.18 mg of lofexidine (base). There are no concerns regarding the safety of the excipients, drug substance or drug product impurity specifications for LUCEMYRA. The specifications for two of the drug substance impurities exceed the ICH qualification threshold, [REDACTED] (b) (4)

[REDACTED] The primary pharmacology of lofexidine and the structurally similar central alpha-2 adrenergic agonist, clonidine, were demonstrated to be practically identical via receptor binding and functional activity screens. Additional secondary pharmacology binding screens were conducted on lofexidine and its major human metabolites, LADP, LDPA, and 2,6-DCP. Lofexidine displayed moderate binding at additional serotonin and dopamine-related receptors, enzymes and transporters. In contrast, the metabolites did not show any significant binding to primary or secondary targets. Pharmacokinetics studies demonstrated that lofexidine was rapidly absorbed and distributed widely throughout the body and is extensively metabolized. Three major human metabolites have been identified that are also detected in the urine of rats, dogs, and rabbits. Studies are currently underway to confirm that these human major metabolites are produced in rats at adequate exposures to qualify the safety of these metabolites [REDACTED] (b) (4) in the drug formulation. Given the human experience and existing data in urine, this study can be submitted as a post marketing requirement.

General toxicology studies were conducted in the rat and dog, which characterize the toxicological effects of the drug. Although these studies suggested adequate exposure margins based on body surface area, evaluation of the existing human and animal pharmacokinetic data suggest exposure margins at the NOAEL that are less than 1 in

the rat and 2x in the dog. Further, the GLP 4-week rat study selected doses that were too high and had to be reduced due to adverse effects, which complicates the interpretation of the study and reduces utility to define a NOAEL. The shortest dog study was 90-days in duration, which likely overestimates the toxicity of the drug for an acute indication. Nonetheless, these studies do characterize the toxicological potential of the drug. The following target organs were identified in repeat-dose toxicology studies conducted in rats and dogs: central nervous system (CNS), cardiovascular system, hepatic and renal system. CNS toxicities, expressed as dose-dependent increase in clinical signs, were related to sedation and CNS depression (e.g., decreased activity, ataxia, hypothermia) consistent with the expected side effects of an alpha-2 adrenergic agonist. Conversely, lofexidine produced CNS excitation/hypersensitivity at higher dose levels that included hyperactivity, aggressive behavior, self-mutilation, tremors/convulsions. Cardiovascular toxicities were primarily observed in the dog safety pharmacology and repeat-dose toxicology studies and consisted of bradycardia, QT prolongation, and cardiac conduction disturbances. The in vitro hERG assay revealed only mild tail current inhibition at the highest lofexidine concentration evaluated. Additional cardiovascular toxicities observed in rats and dogs in longer-term studies and at higher doses included increased heart weights, myocarditis, and cardiac hemorrhage. Severe myocarditis with degeneration and necrosis and cardiac hemorrhage were only apparent in the 1-year rat and dog studies and occurred at AUC levels that were 24x and 9x, respectively, higher than levels associated with the maximum recommended human dose. Hepatic and renal toxicities were only observed at high doses in repeat-dose toxicology studies conducted in rats and dogs, with greater incidence and severity in studies of longer duration. Hepatic toxicity was characterized by less than 2-fold increases in the liver enzymes (i.e., ALT in rats and dogs; AST in rats and ALP in dogs) with increased liver-to-body weight ratios and cytoplasmic swelling/vacuolation of hepatocytes at the highest doses evaluated. More severe histopathological signs of liver pathology were also observed in dogs, including centrilobular scarring and hepatocellular degeneration, necrosis, and hemorrhage. Renal toxicity was also present and manifested differently in rats and dogs. Renal toxicity in dogs was observed at doses greater than 0.88 mg/kg/day and was characterized by isolated incidences of chronic interstitial nephritis in the 3-month study with additional signs of tubular abnormalities/degeneration and cortical calcinosis in the 1-year study. In rats, renal toxicity was primarily characterized by treatment-related increases in the incidence of chronic progressive nephropathy and hydronephrosis at doses greater than 2.5 mg/kg/day in the 28-day and 3-month studies.

Additional treatment-related findings consistent with dehydration that may or may not be related to renal toxicity, included increased urea nitrogen, electrolyte imbalances (Na^+ , Cl^- , and Ca^{2+}), increased urine specific gravity with decreased urine volume, and salivary gland atrophy. Likely related to drug-induced decreased lacrimation, there was severe ocular toxicity, characterized by keratitis and corneal erosion/ulceration, observed in the 28-day rat study at the MD and HD in males and at all doses evaluated in females. Collectively, the existing toxicology studies suggest the potential for adverse effects that increase with duration of treatment. The 90-day rat study does not provide adequate safety margins based on AUC; although some of the toxicities noted

may well be more related to C_{max} and the physiological changes that occur with this drug following only once a day dosing. If the clinical team recommends post-marketing clinical studies of a duration longer than 14 days, we recommend that the preGLP rat 90-day toxicology study be repeated with a dosing regimen that more closely mimics the clinical setting.

The genetic toxicology of lofexidine was evaluated via two in vitro assays, an Ames bacterial reverse mutation assay and a L5178Y/TK[±] mouse lymphoma assay, and one in vivo rat bone marrow erythrocyte micronucleus test. The Ames assay and the micronucleus test were negative; however, a positive result was observed in the mouse lymphoma assay after 4 hours of exposure to 40 mcg/mL, the highest non-cytotoxic dose evaluated with metabolic activation. The positive result was characterized by an increase in the number of small colonies, suggesting a clastogenic mode of action. Per current FDA guidance, when one of the three standard studies suggest a positive response, a fourth study is recommended to contribute to the weight of evidence for overall concern. As such, an in vivo comet assay testing stomach and liver has been requested and is underway. This study is still pending and, if the NDA is deemed approvable otherwise, may be submitted post marketing.

Two carcinogenicity studies, a 2-year study in rats and an 18-month study in mice, were submitted in the Application; however, upon review these studies and consultation with the Executive Carcinogenicity Assessment Committee, these studies were deemed inadequate to support the safety of lofexidine with respect to carcinogenicity.

The reproductive toxicology of lofexidine was assessed via one new GLP study and four older non-GLP studies in rabbits and rats. A GLP toxicokinetics study was also conducted in rabbits dosed from GD 6 through GD 19 and TK data are available from the GLP pre- and postnatal development study to put these findings into perspective. In two non-GLP studies, one in rabbits and one in rats, no adverse effects of oral lofexidine administration were observed with respect to fertility parameters examined. However, in the rat study, no evaluations of sperm or male reproductive organs were performed, and maternal toxicity was not clearly demonstrated, suggesting that it was not dosed adequate to support the safety of lofexidine with respect to fertility. The rabbit study suggested adverse effects at exposure below the human exposures at the maximum recommended human daily dose. In two non-GLP embryofetal studies, one in rabbits and one in rats, no evidence of teratogenicity was observed in either study, but embryofetal toxicities along with maternal toxicities were observed. In the rabbit embryofetal study maternal toxicity was observed, but post-implantation losses were increased in the absence of maternal toxicity. In the GLP pre- and post-natal development study, increased pup mortality at all doses and developmental toxicities characterized by decreased pup body weights and body weight gains, developmental delays, and fertility impairments in F₁ offspring were observed at doses that also produced maternal toxicity characterized by sedation, and decreased body weight gains. To better understand the mechanism mediating these adverse effects, a cross-fostering study could be completed. Another option to obtain better safety margins may be to repeat the studies with a dosing regimen more akin to the clinical dosing regimen

(more than once a day dosing) to minimize physiological fluctuations in the animals. The existing toxicokinetic data suggest far lower exposure margins (generally less than 1) compared to the margins estimated based on body surface area. Although some of these adverse effects may be due to maternal toxicity, the effects are treatment related and we cannot rule out a direct or indirect effect. Given the adverse effects noted at what appear to be clinically relevant exposures, these studies raise concerns for potential treatment of pregnant women. Granted, the animal studies were dosed once a day rather than the proposed four times a day dosing of the drug in the clinic which can result in different exposure profile (higher C_{max} in the animals compared to humans). However, as detoxifying pregnant women is rarely done (as per clinical review team), use of this drug in this patient population is not likely. No further studies are recommended at this time. However, should use of lofexidine be demonstrated in this population, consideration of additional reproductive (b) (4) toxicology studies may be warranted.

The human equivalent dose (HED) using body surface area-based allometry at the NOAEL for every toxicology study exceeded maximum recommended human dose (MRHD) of 2.88 mg/day. Although toxicokinetics evaluations were not performed in any of the non-GLP toxicology studies, toxicokinetics data were available from at least one study for rabbits (dams only), rats, and dogs, allowing for safety margins to be calculated comparing the exposure at the NOAEL's of toxicology studies to the human exposure at the MRHD. The safety margins based on exposure were approximately 10- to-20-fold more conservative than the HED-based margins for rats and dogs and approximately 500-fold more conservative for rabbits. The rat was the most sensitive species with respect to general toxicology, with an approximate exposure margin of 0.5x at the MRHD. In the pivotal GLP 28-day rat repeat-dose toxicology study, no NOAEL was established in females due to the presence of keratitis with corneal erosion/ulceration in one of ten LD rats; however, the MD can be considered an acceptable LOAEL for both sexes, providing a 17-fold HED-based safety margin and a 3-fold exposure based safety margin. Both the HED-based and exposure-based safety margins for the dog repeat-dose toxicology studies were greater than one. The HED-based safety margins with respect to reproductive toxicology are all greater than one; however, the exposure-based margins are all significantly less than one, suggesting that there may be risks associated with lofexidine treatment during pregnancy. These risks have been incorporated into the drug label in accordance with PLLR.

In summary, although there is considerable human experience with lofexidine to characterize the safety profile, re-evaluation of the existing toxicology studies taking into consideration actual exposure data rather than body surface area suggest the potential for adverse effects at or below exposure in humans, which could be explained by exaggerated pharmacological effects of sedation, reduced food consumption, hypotension and decreased tissue oxygenation, alterations in water balance, and decreased lacrimal secretions. Liver and kidney function were monitored in the clinical studies suggesting that the clinical data can inform adverse effects noted in these tissues. The adverse effects noted in the reproductive and developmental toxicity studies, which suggest no safety margin based on human exposure (AUC)

comparisons, may also be related to similar exaggerated pharmacology and elevated C_{max} values above the human exposures because the animals were dosed once a day whereas humans are dosed four times a day. In fact, the safety margins with respect to C_{max} for these studies were approximately 10-fold and 30-fold higher than the exposure margins in rats and dogs, respectively. Nonetheless, the toxicology study dosing regimens do not mimic the clinical dosing regimen and therefore the results likely overestimate the risk for a drug which has a significant impact on blood pressure and sympathetic tone. Thus, overall safety profile of this drug is largely based on the human experience, which is considerable given the history of this drug back to the late 1970s.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 209229 may be approved, in part based on clinical experience, with the recommended labeling and postmarketing requirements.

1.3.2 Additional Nonclinical Recommendations

If approved this cycle, the following postmarketing requirements (PMRs) are recommended:

1. Conduct an in vivo comet assay testing lofexidine in the liver and stomach.
2. Conduct a pharmacokinetic study in the rat to characterize the plasma levels of lofexidine and the lofexidine metabolites LADP (N-(2-aminoethyl)-2-(2,6-dichlorophenoxy)propenamide), LDPA (2-(2,6-dichlorophenoxy)propionic acid), and 2,6-DCP (2,6-dichlorophenol) using a validated assay.
3. Conduct a juvenile animal study in rats from PND 36 to PND 90 to support pediatric drug development in children aged 12 to 17 years. The study will evaluate the effect of the drug on growth and development, reproductive ^{(b) (4)}, bone development, and the central nervous system.
4. Conduct a juvenile animal study in rats from PND 7 to 90 to support pediatric drug development in children and neonates. The study will evaluate the effect of the drug on growth and development, reproductive ^{(b) (4)}, bone development, and the central nervous system.
5. Conduct a juvenile toxicology in rats to evaluate the impact of lofexidine on early neuronal development during peak synaptogenesis to support pediatric studies in neonates and children under the age of 3.
6. Conduct a fertility and early embryonic development study in rats testing lofexidine administration to males and include histopathology of the testes and sperm assessments (count, motility, and morphology).

7. Conduct a 90-day GLP repeat-dose toxicology study in the rat testing lofexidine HCl to establish a NOAEL to support clinical studies that are longer than 14-days in duration. To avoid the potential confounding impact of C_{max}-induced fluctuations in physiology, which could impact the NOAEL, dose the animals several times a day, as feasible, to mimic the clinical setting.

1.3.3 Labeling

The table below contains the draft labeling proposed by the Applicant with the changes proposed by this Reviewer and the rationale for the proposed changes. The labeling recommendations below have not been discussed with the entire review team or the Applicant. The reader is referred to the final action letter for final drug product labeling.

Table 1. Labeling Review

Applicant's Proposed Labeling	Reviewer's Proposed Changes	Rationale for Changes
<p>HIGHLIGHTS OF PRESCRIBING INFORMATION</p> <p>-----INDICATIONS AND USAGE----- LOFEXIDINE is a (b) (4) adrenergic (b) (4) agonist indicated for ...</p>	<p>HIGHLIGHTS OF PRESCRIBING INFORMATION</p> <p>-----INDICATIONS AND USAGE----- LOFEXIDINE is a central alpha-2 adrenergic agonist indicated for ...</p>	<p>Established Pharmacologic Class should be the same as that for clonidine: Central alpha-2 adrenergic agonist</p>
<p>8 USE IN SPECIFIC POPULATIONS</p> <p>8.1 Pregnancy</p> <p><u>Risk Summary</u></p> <p>The safety of LOFEXIDINE in pregnant women has not been established. (b) (4)</p> <p>(b) (4)</p>	<p>8 USE IN SPECIFIC POPULATIONS</p> <p>8.1 Pregnancy</p> <p><u>Risk Summary</u></p> <p>The safety of LOFEXIDINE in pregnant women has not been established. In animal reproduction studies, oral administration of LOFEXIDINE during organogenesis to pregnant rats and rabbits caused a reduction in fetal weights, increases in fetal resorptions, and litter loss at exposures below that in humans. When oral lofexidine was administered at the beginning of organogenesis through lactation, increased stillbirths, increased litter loss were noted along with decreased viability and lactation indices. The offspring exhibited delayed sexual maturation, delayed auditory startle, and surface righting. These effects occurred at exposures below that in humans. [see <i>Animal Data</i>].</p> <p>The background risk of major birth defects and miscarriage for the</p>	<p>Removed the (b) (4) added pre-postnatal/developmental findings, and qualitatively described exposure margins</p> <p>The last sentence proposed by the Applicant is older CFR language and should be removed.</p> <p>Defer to MHT regarding opening sentence. The remaining three</p>

<p>The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies carry some risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects in the U.S. general population is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.</p>	<p>indicated population is unknown. All pregnancies carry some risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects in the U.S. general population is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.</p>	<p>sentences are standard and should be included.</p>
<p><u>Data</u> <i>Animal Data</i></p> <div style="background-color: #cccccc; width: 100%; height: 150px; display: flex; align-items: center; justify-content: center;"> (b) (4) </div>	<p><u>Data</u> <i>Animal Data</i></p> <p>Increased incidence of resorptions, decreased number of implantations, and a concomitant reduction in the numbers of fetuses when pregnant rabbits were orally administered lofedidine hydrochloride during organogenesis (from GD 7 to 19) at a daily dose of 5.0 mg/kg/day (approximately 0.08 times the maximum recommended human dose [MRHD] of 2.88 mg on an AUC basis). Maternal toxicity evidenced by increased mortality was noted at the highest tested dose of 15 mg/kg/day (approximately 0.4 times the MRHD on an AUC basis).</p>	<p>Corrected exposure margin to be based on AUC rather than body surface area.</p> <p>Per PLLR, added dosing period and maternal toxicities. Data Source: USWM-LX0-TOX-0010</p>
<div style="background-color: #cccccc; width: 100%; height: 150px; display: flex; align-items: center; justify-content: center;"> (b) (4) </div>	<p>Decreased implantations per dam and decreased mean fetal weights were noted in a study in which pregnant rats were treated with oral lofedidine hydrochloride during organogenesis (from GD 7 to 16) at a daily dose of 3.0 mg/kg/day (approximately 0.9 times the MRHD on an AUC basis). This dose was associated with maternal toxicity (decreased body weight gain and mortality). No malformation or evidence of developmental toxicity were evident at 1.0 mg/kg/day (approximately 0.2 times the MRHD on an AUC basis).</p>	<p>Data from Study USWM-LX0-TOX-0018</p>
<div style="background-color: #cccccc; width: 100%; height: 50px; display: flex; align-items: center; justify-content: center;"> (b) (4) </div>	<p>A dose dependent increase in pup mortality was noted in all doses of lofedidine hydrochloride administered orally to pregnant animals from GD 6 through lactation at exposure less</p>	<p>Data from Study USWM-LX0-TOX-0003</p>

<p>(b) (4)</p>	<p>than the human exposure based on AUC comparisons (b) (4) at doses higher than (b) (4) mg/kg/day (approximately 0.2 times the MRHD on an AUC basis) resulted in total litter loss and maternal toxicity (piloerection, decreased body weight gain). (b) (4) mg/kg/day (approximately 0.6 times the MRHD on an AUC basis), increased stillbirths as well as decreased viability and lactation indices were reported. Surviving offspring exhibited lower body weights, developmental delays and increased delays in auditory startle at a dose of (b) (4) mg/kg/day. Sexual maturation was delayed in male offspring (preputial separation) at (b) (4) mg/kg/day and in female offspring (vaginal opening) at (b) (4) mg/kg/day or higher.</p>	
<p>8.2 Lactation Risk Summary</p> <p>There is no information regarding the presence of LOFEXIDINE or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Caution should be exercised when LOFEXIDINE is administered to a nursing woman.</p> <p>The developmental and health benefits should be considered along with the mother's clinical need for LOFEXIDINE and any other potential adverse effects on breast-fed children from LOFEXIDINE or from the underlying maternal condition.</p>	<p>8.2 Lactation Risk Summary</p> <p>There is no information regarding the presence of LOFEXIDINE or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Caution should be exercised when LOFEXIDINE is administered to a nursing woman.</p> <p>The developmental and health benefits should be considered along with the mother's clinical need for LOFEXIDINE and any other potential adverse effects on breast-fed children from LOFEXIDINE or from the underlying maternal condition.</p>	<p>Defer to clinical and maternal health teams. There are no animal data.</p>

	<p>8.3 Females and Males of Reproductive Capacity</p> <p>In animal studies that included some fertility endpoints, lofexidine decreased breeding rate and increased resorptions at exposures below human exposures. The impact of lofexidine on male fertility has not been adequately characterized in animal studies [see <i>Impairment of Fertility (13.1).</i>]</p>	<p>Section added due to adverse effects noted in the animal studies.</p>
<p>12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action</p> <p>LOFEXIDINE is a (b) (4) adrenergic (b) (4) agonist that binds to receptors on adrenergic neurons. This reduces the release of norepinephrine and (b) (4)</p>	<p>12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action</p> <p>LOFEXIDINE is a central adrenergic alpha-2 receptor agonist that binds to receptors on adrenergic neurons. This reduces the release of norepinephrine and decreases sympathetic tone.</p>	<p>Established Pharmacologic Class: Central alpha-2 adrenergic agonist</p> <p>The removed statement regarding the mechanism of action is hypothetical and promotional.</p> <p>These data are not clinically useful.</p>
<p>13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p>	<p>13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p><u>Carcinogenesis</u> No adequate long-term animal studies have been completed to evaluate the carcinogenic potential of lofexidine.</p> <p><u>Mutagenesis</u> Lofexidine tested positive in the in vitro mouse lymphoma assay. Lofexidine tested negative in the in vitro bacterial reverse mutation assay (Ames assay) and the in vivo rat micronucleus assay.</p>	<p>Heading added</p> <p>(b) (4) and therefore were omitted from labeling.</p> <p>Heading added Placed positive study result first.</p> <p>Removed (b) (4)</p> <p>Removed reference to (b) (4)</p>

(b) (4)		
	<p>Impairment of Fertility In a female fertility study in rabbits, fertility was not adversely impacted by administration of lofexidine hydrochloride up to 6.4 mg/kg/day (approximately 0.1 times the MRHD of 2.88 mg on an AUC basis) when administered orally to female rabbits starting 2 weeks prior to mating and through gestation and lactation. However, decreased breeding rate and higher post-implantation loss was observed at this dose, which correlated with higher resorptions and reduced litter size. Maternal toxicity, which included increased mortality rate, reduced body weight gain, and moderate sedation was observed at 6.4 mg/kg/day. No assessments of sperm or reproductive organs were performed in this study. The NOAEL for female fertility was 6.4 mg/kg/day and the NOAEL for female-mediated developmental parameters was 0.4 mg/kg/day (approximately 0.005 times the MRHD on as AUC basis).</p> <p>In a fertility study in rats, fertility was unaffected by administration of lofexidine up to 0.88 mg/kg/day (approximately 0.2 times the MRHD on an AUC basis) via diet to male and female rats prior to mating and to the dams through gestation and lactation. No evidence of maternal toxicity was observed. However, no assessments of sperm or reproductive organs were performed in this study.</p> <p>Reduced testes, epididymis, and seminiferous tubule weights as well as delayed sexual maturation of males and females and decreases in the number of corpora lutea and implantations after mating were noted in offspring of pregnant rats administered lofexidine hydrochloride orally to from GD 6 through lactation at exposure less than the human exposure based on AUC comparisons.</p>	<p>Heading added</p> <p>Removed references to (b) (4)</p> <p>To conform to PLLR, added more details of the studies, including dosing period, maternal toxicities, and any shortcomings of the study.</p> <p>Data Source: USWM-LX0-TOX-0017</p> <p>Data Source: USWM-LX0-TOX-0016</p> <p>Data Source: USWM-LX0-TOX-0003</p>
(b) (4)		(b) (4)

(b) (4)		(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number

21498-08-8

Generic Name

Lofexidine HCl

Code Name

(b) (4); Ba 168; RMI 14,042A

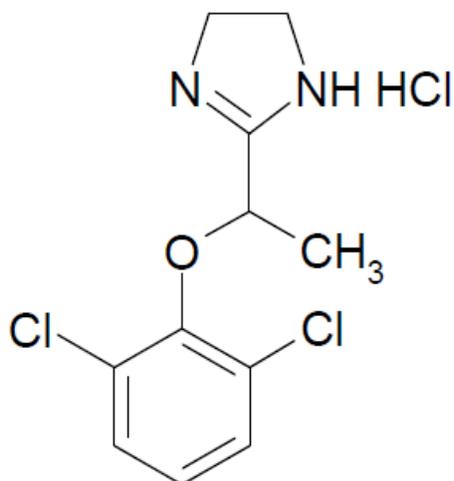
Chemical Name

2-[1-(2,6-dichlorophenoxy)ethyl]-4,5-dihydro-1*H*-imidazoline monohydrochloride

Molecular Formula/Molecular Weight

C₁₁H₁₃Cl₃N₂O / 295.6 g/mol

Structure or Biochemical Description



Pharmacologic Class

Alpha_{2A}-Adrenergic Receptor Agonist [MoA]

Central alpha-2 adrenergic agonist [EPC]

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND#	Drug Name / Dosage Form	Status	Division	Indication	Status Date	Sponsor
47857	Lofexidine / Oral Tablet	Active	DAAAP	To relieve symptoms in patients undergoing opiate detoxication	4/28/1995	US WorldMeds, LLC

NDA#	Drug Name / Dosage Form	Div	Marketing Status	Status Date	Indication	Company
(b) (4)						

2.3 Drug Formulation

LUCEMYRA will be formulated as round, convex-shaped peach colored film-coated 0.18 mg lofexidine tablets debossed with "LFX" on one side and "18" on the reverse. The quantitative composition of the tablet formulation is shown below:

Table 2: Quantitative Composition of Lofexidine Tablets, 0.18 mg (base)

Component	Percentage (%)	Quantity (mg)	Maximum daily intake (mg)	Comments
Lofexidine HCl	(b) (4)	0.20 (salt)	3.20	
Lactose (b) (4)		92.60	1480	Within levels of an approved product.
Citric acid (b) (4)		12.30	197	Within levels of an approved product.
Microcrystalline cellulose		5.7	91.2	Within levels of an approved product.
Calcium stearate		1.4	22.4	Within levels of an approved product.
Povidone (b) (4)		1.1	17.6	Within levels of an approved product.
Sodium lauryl sulfate		0.70	11.2	Within levels of an approved product.
(b) (4)				
Opadry OY-S-9480	(b) (4)		(b) (4)	Although not in IID, the constituents of Opadry OY-S-9480 are within levels of an approved product.
(b) (4)				

2.4 Comments on Novel Excipients

The formulation contains no novel excipients as all excipients are present at greater levels in FDA approved products (Table 2). Qualitative composition of Opadry (b) (4) OY-S-9480 was provided (Table 2). Although the quantitative chemical composition was not provided, the levels of the ingredients of the Opadry (b) (4) OY-S-9480 are acceptable even if each component is present at a level equal to the total mass of Opadry (b) (4) OY-S-9480.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance

For a drug product with a maximum daily dose of 3.2 mg (salt), the ICH Q3A(R2) qualification threshold is NMT 0.15% (4.8 mcg) or 1.0 mg, whichever is lower. The drug substance specifications (Table 3) for impurities and residual solvents in LUCEMYRA are set in accordance with ICH Q3A(R2) and Q3C with the exception of the following impurities (b) (4)

The specifications for the related substance impurities, (b) (4)

The Sponsor proposed a specification of NMT (b) (4) ppm for the residual solvent (b) (4) which is not classified by ICH Q3C. The proposed specification corresponds to a maximum daily intake of (b) (4) mcg/day at the MTDD of 3.2 mg/day lofexidine HCl. (b) (4)

(b) (4) No test-article related findings were observed at the LD, which is designated by this Reviewer to be the NOEL.

To convert from a mg/m³ dose to mg/kg the following calculations were performed¹:

Continuous exposure =



Daily Dose (mg/kg) =

PDE = NOEL X Weight Adjustment / F1 x F2 x F3 x F4 x F5		
Modifying Factors		
F1	Extrapolation between species	5 (rat)
F2	Variability between individuals	10
F3	Accounting for toxicity studies of short-term duration	1 (3-month study) As the proposed indication is acute use an increased factor was not warranted
F4	Presence of severe toxicity	1 Severe toxicities have not been reported with (b) (4)
F5	If a NOEL level was not established	1 A NOEL was established in the 3-month inhalational toxicity study
PDE	(b) (4)	Exposure Margin of (b) (4)

The Sponsor has proposed a specification of NMT (b) (4) ppm for the solvent-related genotoxic impurity (b) (4), which corresponds to a maximum daily intake of (b) (4) mcg/day at the MTDD of 3.2 mg/day lofexidine HCl. This level exposure is acceptable as it is below the 120 mcg/day threshold specified in ICH M7 for potentially genotoxic impurities associated with an acute indication with a lifetime exposure of less than 1 month. It is also below a conservative qualification threshold of 1.5 mcg/day.

¹ Based on calculations in ICH Q3C(R5): *Impurities: Guideline for Residual Solvents*

Table 3: Drug Substance Specifications for LUCEMYRA

Impurity	Structure	Proposed Specification	Reviewer's Comment
(b) (4)			<p>Exceeds ICH Q3A(R2) qualification threshold of NMT 0.15% Acceptable. In silico analysis was negative for the mutagenicity endpoint (Derek and Leadscope). (b) (4)</p>
			<p>Exceeds ICH Q3A(R2) qualification threshold of NMT 0.15% Acceptable. In silico analysis was negative for the mutagenicity endpoint (Derek and Leadscope). (b) (4)</p>
			<p>Acceptable. Within ICH Q3A(R2) qualification threshold. In silico analysis was negative for the mutagenicity endpoint (Derek and Leadscope).</p>
			<p>Acceptable. Within ICH Q3A(R2) identification and qualification thresholds.</p>
			<p>Acceptable. Within Q3C permissible daily exposure.</p>
			<p>Acceptable. Q3C does not have permissible daily exposure level as it states that there is no adequate toxicological data. Not a known carcinogen. (b) (4) Specification results in maximum daily exposure of (b) (4) mcg/day</p>
			<p>Acceptable. Within Q3C permissible daily exposure.</p>
			<p>Acceptable. Within Q3C permissible daily exposure.</p>
			<p>Acceptable. Within ICH M7 levels for a known genotoxicant or carcinogen.</p>

Drug Product

The ICH Q3B(R2) qualification threshold for a drug with a maximum daily dose of 3.2 mg (salt) is 1.0% (32 mg) or 50 mcg, whichever is lower. The drug substance specifications (Table 34) for impurities in LUCEMYRA are set in accordance with ICH Q3A(R2). The drug product specification for the related substance degradant, (b) (4), of NMT (b) (4)% and the specification for any single unspecified impurity of NMT (b) (4)% are both acceptable in accordance with ICH Q3B(R2). The specification for the related substance degradant, (b) (4) of NMT (b) (4)%, on the other hand, exceeds ICH Q3B(R2) qualification threshold of NMT 1.0%;

(b) (4)

A risk analysis for heavy metals was conducted per ICH Q3D, which concluded that the risk of heavy metals is low and therefore controls for elemental impurities were not considered necessary. This risk analysis was deemed acceptable by Dr. Venkateswara Pavuluri (see Chemist review for additional details).

Table 4: Drug Product Specifications for LUCEMYRA

Impurity	Structure	Proposed Specification	Reviewer's Comment
(b) (4)			Exceeds ICH Q3B(R2) qualification threshold of NMT 1% Acceptable. In silico analysis was negative for the mutagenicity endpoint (Derek and Leadscope)
			Acceptable. Within ICH Q3B(R2) qualification thresholds. In silico analysis was negative for the mutagenicity endpoint (Derek and Leadscope).
			Acceptable. Within ICH Q3B(R2) identification and qualification thresholds.

2.6 Proposed Clinical Population and Dosing Regimen

The Applicant has proposed two indications for LUCEMYRA: (1) mitigation of symptoms associated with opioid withdrawal and (2) facilitation of completion of opioid discontinuation treatment. The proposed dosing regimen is for patients to take three or four 0.18 mg (base) tablets orally four times daily for seven days, yielding a maximum daily dose of 2.88 mg base/day (16 tablets/day).

2.7 Regulatory Background

The Applicant has submitted NDA 209229 as a 505(b)(1) application. The pivotal clinical studies conducted by the Applicant to support this application were performed under IND 47857. The Applicant submitted nonclinical studies conducted prior to GLPs to support the proposed indication. In addition, they cited the significant human experience with lofexidine to support the clinical development program.

The current Applicant met with the Agency on several occasions to discuss the nonclinical, clinical and regulatory requirements for lofexidine. The Division recommended that several new studies, be completed to confirm the older study findings. Specifically, the following nonclinical GLP studies were requested for the NDA at the End-of-Phase 2 meeting held on November 10, 2003:

- Pre- and post-natal developmental reproductive toxicology
- *In vitro* (hERG assay) and *in vivo* (ECG) cardiovascular safety pharmacology
- Standard battery of genetic toxicology
- Repeat-dose toxicology of adequate duration to cover the indicated clinical use
- Qualification of any novel excipients, any impurities or degradation products that exceed ICH guidelines, and any human specific metabolites
- Comparison of the nonclinical ADME data with the clinical ADME data

Further clarification regarding these requirements was provided at a Type C-Guidance meeting on February 5, 2009 and a Pre-NDA meeting on September 24, 2015.

3 Studies Submitted

3.1 Studies Reviewed

Primary/Secondary Pharmacology

USWM-LX0-PHK-0010: In Vitro Pharmacology and ADME Tox Study of Lofexidine HCL reference standard (non-GLP)

USWM-LX0-PHA-0005: The In Vitro Pharmacology of Lofexidine HCL and Clonidine (non-GLP)

USWM-LX0-PHA-0006: The In Vitro Pharmacology Study of LADP, LDPA and 2,6-DCP (non-GLP)

USWM-LX0-PHA-0007: Review of the In Vitro Studies to Assess the Efficacy, Side-Effect and Abuse Potential of Lofexidine (non-GLP)

Safety Pharmacology

USWM-LX0-PHA-0001: A Pharmacological Assessment of the Effect of Lofexidine Hydrochloride on the Outward Potassium Current Generated by h-ERG Expressing Chinese Hamster Ovary Cells (GLP)

USWM-LX0-PHA-0002: Evaluation of the Cardiovascular and Respiratory Safety of Orally Administered Lofexidine Hydrochloride in Beagle Dogs (GLP)

Pharmacokinetics

USWM-LX0-PHK-0001: The Pharmacokinetics of “³H-Ba 168” (lofexidine) in Rats and Dogs (non-GLP)

USWM-LX0-PHK-0002: The Metabolic Fate of 2-Ethyl [1-2,6 dichlorophenoxy] Imidazoline Hydrochloride (Ba 168) in Rats, Dogs and Male Rhesus Monkeys (non-GLP)

USWM-LX0-PHK-0004: Determination of the Blood Cell Binding of Lofexidine HCl in Human, Rat, and Dog Blood (non-GLP)

USWM-LX0-PHK-0005: Determination of the Plasma Protein Binding of Lofexidine HCl in Human, Rat, and Dog Plasma

USWM-LX0-PHK-0003: Amount and Structure of Eliminated Substances After Dosage with ³H – Ba 168 in the Dog, Rabbit, and Rat (non-GLP)

USWM-LX0-PHK-0009: Metabolic Stability and Metabolite Characterization of Lofexidine Hydrochloride in Human Liver Microsomes and Recombinant Human CYP Enzymes (non-GLP)

Repeat-Dose Toxicology

USWM-LX0-TOX-0005: Lofexidine Hydrochloride: A 4 Week Oral Toxicity Study in Rats (GLP)

USWM-LX0-TOX-0006: Lofexidine: Sub-Acute (90 Day) Oral Toxicity Study in Rats (non-GLP)

USWM-LX0-TOX-0019: Subacute Oral Toxicity Study with RMI 14,042A in Dogs (non-GLP)

USWM-LX0-TOX-0020: Chronic Oral Toxicity Study with Lofexidine in Dogs (non-GLP)

Genetic Toxicology

USWM-LX0-TOX-0009: Mutagenicity Evaluation of Lofexidine in the Ames Salmonella/Microsome Plate Test (GLP)

USWM-LX0-TOX-0001: In Vitro Mammalian Cell Gene Mutation Test (L5178y/TK⁺/Mouse Lymphoma Assay) (GLP)

USWM-LX0-TOX-0002: Rat Bone Marrow Erythrocyte Micronucleus Test Following Oral Administration of Lofexidine Hydrochloride (GLP)

Carcinogenicity

USWM-LX0-TOX-0014: Chronic Toxicity and Carcinogenicity Study of Lofexidine in Rats (non-GLP)

USWM-LX0-TOX-0015: Carcinogenicity Evaluation of Lofexidine in Mice (non-GLP)

Reproductive Toxicology

USWM-LX0-TOX-0017: Testing the Fertility and Breeding Capacity of New Zealand Rabbits Given Ba 168 by Stomach Tube (non-GLP)

USWM-LX0-TOX-0018: Teratology Study with RMI 14,042A in Rats (non-GLP)

USWM-LX0-TOX-0010: Teratologic Study with RMI 14,042A in Rabbits (non-GLP)

USWM-LX0-TOX-0004: Lofexidine Hydrochloride: an Oral Toxicokinetic Study in Pregnant Rabbits (GLP)

USWM-LX0-TOX-0016: Reproduction Study with Lofexidine in Rats (non-GLP)

USWM-LX0-TOX-0003: Lofexidine Hydrochloride: Pre- and Post-Natal Development Study in Rats, Including Maternal Function (GLP)

3.2 Studies Not Reviewed

Pharmacodynamic Drug Interactions

USWM-LX0-PHA-0003: Evaluation of the Interaction Between Lofexidine Administered Orally and Cocaine Administered Intraperitoneally in Rats: Effects on Mortality (GLP)

USWM-LX0-PHA-0004: Evaluation of the Interaction between Lofexidine Administered Orally and Cocaine Administered Intravenously in Freely Moving Beagle Dog: Effects of Lofexidine on Cocaine-Induced Hemodynamic and ECG Responses (GLP)

Pharmacokinetics

USWM-LX0-PHK-0006: P-gp Substrate and Inhibitor Assessment of Lofexidine in a Caco-2 Cell Monolayer System (non-GLP)

USWM-LX0-PHK-0007: Determination of the Potential for Lofexidine HCl to Induce the Activities of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, and CYP3A4 in Human Hepatocytes (non-GLP)

USWM-LX0-PHK-0008: Determination of the Potential for Lofexidine HCl to Inhibit the Activities of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in Human Liver Microsomes (non-GLP)

USWM-LX0-PHK-0012: In Vitro Evaluation of LADP, LDPA and 2,6-DCP as Inducers of Cytochrome P450 Expression in Cultured Human Hepatocytes (non-GLP)

USWM-LX0-PHK-0011: In Vitro Evaluation of LADP, LDPA and 2,6-DCP as Inhibitors of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes (non-GLP)

USWM-LX0-PHK-0013: Assessment of Lofexidine as an Inhibitor of Human BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 and BSEP Mediated Transport (non-GLP)

Repeat-Dose Toxicology

USWM-LX0-TOX-0007: The Sub-Acute Toxicity of Ba 168 in Wistar Rats (Oral Administration) (non-GLP)

Genetic Toxicology

USWM-LX0-TOX-0008: Bacterial Reverse Mutation Assay (non-GLP: not reviewed because a GLP Ames bacterial reverse mutation assay [USWM-LX0-TOX-0009] was submitted and reviewed)

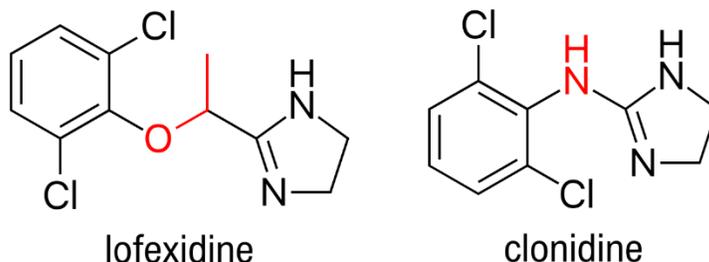
3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

Lofexidine is a central alpha-2 adrenergic agonist with many structural and pharmacological similarities to the FDA approved alpha-2 adrenergic agonist clonidine (see structures below)



The Applicant conducted *in vitro* binding and functional activity assessments to evaluate and compare the primary pharmacological targets of lofexidine and clonidine (Table 5). Both lofexidine and clonidine exhibited greatest affinity for the alpha-2A adrenergic receptor and greatest functional potency at the alpha-2C adrenergic receptor with alpha-2A adrenergic receptors showing the second greatest functional potency. Both molecules exhibited substantially lower (but not negligible) affinity and functional potency for the alpha-2B adrenergic receptor. In contrast to clonidine, lofexidine also exhibited affinity for the 1A, 1D, 2C, and 7 subtypes of serotonin receptors but only showed functional activity at 5-HT_{1A} and 5-HT_{1D} receptors. An anomalous functional activity result was observed for both lofexidine and clonidine at the alpha-1A adrenergic receptor, with each exhibiting an EC₅₀ value below 1 nM. These data points were omitted by the Applicant from Table 5 because these results were considered erroneous as the EC₅₀ for the functional activity assessment of the alpha-1A adrenergic receptor was about 3 orders of magnitude lower than the K_i measured in the binding assay for both compounds. Although both clonidine and lofexidine are generally considered to be alpha-2 adrenergic agonists as these receptors appear to mediate their intended pharmacological effects, at least one independent *in vitro* assessment of the functional activity of clonidine among adrenergic receptor subtypes has found roughly equivalent potency at the alpha-1A and alpha-2A adrenergic receptors (Gil et al., 2009). Based upon these *in vitro* results, the primary pharmacological effects of lofexidine can be expected to be similar to those of clonidine.

Table 5: Comparative in vitro Binding and Functional Activity Profiles of Lofexidine and Clonidine for Adrenergic, Serotonergic, and Dopaminergic Receptors

	ADRENOCEPTORS				5-HYDROXYTRYPTAMINE (5-HT) SEROTONIN										DOPAMINE	
	α_{2A}	α_{2B}	α_{2C}	α_{1A}	1A	1B	1D	2A	2B	2C	4e	5a	6	7	D ₁ D ₃ D _{4,4} D ₅	D _{2S}
Lofexidine																
Ki (nM)	7.2	137	12	287	45	I	513	I	I	510	I	I	I	405	I	I
Selec α_{2A}				40	6		71			71				56		
EC ₅₀ (nM)	4.9	88	0.86	n/a	310	I	57	I	I	I	NT	NT	NT	I	NT	I
Selec α_{2A}					63		12									
Clonidine																
Ki (nM)	20	113	126	1003	I	I	I	NT	I	I	I	I	I	I	NT	I
Selec α_{2A}				50												
EC ₅₀ (nM)	15	420	5.1	n/a		I		I	I		NT	NT	NT	I	NT	I
Selec α_{2A}																

I = Inactive at 10^{-5} M (<50% displacement) or value greater than 1000 nM. Selec α_{2A} = Selectivity versus α_{2A} -adrenoceptors. NT = Not tested. N/A not applicable. Neither lofexidine nor clonidine exhibited affinity for the monoamine transporter.

4.2 Secondary Pharmacology

The potential for off-target pharmacological effect of lofexidine as well as its three major human metabolites, LADP, LDPA, and 2,6-DCP, was evaluated by assessing their binding affinity at 10,000 nM to a screen of 44 receptors, including a variety associated with CNS activities, some ion channel molecules, and enzymes associated with inflammatory responses and smooth muscle contractility. Lofexidine exhibited affinity to adrenergic, serotonergic, dopaminergic and kappa-opioid receptors as well as at the monoamine oxidase and serotonin transporter enzymes (Table 6). Very high binding inhibition was observed for lofexidine at alpha-1A and alpha-2A adrenergic receptors as well as at 5-HT_{1A} receptors. As discussed above, the primary pharmacology binding and functional assessment of lofexidine revealed that although significant binding was observed at the 5-HT_{1A} receptor, functional potency at this target was relatively low (Table 5). Moderate binding affinity was demonstrated at the 1B, 2A, and 2B serotonin receptor subtypes as well as at D_{2S} receptors. Low binding affinity was demonstrated at kappa-opioid receptors as well as the monoamine oxidase-A and serotonin transporter enzymes. Analysis of the secondary pharmacology of LDPA and 2,6-DCP did not reveal any targets with significant binding affinity; however, moderate affinity for the serotonin transporter, 73.4% binding inhibition, was observed. A follow up evaluation of the affinity of LDPA for the serotonin transporter as well as several subtypes of serotonin receptors revealed no significant binding affinity at any of these targets.

Table 6: Positive Results from Lofexidine Secondary Pharmacology Binding Screen of 44 Receptors

Receptor Name	% Inhibition at 10,000 nM Lofexidine HCl
α_{1A}	97.9%
α_{2A}	98.6%
5-HT _{1A}	98.6%
5-HT _{1B}	53.8%
5-HT _{2A}	48.1%
5-HT _{2B}	72.2%
D _{2S}	82.3%
κ (KOP)	40.5%
MAO-A	38.6%
5-HT transporter	25.8%

α = alpha adrenergic receptor; 5-HT = 5-hydroxytryptamine, serotonin receptor

D = dopamine receptor

Source: [USWM-LX0-PHK-0010](#)

4.3 Safety Pharmacology

Central Nervous System (CNS)

Formal CNS safety pharmacology studies were waived by the Division given the significant human experience with the drug to date. No dedicated CNS safety pharmacology studies of lofexidine were submitted; however, the clinical signs assessments performed in the repeat-dose toxicology studies reviewed below indicated several CNS-related effects. The following CNS-related clinical signs were associated with lofexidine treatment in rats: depression, decreased activity, ataxia, salivation, aggressive behavior, hypersensitivity, and hyperexcitability. In dog, CNS-related clinical signs associated with lofexidine treatment were limited to depression and ataxia. These observed clinical signs are collectively expected pharmacological effects of an α_2 -adrenergic receptor agonist.

Cardiovascular and Respiratory Systems

Based on the extensive clinical experience with the drug, an extensive battery of cardiovascular safety pharmacology studies were not deemed necessary to support this application. As such, there are no assessments that specifically characterize the impact of the drug on blood pressure or heart rate in rats or rabbits. A GLP hERG assay was

conducted and found that lofexidine treatment significantly inhibited tail currents at the highest concentration evaluated, 60.0 mcg/mL. A GLP in vivo assessment of the impact of oral lofexidine administration (up to 3.0 mg/kg) in dogs on cardiovascular and respiratory function found the lofexidine produced dose-dependent reductions in body temperature and heart rate. Lofexidine treatment at the 1.0 and 3.0 mg/kg was also associated with prolonged QT and QTc intervals. Additional conduction irregularities, e.g., prolonged PR interval and atrioventricular (AV) block, were also noted in isolated incidences at 3.0 mg/kg.

Lofexidine treatment had no impact on respiratory function.

Study Title: A Pharmacological Assessment of the Effect of Lofexidine Hydrochloride on the Outward Potassium Current Generated by h-ERG Expressing Chinese Hamster Ovary Cells

Key Findings

- A statistically significant 16.7% inhibition of hERG tail current was observed only at the highest concentration of lofexidine HCl evaluated, 60.0 mcg/mL.

Methods

The effects of lofexidine HCl on the potassium selective I_{Kr} (tail) current were investigated using the I_{Kr} -like outward potassium current generated by hERG-expressing CHO cells employing the whole-cell patch-clamp technique. After recording with the vehicle control solution, patched cells (n=7 per concentration) were sequentially exposed to the following nominal salt-based concentrations of lofexidine HCl: 0.06, 0.6, 6.0, 18.0 and 60.0 mcg/mL and currents were recorded at each concentration after a 4-minute equilibration period (Table 7). The actual concentrations were verified by an LCMS-based method and found to be within ± 1 mcg/mL of the nominal values. Additionally, a positive control, E-4031 (100 nM), was evaluated after a 3-minute washout period. All data points were corrected for time-dependent current run-down, which was estimated by applying control conditions over the exact duration of the test-article exposure experiment.

Table 7: Experimental Design of hERG Assay

Treatment	Concentration ($\mu\text{g/mL}$)		Number of Patched Cells	Multiple of Anticipated plasma concentration *	Volume applied (ml)
	Nominal	Measured			
Control	hERG External	-	7	---	12
Lofexidine	0.06	#	7	0.1 x	10-12
Lofexidine	0.6	0.71	7	1.0 x	10-12
Lofexidine	6.0	5.50	7	10 x	10-12
Lofexidine	18.0	17.00	7	30 x	10-12
Lofexidine	60.0	60.92	7	100 x	10-12
Washout #1	hERG External	-	6	---	16-20
E-4031	500.0 nM	-	4	---	16-20
Washout #2	hERG External	-	4	---	16-20

* The Lofexidine HCl plasma concentrations were estimated from clinical pharmacokinetics data and were selected to reflect multiples of the highest proposed daily dose of Lofexidine.

This determination was not considered reliable because the nominal concentration was well below the lowest calibration point in the qualified assay.

Results

Statistically insignificant tail current inhibition ranging from 10.1% to 15.0% was observed across all concentrations of lofexidine HCl up to 18.0 mcg/mL without clear dose-dependent increase (Table 8; Figure 1). At the highest 60.0 mcg/mL concentration, the tail current inhibited by 16.7% and was statistically significant. This effect persisted throughout the subsequent washout period and was followed by an 80.9% tail current inhibition after application of the positive control article, E-4031.

Table 8: Impact of Lofexidine HCl on hERG Tail Current

Treatment	Concentration ($\mu\text{g/mL}$)		Patched Cells	Net Normalized Current Density (% of Control)	SEM
	Nominal	Measured			
Control	hERG External	-	7	100.0	0.00
Lofexidine HCl	0.06	#	7	89.9	12.4
Lofexidine HCl	0.6	0.71	7	85.8	12.4
Lofexidine HCl	6.0	5.50	7	85.0	12.4
Lofexidine HCl	18.0	17.00	7	88.0	11.6
Lofexidine HCl	60.0	60.92	7	84.3 *	10.7
Washout #1	hERG External	-	6	79.6 *	6.1
E-4031	500.0 nM	-	4	19.1 *	3.9
Washout #2	hERG External	-	4	14.0 *	4.3

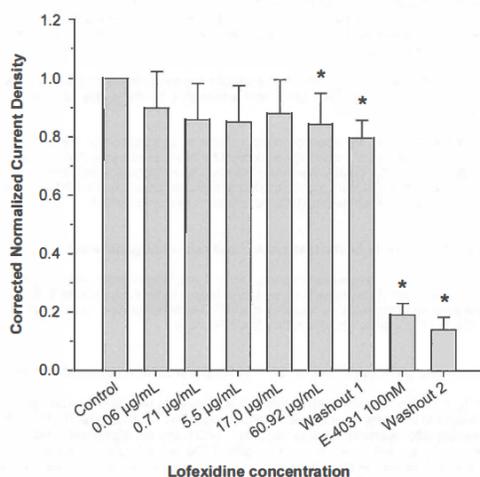
This determination was not considered reliable because the nominal concentration was well below the lowest calibration point in the qualified assay.

*: $P \leq 0.05$ when compared to control value

SEM: Standard Error of the Mean

Net: Current density corrected for time-dependent current run-down

Normalized: Net current density data divided by net current density data recorded at the beginning of the experiment, in the presence of the vehicle.

Figure 1: Impact of Lofexidine HCl on hERG Tail Current

Study Title: Evaluation of the Cardiovascular and Respiratory Safety of Orally Administered Lofexidine Hydrochloride in Beagle Dogs

Key Findings

- Single dose oral lofexidine administration at 0.3, 1.0, and 3.0 mg/kg dose-dependently decreased body temperature and heart rate.
- QT and QTc intervals were statistically significantly increased at the MD and HD.
- Isolated incidences of conduction disturbances, e.g., an abnormally long PR interval and an atrioventricular (AV) block of 1 atrial beat, were observed at the HD.
- Treatment-related clinical signs were limited to emesis and cold skin to the touch at the HD.
- Toxicokinetic analysis showed that the C_{max} and AUC at the HD were 192 ng/mL and 548 ng/mL*h, respectively.

Methods

Six male beagle dogs, surgically implanted with telemetry units, were administered the control article (empty capsule) orally on Day 1 and 31, and lofexidine orally via capsule at 0.3 mg/kg on Day 8, 1.0 mg/kg on Day 15, and 3.0 mg/kg on Day 22, 24, and 32. Cardiovascular parameters were measured and collected via a telemetry system on Day 1, 8, 15, and 22. The following cardiovascular parameters were measured: body temperature, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, T-wave morphology, and interval durations for PR, QT, and QRS. The following cardiovascular parameters were calculated: RR duration, rate-pressure

product, and corrected QT (QTc, performed using the Spence method). Effects on respiratory function were assessed on Day 31 (control) and 32 (lofexidine at 3.0 mg/kg). The following respiratory parameters were measured: saturated blood oxygen, end tidal CO₂, and respiratory rate. Additionally, blood was collected on Day 24 for pharmacokinetics, and the following general toxicological endpoints were also assessed: mortality (daily), clinical signs (daily), and body weights (weekly).

Results

Lofexidine treatment was associated with a dose-dependent decrease in body temperature, peaking with a 2.7°C decrease at the HD after 4 hours (Figure 2). Similarly, heart rate was also dose-dependently decreased by lofexidine treatment, peaking with a 67 bpm decrease at the HD after 2 hours (Figure 3). Notably, only the average heart rate at the HD fell outside of the normal range for Beagle dogs, which is 60 to 180 bpm. There were no treatment-related effects on systolic blood pressure, diastolic blood pressure, or mean arterial blood pressure.

ECG analysis revealed several treatment-related findings in dogs at the HD. One HD dog exhibited a long PR interval of 0.18 seconds after 2 hours and a long QT interval of 0.28 seconds after 4 hours, both of which exceeded the high end of the normal range for PR and QT intervals by 0.4 seconds and 0.2 seconds, respectively. This dog also exhibited the greatest decrease in heart rate in the group at the 2-hour and 4-hour time points postdose. A different HD dog exhibited an AV-block of one atrial beat at 4 hours postdose. Statistical evaluation of the impact of lofexidine treatment on ECG intervals revealed significant increases in QT and QTc intervals during the first 4 hours postdose at the MD and HD (Figure 4; Figure 5).

Treatment with lofexidine had no adverse effect on any of the respiratory parameters measured on Day 32.

With respect to the general toxicological endpoints assessed, treatment with lofexidine up to 2.6 mg/kg had no impact on mortality or body weights but was associated with emesis after dosing at the HD in 4/6 dogs on Day 24 and 2/6 dogs Day 32. Comparison of the pharmacological/toxicological effects of lofexidine at the HD in dogs with and without emesis revealed no significant differences. It was also noted that 2/6 dogs were cold to the touch after dosing at the HD on Day 32.

Toxicokinetics analysis of blood samples drawn on Day 24 after a HD treatment yielded the following results:

- C_{max} = 192 ng/mL
- AUC_{0-last} = 548 ng/mL*h
- t_{1/2} = 2.37 h
- T_{max} = 3.5 h

Figure 2: Impact of Lofexidine Treatment on Body Temperature

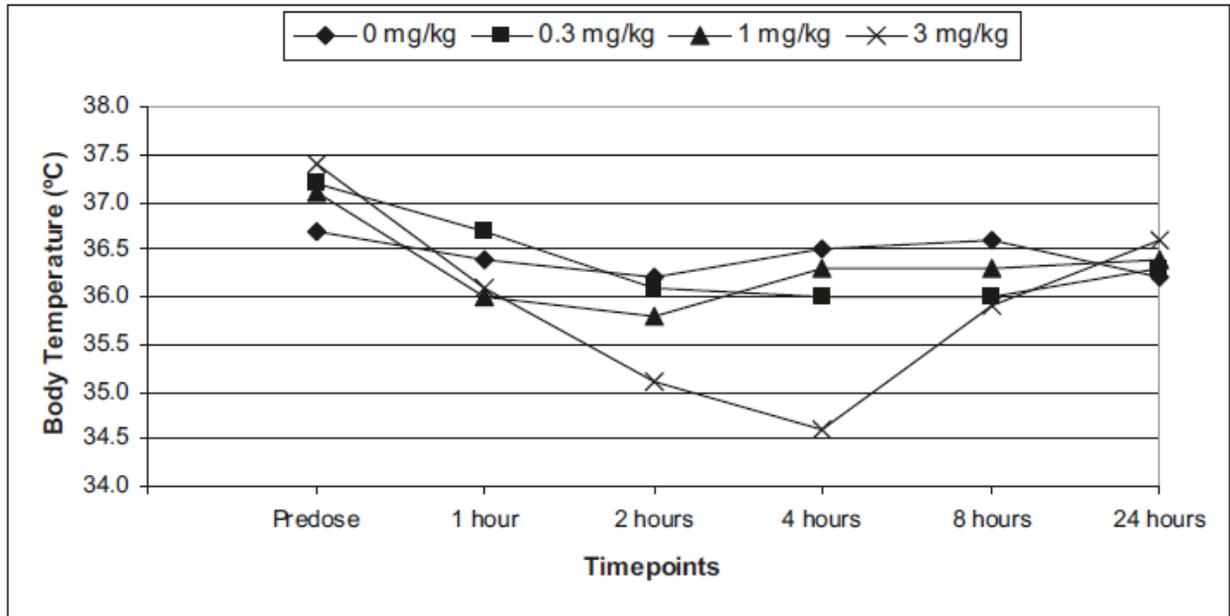


Figure 3: Impact of Lofexidine Treatment on Heart Rate

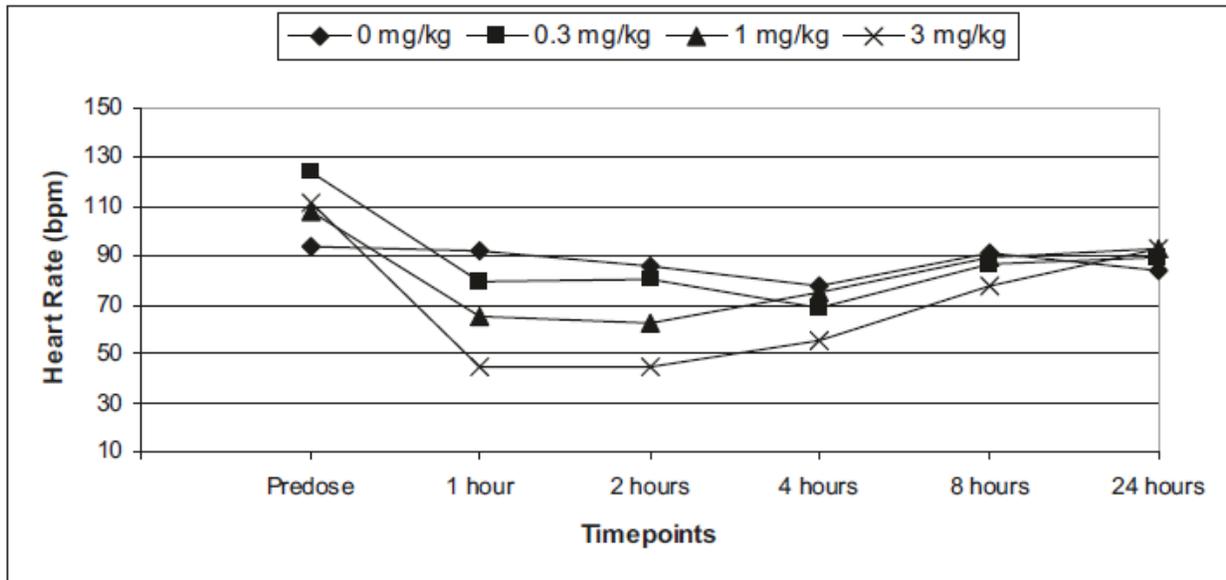


Figure 4: Impact of Lofexidine Treatment on QT Interval

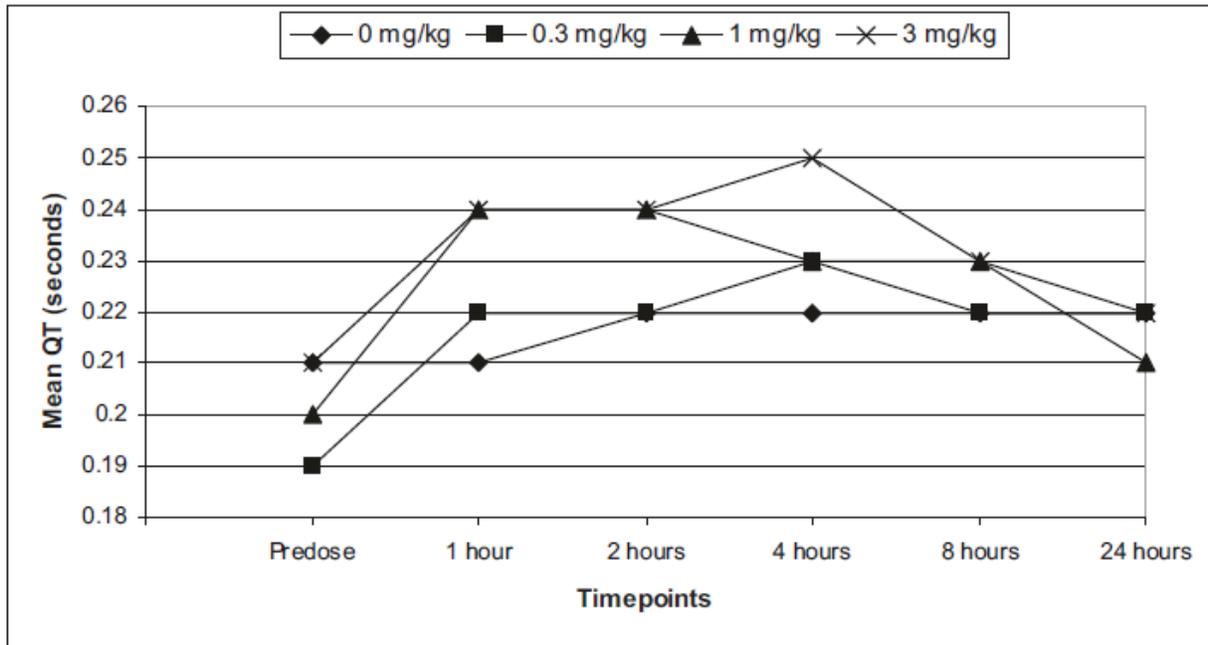
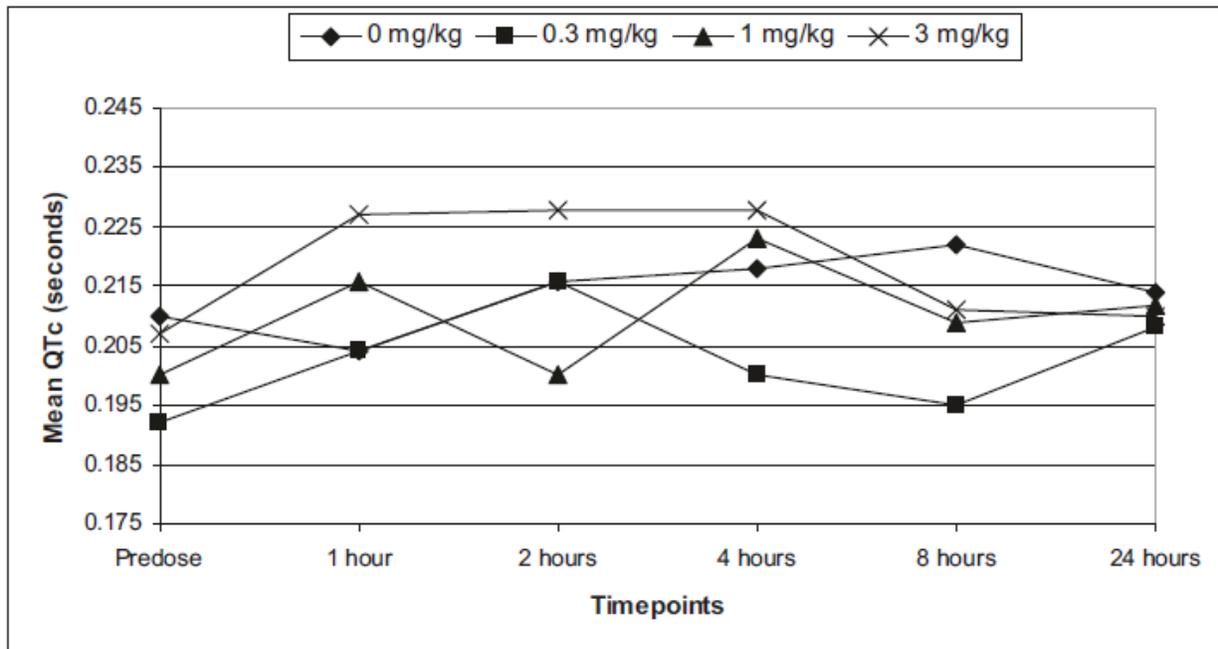


Figure 5: Impact of Lofexidine Treatment on QTc Interval



5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption

Plasma concentrations of radiolabeled lofexidine were assessed after a single oral dose of 0.1 mg/kg in two studies, USWM-LX0-PHK-0001 (PK Study 1) and USWM-LX0-PHK-0002 (PK Study 2). In PK Study 1, tritium radiolabeling was applied to the dichlorophenoxy ring of lofexidine (Figure 7), and plasma concentrations were measured in rats and dogs at various time points. Ten rats were dosed, and one rat was sacrificed for blood collection at each time point. Three male dogs were dosed, and blood was collected from all surviving dogs at each time point with sacrifices occurring at the 2-hour, 24-hour and 120-hour time points. In PK Study 2, carbon-14 labeling was applied to positions 4 and 5 of the imidazoline ring of lofexidine (Figure 8), and plasma concentrations were measured in rats, dogs, monkey at various time points postdose. In rats, blood was drawn from 3 males and 3 females for each time point assessed. In dogs, blood was drawn from 2 males and 2 females for each time point. In monkeys, blood was drawn from 2 males for each time point.

The results of these two studies are summarized in Table 9 and plotted in Figure 6. C_{max} values were the highest for dogs, 77.6 – 96.3 ng/mL, in the middle for monkeys, 65.0 ng/mL, and the lowest for rats, 11.9 – 62.1 ng/mL. T_{max} values were highest for dogs, 2 – 4 hours, then monkeys, 2 hours, and lowest for rats, 0.5 – 1.5 hours.

Table 9: Summary of Plasma Concentrations (ng/mL) Across Species and Studies Following Oral Administration of 0.1 mg/kg Lofexidine

Time (h)	Rat		Dog		Monkey
	PK Study 1* (n = 1)	PK Study 2 (n = 6)	PK Study 1* (n = 1-3)**	PK Study 2 (n = 4)	PK Study 2 (n = 2)
0.08				0.90	
0.33		10.2		9.05	2.6
0.5	62.1		51.5		
0.75		10.5		26.8	27.3
1	37.9	11.3	88.1	38.3	48.3
1.5		11.9		66.4	57.8
2	23.5	11.3	96.3	75.5	65.0
3			94.3		
4	24.8	8.5		77.6	62.7
5			42.6		
6	25.3	10.1		69.2	48.3
7			38.4		
8	25.3			61.8	42.9
24	21.7	4.4	28.3	35.3	18.4
48	15.4		25.2	26.9	11.5
72			19.7	18.6	10.4
96	11.1		17.9	15.6	
120	8.04		15.3	13.8	

* Plasma concentrations calculated based on total radioactivity

** One of three total dogs was sacrificed at each of the following time points: 2, 24, and 120 hours postdose

Figure 6: Plots of Plasma Concentrations (ng/mL) Across Species and Studies Following Oral Administration of 0.1 mg/kg Lofexidine

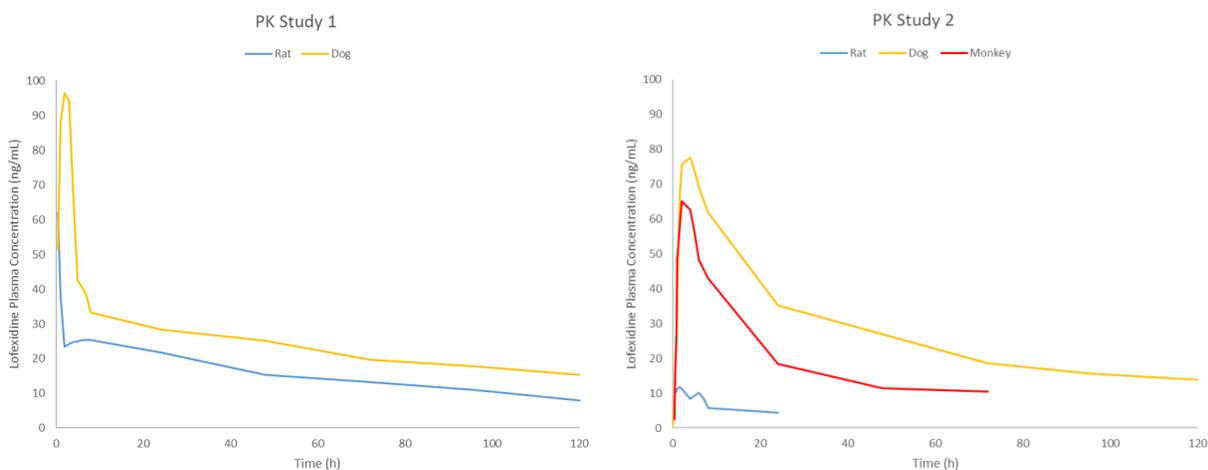
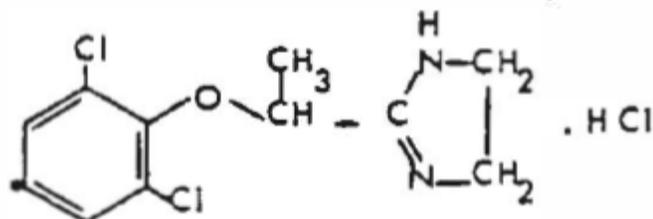
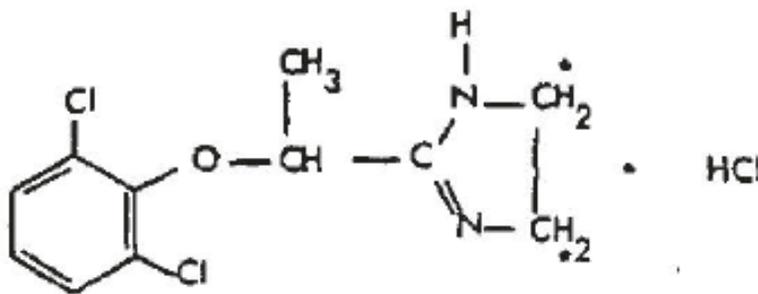


Figure 7: Location of Tritium Labeling in PK Study 1

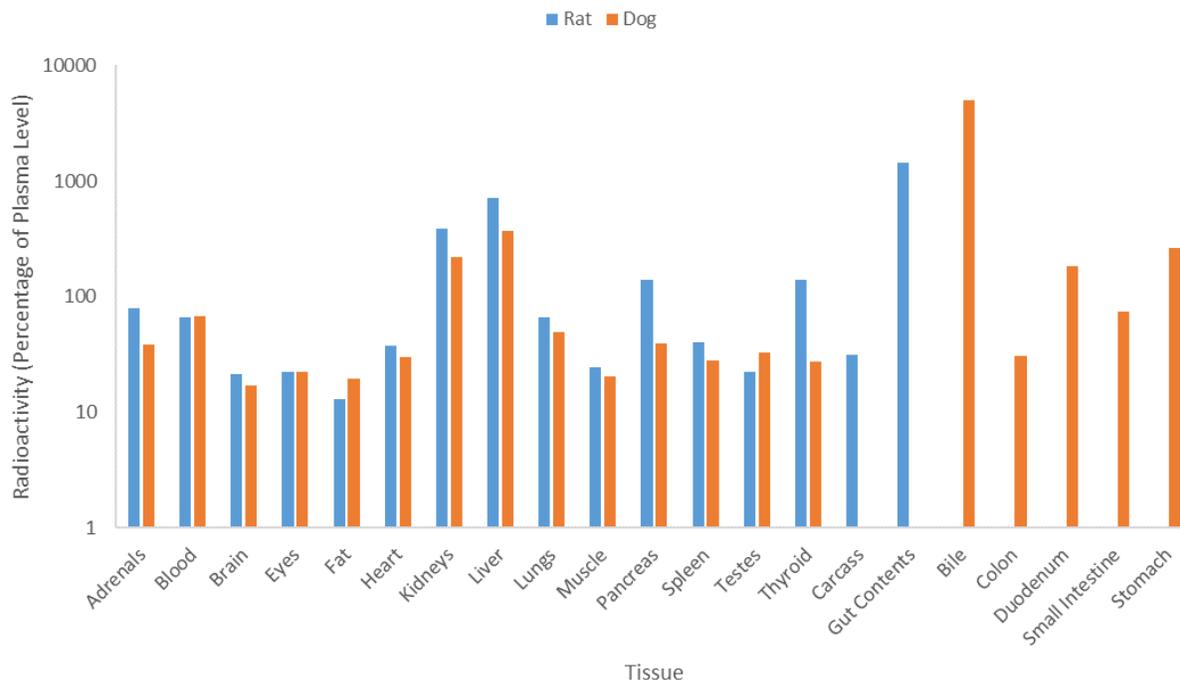
Ba 168 (* indicates the location of the tritium label)

Figure 8: Location of Tritium Labeling in PK Study 2

Ba 168 (* = position of ¹⁴C).

Distribution

Tissue distribution of radiolabeled lofexidine was also evaluated in both of the pharmacokinetics studies described above. In PK Study 1, analysis of radioactivity across organs at T_{max} , i.e., 0.5 hours postdose for rats and 2 hours postdose for dogs, revealed a similar distribution profile across species (Figure 9). Concentrations of lofexidine were notably greater than plasma levels in the liver, kidneys, and gut whereas concentrations were notably lower than plasma levels in the brain, eyes, fat, and muscle. In PK Study 2, tissue distribution was evaluated in rats and monkey but not dogs. The results in rats were similar to those observed in PK Study 1 with the notable exception that concentrations of lofexidine were not higher than plasma levels in the kidneys. In monkeys, tissue distribution analysis was not informative with respect to T_{max} as it was only evaluated at 120 hours postdose.

Figure 9: Comparative Distribution of Lofexidine Across Species at T_{max} in PK Study 1

In PK Study 2, plasma protein binding of lofexidine, evaluated in dogs and monkeys, ranged between 58% and 78%. In vivo analysis found that the percentage of bound lofexidine increased from approximately 60% in both species around 1 hour postdose up to 78% in dogs at 4 hours postdose and 71% in monkeys at 8 hours postdose. Notably, during this time period the ratio of unchanged ^{14}C -lofexidine to total radioactivity dropped nearly to zero, indicating that these results actually demonstrate the plasma protein binding of lofexidine's metabolites. In vitro analysis demonstrated similar plasma protein binding of lofexidine across the range of concentrations observed in plasma during the in vivo experiment for both species.

In vitro blood cell and plasma protein binding were also evaluated in two recently conducted studies, USWM-LX0-PHK-0004 and USWM-LX0-PHK-0005. Evaluation of blood cell binding revealed that lofexidine has greater affinity for plasma than for blood in rats, dogs, and humans. Evaluation of plasma protein binding was performed at concentrations, ranging from 2.7 to 270 mcg/mL, greatly exceeding the plasma concentrations observed in nonclinical toxicology or clinical safety/efficacy studies. Nevertheless, plasma protein binding in dogs of approximately 60% was observed to be within the range of binding demonstrated in the previously conducted PK Study 2. Binding to human (55%) and rat (60%) plasma was also found to be moderate.

Metabolism

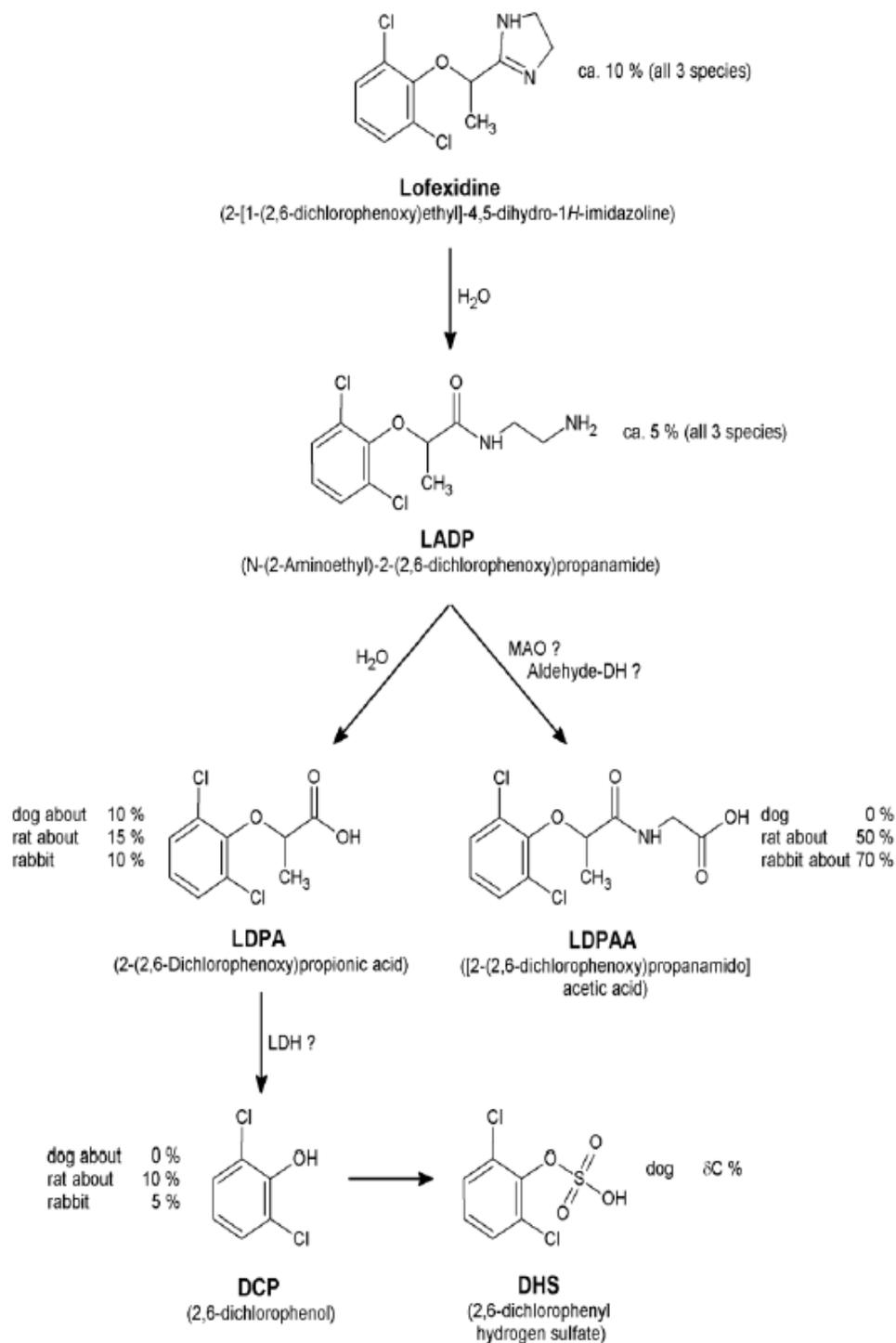
The metabolism of lofexidine was evaluated in vivo for rats, rabbits, and dogs in USWM-LX0-PHK-0003. Single doses of 0.10 mg lofexidine HCl (0.09 mg free base) for rats and 0.066 mg/kg lofexidine HCl (0.058 mg/kg free base) for rabbits and dogs were administered orally. These doses were too low for adequate chromatographic demonstration of lofexidine metabolites in plasma, but as the major portion of eliminated radioactivity was found in urine, urine samples collected between 8 and 24 hours were used for assessment of lofexidine metabolism. Urine was adjusted for pH to either 1.0 or 9.0, extracted with ethyl acetate, and then subjected to mass spectral analysis to determine the nature of the metabolites.

Figure 10 depicts the putative biotransformation pathways of lofexidine metabolism in rats, rabbits, and dogs. In all three species, urine samples showed less than 10% of the total eliminated radioactivity in the form of unaltered ³H-lofexidine, providing evidence of extensive metabolism. Likewise, the hydrolysis product, LADP, was present in small quantities, approximately 5%, for all three species. After this step in the biotransformation pathway, interspecies differences emerged. The LDPAA metabolite was observed at levels of 70% and 50% in rabbits and rats, respectively. A mechanistic understanding of the formation of LDPAA in these species has not been fully determined, but this does not appear to be a primary biotransformation pathway in dogs or humans. All three species showed evidence of hydrolysis of LADP to form LDPA and subsequent formation of 2,6-DCP. In dogs 2,6-DCP was further conjugated with sulfuric acid to form DHS, which was detected at 80% of total urine radioactivity, indicating that this was the primary biotransformation pathway in dogs. Notably, this pathway contains all three major human metabolites, LADP, LDPA, and 2,6-DCP. This study provides evidence to support the presence of each of these major human metabolites in repeat-dose toxicology studies of lofexidine conducted in rats and dogs, but as plasma levels of these metabolites were not measured, it is not possible to extrapolate the levels of these metabolites that were present in these toxicology studies.

In vitro identification of metabolites was also evaluated using human, rat, rabbit, and dog hepatocytes in USWM-LX0-PHK-0010. Solutions of 270 mcg/mL lofexidine were incubated at 37°C for 2 hours in hepatocytes for each species and high performance liquid chromatography-mass spectrometry analysis was performed. Two putative human metabolites were observed with spectra consistent with hydroxylation of the parent molecule on the imidazoline ring and with hydroxylation followed by reduction. Both metabolites were also produced by incubation of lofexidine in dog hepatocytes and the second metabolite, formed by hydroxylation followed by reduction, was produced by incubation with rat hepatocytes as well. Additional metabolites corresponding to hydroxylation of different sites on the parent molecule with or without glucuronidation were also observed after incubation of lofexidine with rat, rabbit, and dog but not human hepatocytes. Another in vitro study of the metabolic stability and metabolite characterization of lofexidine using human liver microsomes and recombinant human CYP enzymes, USWM-LX0-PHK-0009, identified two human metabolites. The spectra of one of these metabolites was also consistent with the hydroxylation of the parent

molecule whereas the levels of the second metabolite were too low to allow for accurate structural characterization. None of the major human metabolites were observed in these in vitro studies.

Figure 10: Schematic Diagram of the Biotransformation of Lofexidine in Rats, Rabbits, and Dogs



Excretion

Excretion of lofexidine was quantitatively evaluated in rats and dogs in both PK Study 1 and PK Study 2 and was also evaluated in monkeys in PK Study 2. Significant levels of lofexidine were detected in both urine and feces of rats, with slightly more detected in urine than feces in PK Study 1 and relatively equal proportions detected in urine and feces in PK Study 2 (Figure 11). Regardless of the route, the majority of lofexidine was excreted during the first 24 hours postdose. Excretion of lofexidine was also nearly complete within the first 24 hours postdose in dogs and monkeys; however, relatively little lofexidine was detected in the feces of these species compared to urine (Figure 12; Figure 13). Excretion of lofexidine in urine was also qualitatively observed in rats, rabbits, and dogs in USWM-LX0-PHK-0003.

Figure 11: Excretion of Lofexidine in Rats

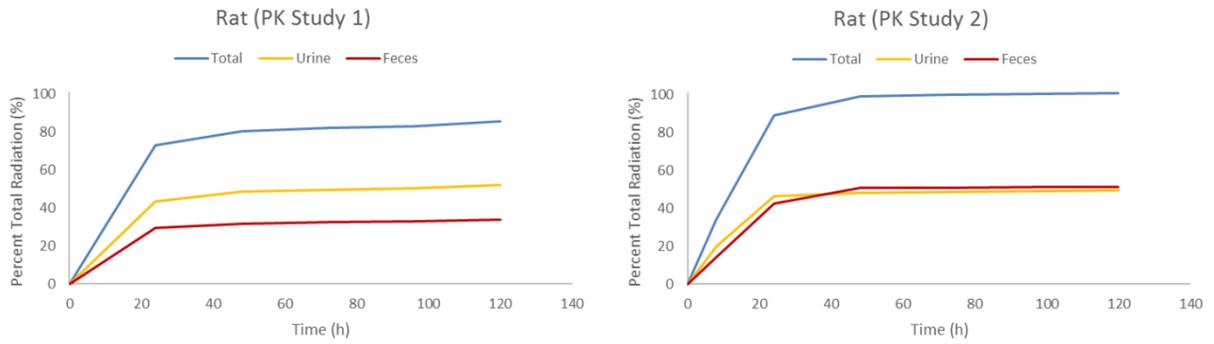


Figure 12: Excretion of Lofexidine in Dogs

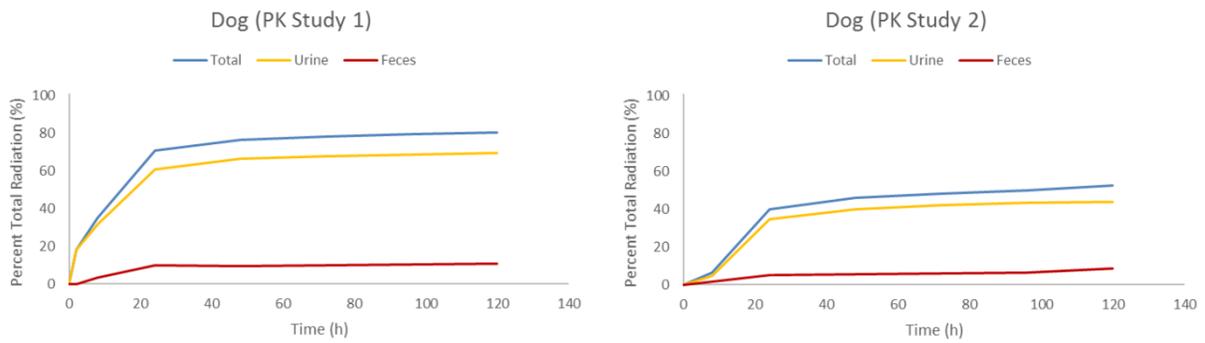
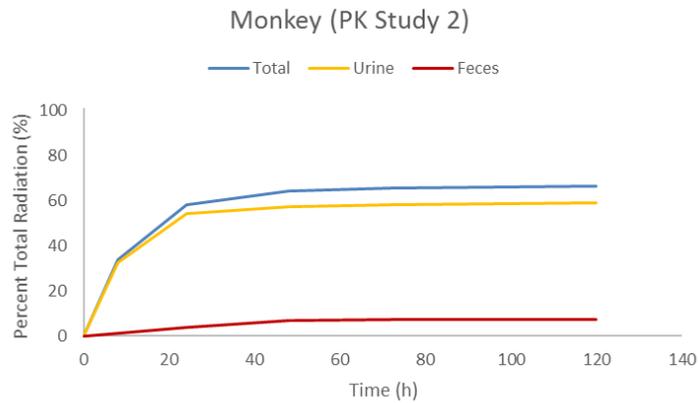


Figure 13: Excretion of Lofexidine in Monkeys



5.2 Toxicokinetics

Table 10 collates the pharmacokinetics parameters collected from all GLP toxicology studies that contained toxicokinetics data:

Table 10: Summary of Toxicokinetics Data Across GLP Toxicology Studies

Species	Study	Sex	Dose (mg/kg/day)	Dosing Day	C _{max} (ng/mL)	AUC _{0-tlast} (ng/mL*h)	t _{1/2} (h)	T _{max} (h)	
Rabbit	USWM-LX0-TOX-0004	Female (Dams)	1.5	1 (GD 6)	0	0	0	0	
				14 (GD 19)	1.76	2.20	1.28	0.50	
			5.0	1 (GD 6)	1.06	1.96	9.26	1.00	
				14 (GD 19)	2.41	7.52	2.71	0.875	
			15.0	1 (GD 6)	2.89	14.7	7.39	1.40	
				14 (GD 19)	7.95	36.7	2.83	1.80	
Rat	USWM-LX0-TOX-0005	Male	5/2.5	28	14.4	43.4	1.96	1.00	
			5	1	19.6	46.5	6.61	1.00	
			10/5	28	37.4	251	2.66	1.00	
			20/10/8	28	116	562	2.68	3.00	
			10	1	74.8	213	7.8	1.00	
			20	1	125	513	4.47	1.00	
		Female	5/2.5	28	20.7	111	3.08	1.00	
			5	1	60.0	258	11.0	1.00	
			10/5	28	89.7	351	2.87	3.00	
			20/10/8	28	282	903	4.04	1.00	
			10	1	224	1040	6.27	1.00	
			20	1	334	2670	7.71	1.00	
	USWM-LX0-TOX-0003	Female (Dams)	0.3	29 (LAC 14)	1.76	3.67	1.07	1.00	
			1.0	29 (LAC 14)	3.63	16.5	1.51	0.50	
			2.0	29 (LAC 14)	21.1	55.0	5.26	1.00	
		USWM-LX0-TOX-0002	Male	25	1	214	231	-	0.50
				50	1	990	1250	-	1.00
				65	1	910	1140	-	1.17
	Female	25	1	1360	1910	-	0.67		
		50	1	3180	3470	-	1.17		
65		1	1740	2350	-	1.00			
Dog	USWM-LX0-PHA-0002	Male	3.0	1	192	548	2.37	3.5	

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicology studies were submitted.

6.2 Repeat-Dose Toxicity

Study title: Lofexidine Hydrochloride: A 4 Week Oral Toxicity Study in Rats

Study no.: USWM-LX0-TOX-0005

Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\uswm-lx0-tox-0005\uswm-lx0-tox-0005.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: July 3, 2008

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: Lofexidine HCl, 24004970, 100.07%

Key Study Findings

- Lofexidine was administered via oral gavage to Sprague-Dawley rats at 0, 5/2.5*, 10/5*, or 20/10*/8** mg/kg/day for 28 days.
 - * The dose in each treatment group was decreased by 50% on Day 2
 - ** The HD was decreased further by 20% on Day 6.
- 3/10 HD females were found dead between Day 6 and Day 7.
 - These rats displayed the following clinical signs: decreased activity, few/absent feces, cold-to-touch skin, and unkempt appearance.
 - The following histopathological findings were noted in these rats: keratitis, bacterial colonies, degeneration/necrosis, hypopyon (pus in the anterior chamber of the eye), and/or erosion/ulcer in the eyes and lymphoid depletion in the spleen and thymus.
- Decreased activity, splayed limbs, yellow discolored hair, and material around the eyes/mouth/nose were observed at all dose levels evaluated with dose-dependently increasing incidence and duration.
 - Additional clinical signs observed at the MD and/or HD included: ataxia, salivation, aggressive behavior, hypersensitivity to touch, vocalization, few/absent feces, distended abdomen, piloerection, unkempt appearance, discolored eyes, lacrimation, and thinness.

- Body weights of lofexidine-treated male rats were dose-dependently lower than controls by up to 30% whereas body weights in females were decreased by approximately 17% across all dose levels.
 - Correlated with a dose-dependent decrease in food consumption in both sexes, primarily during Week 1.
- Keratitis was observed via ophthalmoscopic evaluations with dose-dependent increases in incidence at the LD in females and at the MD and HD in both sexes.
 - Correlated with clinical signs of cloudy eyes, observed as early as Day 4 in males and Day 2 in females.
- Leukocytes counts were dose-dependently decreased in both sexes. This finding was primarily due to decreased lymphocytes in both sexes, although decreased basophils and increased neutrophils were also observed in females.
- Clinical chemistry and urinalysis results indicated signs of dehydration/renal dysfunction:
 - Clinical Chemistry:
 - Increased urea nitrogen, creatinine, albumin/globulin ratio, cholesterol (males only), and triglycerides (females only).
 - Decreased sodium, chloride, calcium, and triglycerides (males only).
 - Urinalysis:
 - Increased urine specific gravity, glucose, bilirubin, ketones (females only), protein, urobilinogen, and yeast.
 - Decreased urine volume and pH.
- Determination of the impact of lofexidine-treatment on organ weights was difficult due to the pronounced effects of lofexidine on body weight; however, a few treatment effects were identified to be independent of body weight changes.
 - Adrenal weights decreased, primarily in females.
 - Heart weights increased in both sexes.
 - Liver weights increased in females only.
- Histopathological findings included keratitis at the LD in females and at the MD and HD in both sexes, accompanied by erosion/ulcer, hyperplasia, and regeneration, acinar atrophy of the parotid salivary glands also at the LD in females and at the MD and HD in both sexes, and chronic progressive nephropathy at all dose levels (including one vehicle-treated female) in both sexes.
- The study NOAEL was the LD of 2.5 mg/kg/day for males, on the basis of decreased body weights and eye keratitis at the MD of 5 mg/kg/day, providing an 8-fold safety margin to the MRHD of 2.88 mg/day based on body surface area allometric scaling. A NOAEL was not established for females due to decreased

body weights and eye keratitis with erosion/ulcer at the LD, suggesting that the safety margin for this study to the MRHD of 2.88 mg/day is less than 8-fold based on body surface area allometric scaling. The average C_{max} and AUC values at the NOAEL in males on the last day of treatment were 14.4 ng/mL and 43.4 ng*h/mL, respectively, providing a 0.5-fold safety margin to human exposure at the MRHD.

Methods

- Doses: 0, 5/2.5*, 10/5*, 20/10*/8** mg/kg/day
 * Dose was lowered to this level starting on Day 2
 ** Dose was lowered to this level starting Day 6 (for HD only)
- Frequency of dosing: Once daily
- Route of administration: Oral gavage
- Dose volume: 10/5*/4** mL/kg/dose
 * Dose volume was lowered to this level starting on Day 2
 ** Dose volume was lowered to this level starting Day 6 (for HD only)
- Formulation/Vehicle: Phosphate buffered saline, pH 7.2
- Species/Strain: Rat/Crl:CD (SD)
- Number/Sex/Group: 10 (toxicology)
 4 (toxicokinetics: vehicle group)
 8 (toxicokinetics: lofexidine HCl groups)
- Age: 6 weeks***
- Weight: Males: 130 to 210 grams***
 Females: 100 to 170 grams***
 *** Upon arrival, prior to at least 2 week acclimation period
- Satellite groups: Toxicokinetics
- Unique study design: None
- Deviation from study protocol:
 - The following blood samples collected from toxicokinetics rats were clotted:

Clotted TK Samples				
Animal Number	Dose Level (mg/kg/day)	Sex	Interval (Day)	Time Point (Hours Postdose)
1063	20/10	Male	1	0
1130	20/10	Female	1	3
1132	20/10	Female	1	6
1115	5/2.5	Female	1	12
1053	10/5	Male	1	12
1054	10/5	Male	1	12
1055	10/5	Male	1	12
1061	20/10	Male	1	12
1130	20/10	Female	1	12
1131	20/10	Female	1	12

- Clinical observations were performed more than once during Week 1 due to the state of the animals.
- Terminal urine samples could not be analyzed

from 3 LD males and 2 MD females due to insufficient volume of urine collected.

- A liver weight was not obtained for 1 vehicle female due to the liver having been immersed into formalin prior to the weight being measured and recorded.

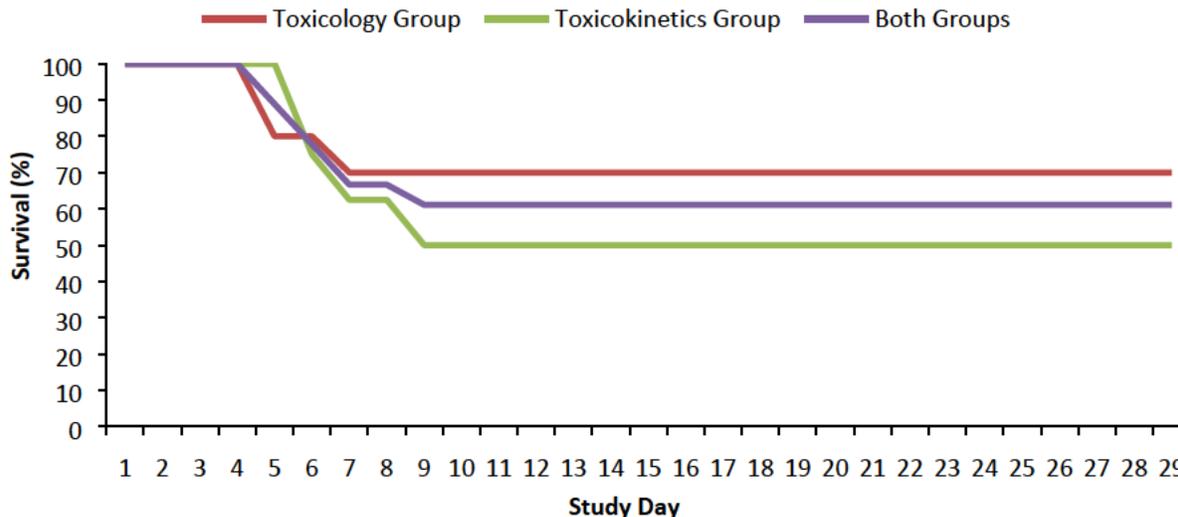
These minor deviations did not compromise the quality or integrity of the study.

Group Assignments			
Group Number	Dose Level (mg/kg/day) ^a	Number of Animals	
		Male	Female
<u>Main Study</u>			
1	0 (Vehicle)	10	10
2	5/2.5	10	10
3	10/5	10	10
4	20/10/8	10	10
<u>Toxicokinetics</u>			
5	0 (Vehicle)	3+1 ^b	3+1 ^b
6	5/2.5	6+2 ^b	6+2 ^b
7	10/5	6+2 ^b	6+2 ^b
8	20/10/8	6+2 ^b	6+2 ^b
<p>^aStarting Day 2, the dose levels for the treated groups were lowered from 5 to 2.5, 10 to 5, and 20 to 10 mg/kg/day, respectively. Starting Day 6, the dose level for the high dose groups were lowered to 8 mg/kg/day.</p> <p>^bAdditional animals as possible replacements.</p>			

Mortality

All rats were observed for morbidity and mortality at least twice daily throughout the duration of the study.

Unscheduled deaths occurred only in female rats at the HD as 3/10 toxicology group rats and 4/8 toxicokinetics group rats were found dead between Day 5 and Day 9 (Figure 14). As a result, the HD was decreased from 10 mg/kg/day to 8 mg/kg/day starting on Day 6. No unscheduled deaths occurred later than 3 days after this dose adjustment was made. Clinical signs noted in these rats included decreased activity, few/absent feces, cold-to-touch skin, and unkempt appearance. Histopathological evaluation of these rats did not reveal a cause of death.

Figure 14: Survival Rate of HD Female Rats throughout 28-Day Study

Clinical Signs

A detailed clinical examination of each rat was performed prior to initiation of treatment, at various intervals during Week 1, and daily during the remainder of the study at approximately 3 hours postdose. Observations included evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects (e.g. salivation), and nervous system effects (e.g. tremors, convulsions, reactivity to handling, bizarre behavior).

Several clinical signs were observed in association with lofexidine treatment that were not observed in vehicle-treated rats. Decreased activity, splayed limbs, yellow discolored hair, and material around the eyes/nose/mouth were observed in at least one rat at all lofexidine dose levels. Both the incidence among rats in each treatment group as well as the frequency of occurrence throughout the study days in rats displaying these signs generally increased with dose. Additional clinical signs that occurred only in MD and HD treated rats included ataxia, salivation, aggressive behavior, hypersensitivity to touch, vocalization, few/absent feces, distended abdomen, piloerection, and unkempt appearance (Figure 16). At the MD, these findings were generally more prevalent in female rats, likely due to the increased exposure observed in female rats compared to males (Table 16). Discolored eye(s), lacrimation, and thin appearance were also observed primarily at the HD (Figure 17), also with generally greater prevalence in female rats. Although a NOEL with respect to lofexidine treatment was not observed for decreased activity, splayed limbs (females only), yellow discolored hair, and material around eyes/nose/mouth, the incidence and frequency of these findings was relatively low at the LD.

Figure 15: Treatment-Related Clinical Signs in Rats with Full Dose Response

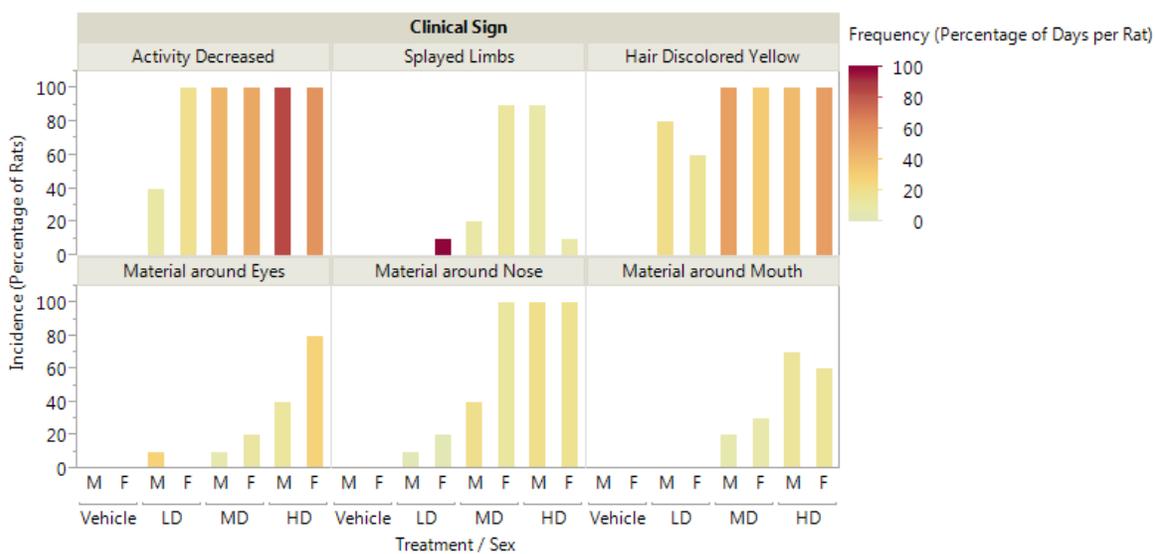


Figure 16: Treatment-Related Clinical Signs in Rats at MD and HD

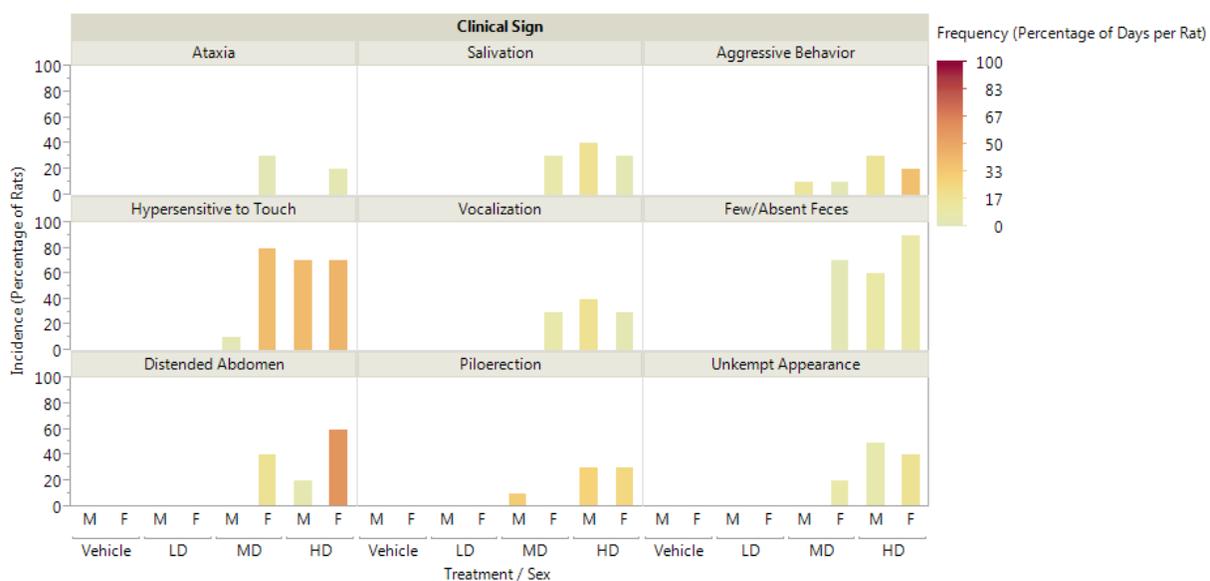
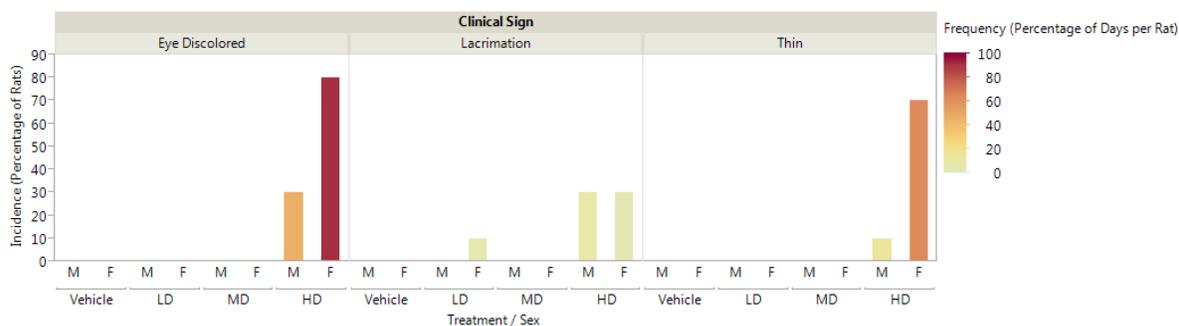


Figure 17: Treatment-Related Clinical Signs in Rats at HD only



Body Weights

Body weights for all rats were measured and recorded prior to initiation of treatment and weekly during the study.

Statistically significant decreases in body weights were observed in all lofexidine treatment groups on Week 3 and Week 4 and in all but LD male rats on Week 1 and Week 2. By Week 4, the mean body weights for male rats (Figure 18) were decreased by 10%, 25%, and 30% at the LD, MD, and HD, respectively, and the mean body weights for female rats (Figure 19) were decreased by approximately 17% at all dose levels.

Figure 18: Body Weights of Male Rats throughout 28-Day Lofexidine Treatment

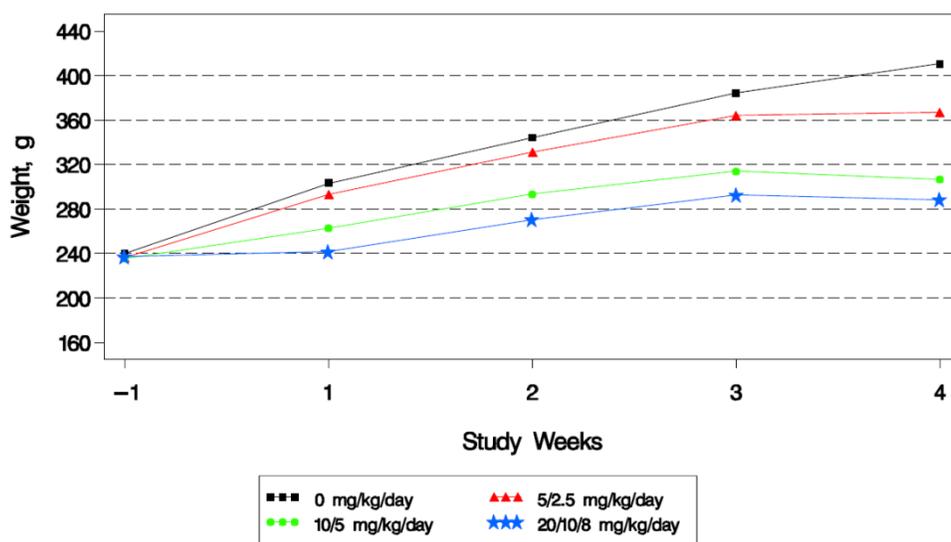
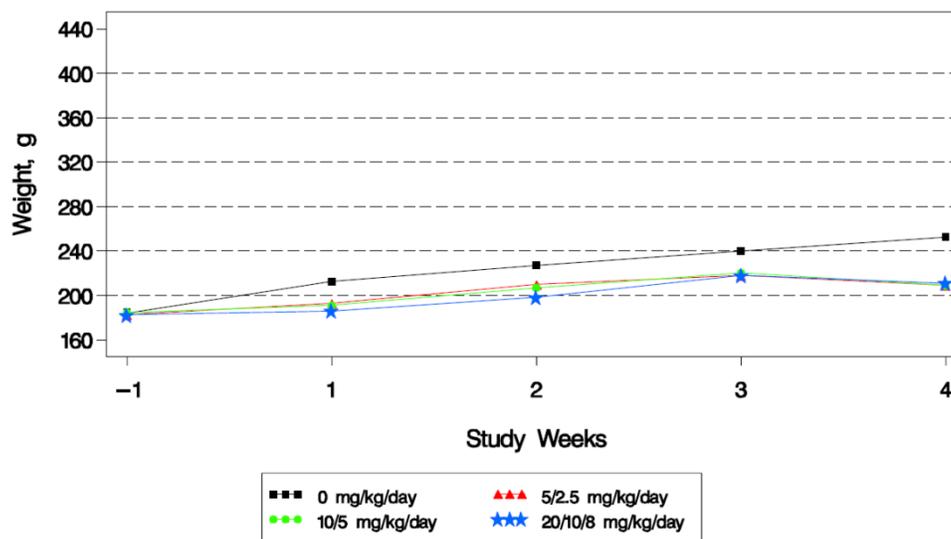


Figure 19: Body Weights of Female Rats throughout 28-Day Lofexidine Treatment



Food Consumption

Food consumption was measured and recorded weekly.

Dose-dependent decreases in food consumption of up to -50% in males (Figure 20) and -66% in females (Figure 21) at the HD were observed on Week 1. Food consumption in female rats subsequently returned to the normal levels observed in the vehicle treatment group following Week 1 whereas partially attenuated decreases in food consumption of up to -20% at the HD were observed in male rats on Weeks 2, 3, and 4. These decreases in food consumption were correlated with decreased body weights.

Figure 20: Food Consumption of Male Rats throughout 28-Day Lofexidine Treatment

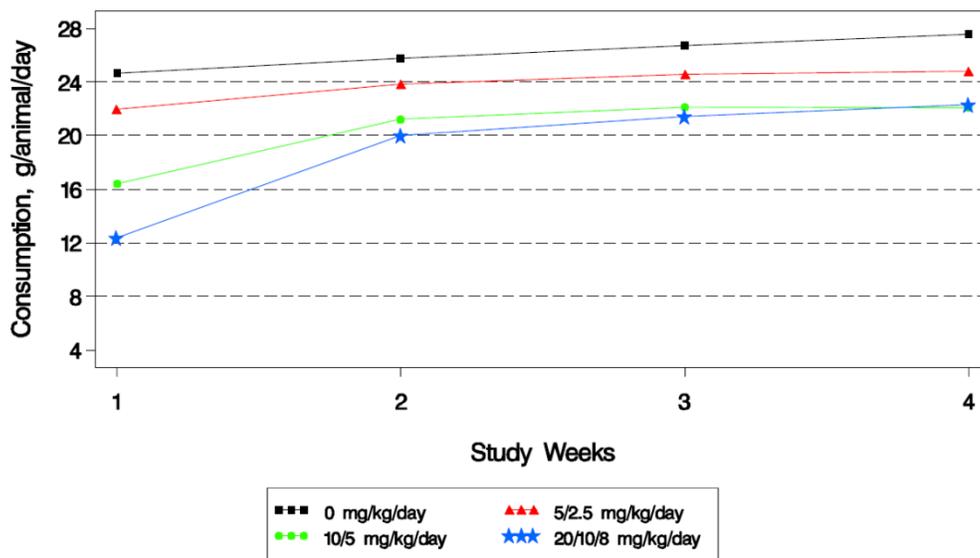
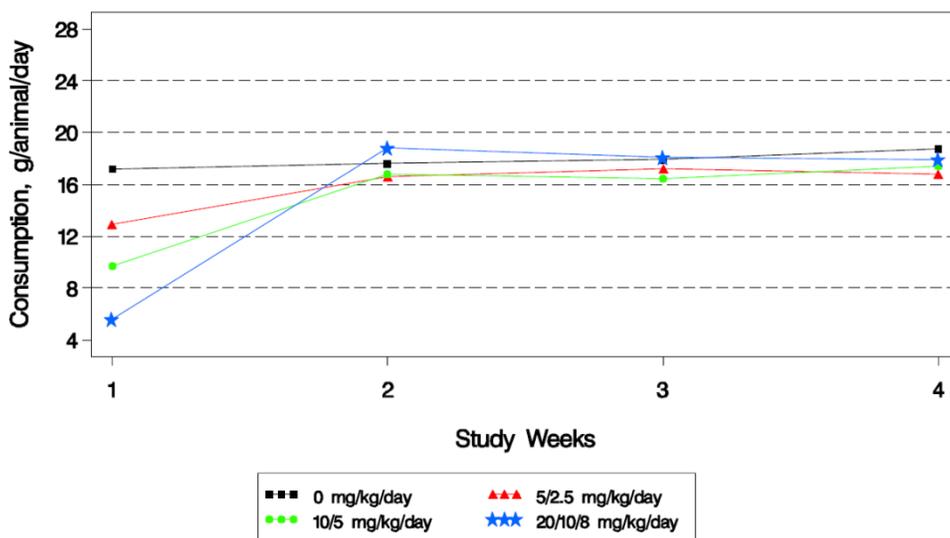


Figure 21: Food Consumption of Female Rats throughout 28-Day Lofexidine Treatment



Ophthalmoscopy

Ophthalmoscopic examinations were conducted on all rats prior to initiation of treatment and prior to scheduled necropsy for all surviving rats.

Superficial keratitis was observed at the MD and HD in male rats and at all dose levels in female rats, which was dose-dependent in incidence (Table 11). Additional potentially treatment-related findings were panophthalmitis observed in 1 HD male, retinal and vitreal hemorrhage in 1 MD female, and phthisis bulbi in 1 HD female. Keratitis findings were correlated with microscopic findings of keratitis, synechia, erosion/ulceration, and hyperplasia during the histopathological examination.

Table 11: Incidence of Keratitis Observed in Ophthalmoscopic Evaluation of Rats

Treatment	Sex	Incidence of Keratitis in at Least One Eye	Incidence of Keratitis in Both Eyes
Vehicle	Male	0	0
	Female	0	0
5/2.5 mg/kg/day	Male	0	0
	Female	2	0
10/5 mg/kg/day	Male	7	6
	Female	5	5
20/10/8 mg/kg/day	Male	4	2
	Female	7	6

Hematology

Hematology evaluations were conducted prior to scheduled necropsy. Rats had access to drinking water but were fasted overnight prior to sample collection. Blood samples (approximately 4 mL) were collected via the vena cava after carbon dioxide inhalation into tubes containing K₃EDTA for evaluation of hematology parameters and sodium citrate for evaluation of coagulation parameters. The following parameters were evaluated:

- Leukocyte Count (total and absolute differential)
- Erythrocyte Count
- Hemoglobin
- Hematocrit
- Mean Corpuscular Hemoglobin
- Mean Corpuscular Volume
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- Absolute Reticulocytes
- Platelet Count
- Automated Red Cell and Platelet Morphology
- Prothrombin Time
- Activated Partial Thromboplastin Time

Lofexidine treatment was associated with moderate changes in white blood cell parameters (Table 12). Dose-dependent decreases in leukocyte count of up to -25% were observed in both male and female rats treated with lofexidine. This decrease was

primarily driven by decreases in lymphocytes by up to -31% in males and -40% in females. Additional changes in white blood cell parameters included decreases in basophils (up to -34% in males and -45% in females) and increases in neutrophils (up to +33% in males and +88% in females).

Additional treatment-related findings in males included a dose-dependent increase of up to 2.1% in MCHC and a decrease of up to 34% in platelet count in all lofexidine treatment groups. A dose-dependent increase of up to 5% in prothrombin time was also observed in females.

Table 12: Impact of Lofexidine Treatment on White Blood Cell Parameters in Rats

WBC Parameter	Percent Change from Control					
	LD		MD		HD	
	Male	Female	Male	Female	Male	Female
Leukocytes	+10%	-5%	-12%	-13%	-25%*	-25%
Basophils	+15%	-14%	-34%	-25%	-22%	-45%*
Eosinophils	+25%	+18%	+18%	-14%	-15%	-12%
Lymphocytes	+1%	-11%	-18%	-20%	-31%**	-40%**
Monocytes	-4%	-18%	-14%	+3%	-25%	-15%
Neutrophils	+10%	+46%	+33%*	+52%	+12%	+88%**

* Significantly different from control ($p < 0.05$)

** Significantly different from control ($p < 0.01$)

Clinical Chemistry

Clinical chemistry evaluations were conducted prior to scheduled necropsy. Rats had access to drinking water but were fasted overnight prior to sample collection. Blood samples (approximately 4 mL) were collected via the vena cava after carbon dioxide inhalation, and a serum separator was used. The following parameters were evaluated:

- Alkaline Phosphatase
- Total Bilirubin (with direct bilirubin if total bilirubin exceeds 1 mg/dL)
- Aspartate Aminotransferase
- Alanine Aminotransferase
- Gamma Glutamyl Transferase
- Sorbitol Dehydrogenase
- Urea Nitrogen
- Creatinine
- Total Protein
- Albumin
- Globulin
- Albumin/Globulin Ratio (calculated)
- Glucose
- Total Cholesterol
- Triglycerides
- Electrolytes (sodium, potassium, chloride)
- Calcium
- Phosphorus

Treatment-related changes in clinical chemistry parameters (Table 13) appear to be, for the most part, related to renal impairment/dehydration associated with lofexidine treatment (see urinalysis results below). This is most directly evidenced by statistically

significant and dose-dependent increases in urea nitrogen in both sexes at all dose levels of up to 48% in males and 85% in females. Creatinine levels were also modestly increased in both sexes, reaching statistical significance only in females at the MD. Electrolyte imbalances, characterized by a dose-dependent decrease in calcium, up to 7% in males and 6% in females, along with decreased sodium and chloride levels primarily in LD females. Increased liver enzyme levels, AST in both sexes and ALT in females, were less than 2-fold in magnitude and were not correlated with histopathological signs of liver pathology. Changes in serum protein levels were also observed, characterized by a dose-dependent increase in albumin: globulin ratio in males and decreased globulin in females. Lipid levels, i.e. triglycerides and cholesterol, were also altered by lofexidine treatment but inconsistently across sexes. Triglyceride levels were dose-dependently decreased in males by up to 36% and decreased in females by up to 38%. Cholesterol levels were dose-dependently increased only in males by up to 48%. Increased cholesterol levels were correlated with chronic progressive nephropathy observed histopathologically in the kidneys of MD and HD male rats, although increased levels of cholesterol were still observed to some extent at the MD and HD in rats without nephropathy (Figure 22), as abnormalities observed in the lipid levels may be related to renal dysfunction (Trevisan et al., 2006).

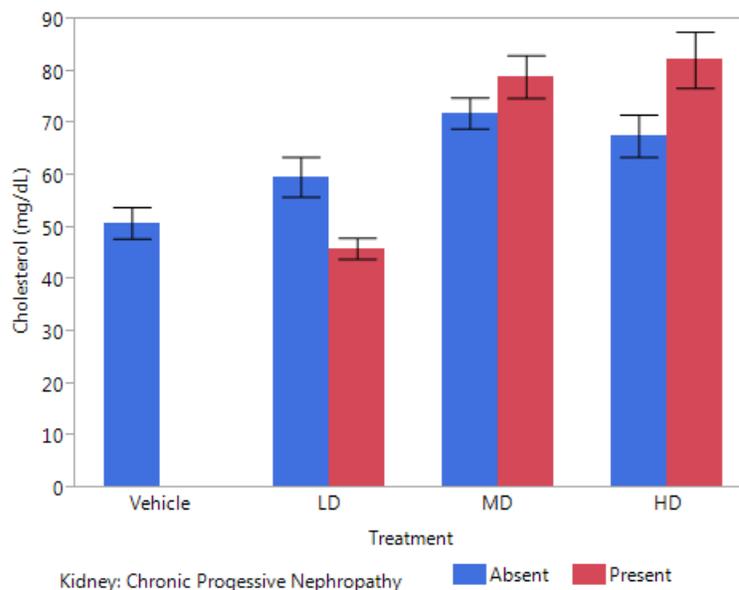
Table 13: Impact of Lofexidine on Selected Clinical Chemistry Parameters in Rats

Clinical Chemistry Parameter	Percent Change from Control					
	LD		MD		HD	
	Male	Female	Male	Female	Male	Female
<u>Renal Markers</u>						
Urea Nitrogen	+30%**	+35%**	+39%**	+69%**	+48%**	+85%**
Creatinine	+9%	+13%	+14%	+18%*	+17%	+10%
<u>Electrolytes</u>						
Sodium	-1.0%	-1.9%*	-1.2%	-0.9%	-1.1%	-0.3%
Chloride	-2.3%*	-5.1%**	-1.7%	-2.2%	-1.8%	+0.1%
Calcium	-3.6%	-2.1%	-6.3%**	-5.7%**	-7.3%**	-4.9%*
<u>Liver Enzymes</u>						
AST	+15%*	+37%**	+22%**	+29%**	+24%**	+31%**
ALT	+5%	+20%	+14%	+23%	+16%	+45%**
<u>Proteins</u>						
Total Protein	-2%	-1%	-1%	-6%	-2%	-6%
Albumin	+1%	+2%	+3%	-5%	+2%	-4%
Globulin	-6%	-3%	-6%	-7%*	-7%	-7%
Albumin/Globulin Ratio	+5%	+6%	+9%*	+4%	+8%*	+5%
<u>Lipids</u>						
Triglycerides	-16%	+3%	-36%**	+20%	-25%*	+38%*
Cholesterol	+12%	-8%	+48%**	+1%	+47%**	+3%

* Significantly different from control ($p < 0.05$)

** Significantly different from control ($p < 0.01$)

Figure 22: Cholesterol Levels in Lofexidine-Treated Male Rats with and without Chronic Progressive Nephropathy of the Kidneys



Urinalysis

Rats were placed in stainless steel metabolism cages for at least 16 hours to collect urine prior to scheduled. The following parameters were evaluated:

- Volume
- Specific Gravity
- pH
- Color and Appearance
- Protein
- Glucose
- Bilirubin
- Ketones
- Blood
- Urobilinogen
- Microscopy of Centrifuged Sediment

The results of urinalysis suggest that lofexidine treatment produced significant dehydration in both sexes at all dose levels evaluated (Figure 23). This was evidenced by statistically significant decreases in urine volume and specific gravity at all dose levels compared to controls in both sexes. Urine pH was also significantly more acidic in lofexidine treated rats than controls at all dose levels in males and at the MD in females. Qualitatively described levels of urine glucose, bilirubin, ketones (females only), protein, urobilinogen, and yeast were also increased in lofexidine treated rats of both sexes across all dose levels. Furthermore, decreased urine volume was correlated with the presence of histopathologically identified chronic progressive nephropathy particularly in HD male and MD females, suggesting that the observed signs of dehydration were likely related to test article-induced renal impairment (Figure 24).

Figure 23: Impact of Lofexidine Treatment on Urine Volume, Specific Gravity, and pH in Male and Female Rats

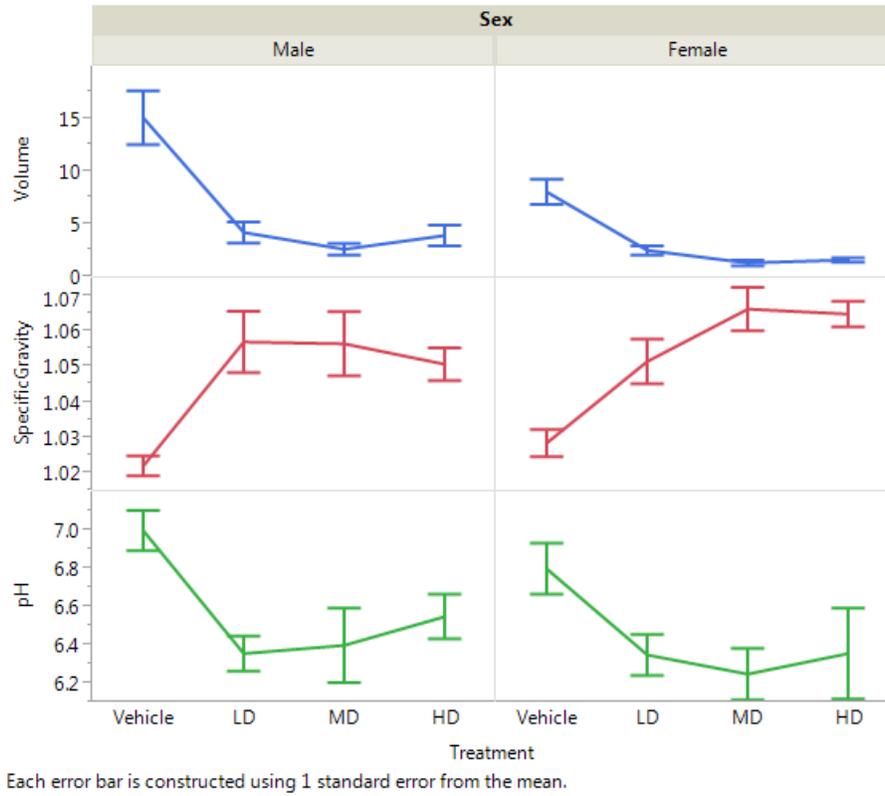
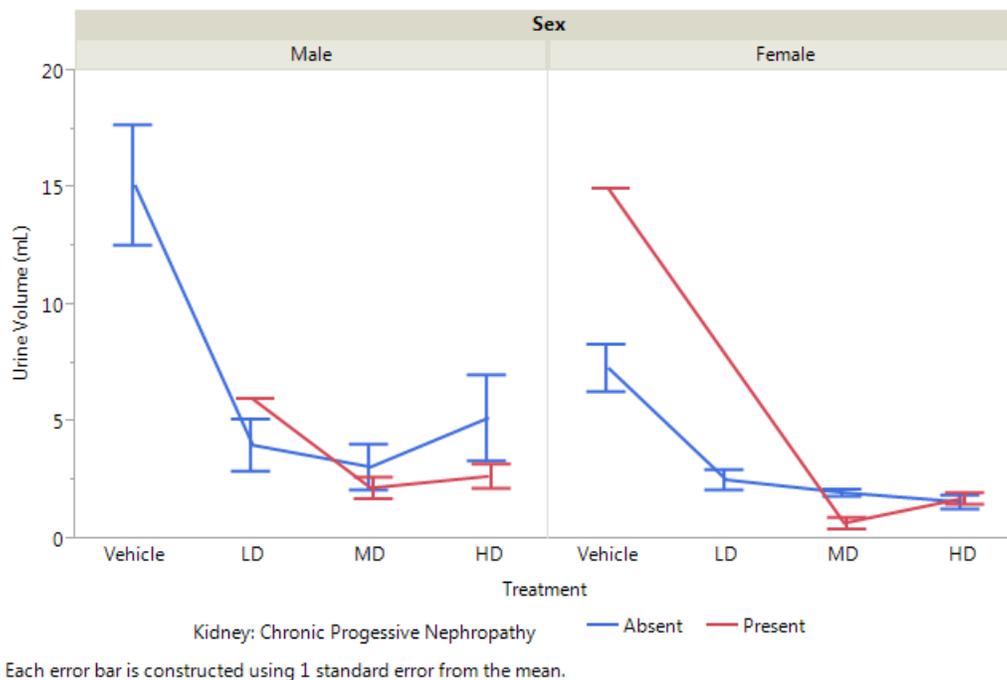


Figure 24: Urine Volumes in Lofexidine-Treated Rats with and without Chronic Progressive Nephropathy of the Kidneys



Gross Pathology

Necropsy examinations were performed on all rats. Rats were euthanized by carbon dioxide inhalation, followed by exsanguination via the abdominal vena cava. Gross necropsy examinations were also performed on toxicokinetics group rats that were found dead during the study. Rats were examined carefully for external abnormalities including palpable masses. The skin was reflected from a ventral midline incision and any subcutaneous masses were identified and correlated with antemortem findings. The abdominal, thoracic, and cranial cavities were examined for abnormalities and the organs removed, examined, and, where required, placed in fixative. The pituitary was fixed in situ. All designated tissues were fixed in neutral buffered formalin, except for the eye (including the optic nerve) and testes, which were fixed using a modified Davidson's fixative.

Treatment-related macroscopic findings were limited to the eyes in both sexes. Cloudy eyes were noted in 2/10 males and 1/10 females at the HD. One HD female also exhibited phthisis bulbi (a shrunken, non-functional eye). Additional macroscopic findings observed in the three HD females that were found dead included depleted body fat, abrasion/scab and white discoloration of the eyes, and distended small intestine, jejunum, and stomach. Incidental isolated findings that were neither dose-dependent nor sex-specific included enlarged lymph nodes (in a LD male and a MD female), sparse hair, a brown lung foci, and an enlarged uterus.

Organ Weights

Body weights and protocol-designated organ weights were recorded for all surviving animals at the scheduled necropsy and appropriate organ weight ratios were calculated (relative to body and brain weights). Paired organs were weighed together. The thyroid/parathyroid gland and pituitary gland were weighed following fixation. The following organs were weighed:

- Adrenals
- Epididymis
- Gonads:
 - Ovaries
 - Testes
- Heart
- Kidneys
- Liver
- Lungs with Bronchi
- Pituitary
- Salivary Gland, Mandibular/Sublingual
- Spleen
- Thymus
- Thyroid/Parathyroid

Determination of test article effects with respect to organ weights was confounded by the interdependent relationship between organ weights and body weights, which were significantly decreased in all lofexidine-treated rats. To account for this, a robust step-wise procedure was implemented to assess the impact of lofexidine treatment on organ weights. First, correlation between organ weight and body weight was assessed for each sex. If this correlation was significant, then organ-to-body weight ratio was evaluated; otherwise, organ-to-brain weight ratio was evaluated. If a treatment-related

effect was observed, then ANCOVA was performed to evaluate the effect of lofexidine treatment on absolute organ weight with body weight as a covariate. This additional step was performed to account for the failure of organ-to-brain and/or organ-to-body weight ratios to properly model the relationship between organ weights and body weights (Bailey et al., 2004). Only treatment effects that survived ANCOVA were deemed statistically significant.

After application of the robust organ weight analysis procedure described above, the weights of three organs were significantly altered by lofexidine treatment (Table 14). Adrenal-to-brain weight ratios were dose-dependently decreased in females by up to 24%. A statistically insignificant trend toward decreased adrenal-to-brain weight ratios was also observed with respect to males, particularly at the HD. Heart-to-body weight ratios were dose-dependently increased in both sexes by up to 18% in males and 22% in females. Liver-to-body weight ratios were dose-dependently increased in females by up to 11%.

Table 14: Impact of Lofexidine Treatment on Organ Weights in Rats

Organ	Ratio Type	Percent Change from Control					
		LD		MD		HD	
		Male	Female	Male	Female	Male	Female
Adrenals	Brain Weight	-10%	-12%	-9%	-19%	-20%	-24%*
Heart	Body Weight	-4%	+7%	+16%**	+18%*	+9%	+22%**
Liver	Body Weight	+2%	+5%	-2%	+5%	-3%	+11%**

* Significantly different from control ($p < 0.05$)

** Significantly different from control ($p < 0.01$)

Histopathology

Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections was performed on protocol-designated sections of tissues. The slides were examined by a board-certified veterinary pathologist. A four-step grading system was utilized to define gradable lesions for comparison between dose groups. Representative samples of protocol-designated sections of tissues from all main study animals were collected and placed in the appropriate fixative for possible future processing and microscopic evaluation. Main study animals at 0 (Vehicle) and 20/10/8 mg/kg/day had a complete list of tissues collected and microscopically examined. The eyes and parotid salivary glands were determined to be potential target organs and were examined for the 5/2.5 and 10/5 mg/kg/day main study groups as well. The following tissues were evaluated:

- Adrenals
- Aorta
- Bone with Marrow, Femur
- Bone with Marrow, Sternum
- Brain (cerebrum, midbrain, cerebellum, medulla/pons)
- Epididymis
- Eye (including optic nerve)
- Gastrointestinal Tract:
 - Esophagus
 - Stomach
 - Duodenum

- Jejunum
- Ileum
- Cecum
- Colon
- Rectum
- Gonads:
 - Ovaries (with oviduct)
 - Testes
- Gross Lesions
- Heart
- Joint, Tibiofemoral
- Kidneys
- Lacrimal Gland (exorbital)
- Larynx
- Liver
- Lungs with Bronchi
- Lymph Nodes:
 - Mandibular
 - Mesenteric
- Mammary Gland
- Pancreas
- Peyer's Patch
- Pituitary
- Prostate and Seminal Vesicles
- Salivary Glands, Mandibular/Sublingual
- Salivary Glands, Parotid
- Sciatic Nerve
- Skeletal Muscle, Biceps Femoris
- Skin
- Spinal Cord (cervical, thoracic, lumbar)
- Spleen
- Thymus
- Thyroid/Parathyroid
- Tongue
- Trachea
- Ureters
- Urinary Bladder
- Uterus/Cervix
- Vagina

Adequate Battery: Yes

Peer Review: No

Histological Findings

Treatment-related findings were noted in the eyes, parotid salivary gland, kidneys, thymus, and spleen of lofexidine-treated rats (Table 15). Minimal to moderate keratitis, characterized by corneal inflammation and/or fibrosis, was noted in a dose-dependent manner in incidence and severity in LD females and at the MD and HD in both sexes. Keratitis was accompanied by erosion/ulcer, hyperplasia, and regeneration in one HD male. In females, keratitis was accompanied by erosion/ulcer in 1 LD and 1 MD female and hyperplasia in 1 HD female. Of the three HD females that were found dead, keratitis was accompanied by bacterial colonies, degeneration/necrosis, hypopyon, and/or erosion/ulcer. Minimal synechia, which is a condition where the iris adheres to the cornea or lens, was also present in both vehicle and lofexidine-treated rats; however, with slightly higher incidence in LD males and higher incidence and severity at the HD in both sexes.

Minimal to moderate acinar atrophy was noted in the parotid salivary gland in LD females and at the MD and HD in both sexes. Minimal to mild chronic progressive nephropathy was dose-dependent in all dosed males as well as in females, although with less dose-dependence. Lymphoid depletion was also noted in the spleen and thymus of all three HD female rats that were found dead.

Table 15: Histopathological Findings Associated with Lofexidine Treatment in Rats

Tissue	Observation	Severity	0 mg/kg/day		5/2.5 mg/kg/day		10/5 mg/kg/day		20/10/8 mg/kg/day	
			DOS	SNC	DOS	SNC	DOS	SNC	DOS	SNC
Males										
eyes										
	erosion/ulcer, corneal	- minimal	0	(10)	0	(10)	0	(10)	0	(10)
	hyperplasia, corneal epithelium	- minimal	0	0	0	0	0	0	0	1
	keratitis		0	0	0	0	0	6	0	5
		- minimal	0	0	0	0	0	4	0	4
		- mild	0	0	0	0	0	2	0	0
		- moderate	0	0	0	0	0	0	0	1
	regeneration	- minimal	0	0	0	0	0	0	0	1
	synechia		0	6	0	8	0	6	0	9
		- minimal	0	6	0	8	0	6	0	8
		- moderate	0	0	0	0	0	0	0	1
	within normal limits		0	4	0	2	0	1	0	1
Females										
eyes										
	bacterial colonies		0	(10)	0	(10)	0	(10)	3	(7)
		- minimal	0	0	0	0	0	0	2	0
		- mild	0	0	0	0	0	0	1	0
	degeneration/necrosis	- minimal	0	0	0	0	0	0	1	0
	erosion/ulcer, corneal		0	0	0	1	0	1	3	0
		- mild	0	0	0	1	0	1	0	0
		- moderate	0	0	0	0	0	0	2	0
		- severe	0	0	0	0	0	0	1	0
	hyperplasia, corneal epithelium	- minimal	0	0	0	0	0	0	0	1
	hypopyon	- mild	0	0	0	0	0	0	3	0
	keratitis		0	0	0	1	0	5	3	6
		- minimal	0	0	0	1	0	3	0	1
		- mild	0	0	0	0	0	2	3	5
	phthisis bulbi	- moderate	0	0	0	0	0	0	0	1
	synechia		0	4	0	3	0	4	3	7
		- minimal	0	4	0	3	0	4	3	6
		- mild	0	0	0	0	0	0	0	1
	within normal limits		0	6	0	6	0	4	0	0
Males										
salivary gland, parotid										
	atrophy, acinar		0	(10)	0	(10)	0	(10)	0	(10)
		- minimal	0	0	0	0	0	2	0	3
		- mild	0	0	0	0	0	2	0	1
		- moderate	0	0	0	0	0	0	0	2
	within normal limits		0	10	0	10	0	8	0	7
Females										
salivary gland, parotid										
	atrophy, acinar		0	(10)	0	(10)	0	(10)	3	(7)
		- minimal	0	0	0	4	0	1	2	0
		- mild	0	0	0	4	0	1	0	0
		- moderate	0	0	0	0	0	0	1	0
	within normal limits		0	10	0	6	0	9	1	7
Males										
kidneys										
	hydronephrosis, unilateral		0	(10)	0	(10)	0	(10)	0	(10)
		- minimal	0	1	0	1	0	0	0	0
		- mild	0	0	0	1	0	0	0	0
	nephropathy, chronic progressive		0	1	0	0	0	0	0	0
		- minimal	0	0	0	2	0	5	0	5
		- mild	0	0	0	2	0	5	0	4
		- moderate	0	0	0	0	0	0	0	1
	within normal limits		0	9	0	7	0	5	0	5
Females										
kidneys										
	mineralization	- minimal	0	(10)	0	(10)	0	(10)	3	(7)
		- mild	0	0	0	2	0	0	1	0
	nephropathy, chronic progressive	- minimal	0	1	0	0	0	5	0	2
	within normal limits		0	9	0	8	0	5	2	5
spleen										
	depletion, lymphoid, generalized	- mild	0	(10)	0	(10)	0	(10)	3	(7)
		- moderate	0	0	0	0	0	0	3	0
	within normal limits		0	10	0	0	0	0	0	7
thymus gland										
	depletion, lymphoid, generalized	- moderate	0	(10)	0	(10)	0	(10)	3	(7)
	hemorrhage	- mild	0	0	0	0	0	0	1	0
	necrosis, lymphoid, generalized	- moderate	0	0	0	0	0	0	3	0
	within normal limits		0	10	0	0	0	0	0	7

Toxicokinetics

Blood samples (approximately 0.5 mL) were collected into tubes containing K₂EDTA via the orbital sinus after anesthesia with carbon dioxide/oxygen inhalation from 3 control toxicokinetics rats per sex at 3 hour postdose on Days 1 and 28 and from cohorts of 3 lofexidine-treated toxicokinetics rats per sex per group prior to dosing and at 1, 3, 6, 12, and 24 hours postdose on Days 1 and 28 for determination of plasma concentrations of lofexidine. Rats were not fasted prior to collection.

As shown below in Table 16, plasma exposures increased greater than dose-proportionally. C_{max} and AUC, were higher in females than males by approximately 3-fold and 5-fold, respectively on Day 1 and approximately 2-fold for both on Day 28. Accumulation is difficult to assess as the dosage was decreased between Day 1 and Day 28, but males generally exhibited roughly equal or greater AUC and C_{max} values on Day 28 than on Day 1, in spite of the decrease in dosage whereas in females, AUC and C_{max} values were roughly dose-proportionally decreased on Day 28. T_{max} ranged from 1 to 3 hours and t_{1/2} ranged from 4 to 8 hours on Day 1 and from 2 to 4 hours on Day 28.

Table 16: Toxicokinetic Parameters for Lofexidine in Male and Female Rats

Day	Dose (mg/kg/day)	Sex	AUC _{0-<i>t</i>last} (hr•ng/mL)	AUC _{0-<i>t</i>last} /Dose ((hr•ng/mL)/mg/kg)	C _{max} (ng/mL)	C _{max} /Dose ((ng/mL)/mg/kg)	t _{1/2} (hr)	T _{max} (hr)	M/F (%)	
									AUC _{0-<i>t</i>last}	C _{max}
1	5/2.5*	M	46.5	9.29	19.6	3.93	6.61	1.00	18	33
		F	258	51.7	60.0	12.0	11.0	1.00		
	10/5*	M	213	21.3	74.8	7.48	7.80	1.00	21	33
		F	1040	104	224	22.4	6.27	1.00		
	20/10/8**	M	513	25.6	125	6.23	4.47	1.00	19	37
		F	2670	133	334	16.7	7.71	1.00		
28	5/2.5*	M	43.4	17.4	14.4	5.75	1.96	1.00	39	70
		F	111	44.4	20.7	8.27	3.08	1.00		
	10/5*	M	251	50.2	37.4	7.48	2.66	1.00	47	42
		F	531	106	89.7	17.9	2.87	3.00		
	20/10/8**	M	562	70.3	116	14.5	2.68	3.00	62	41
		F	903	113	282	35.3	4.04	1.00		

*Dose was reduced from Day 2 onward.

**Dose was reduced on Day 2 and again from Day 6.

Dosing Solution Analysis

Dosing formulations prepared for the study were evaluated for homogeneity (Table 17) and concentration (Table 18). All samples passed the acceptance criteria (recovery within 15% of nominal concentration) indicating that the animals were dosed as described in the protocol.

Table 17: Dosing Solution Homogeneity Analysis

Homogeneity				
Dose Level (mg/kg)	Nominal Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	Average % Recovery ^a	RSD (%)
5	0.5	0.5	100	0.0
20	2.0	2.05	102	2.6

^aAverage % recovery was calculated from the nominal concentration.
RSD - Relative Standard Deviation

Table 18: Dosing Solution Concentration Analysis

Concentration				
Dose Level (mg/kg)	Nominal Concentration (mg/mL)	Average Calculated Concentration (mg/mL)	Average % Recovery ^d	RSD (%)
5 ^a	0.5	0.5	100	0.0
20 ^a	2.0	2.0	100	0.0
0 ^b	0	0	NA	NA
5 ^b	0.5	0.5	100	0.0
10 ^b	1.0	1.0	100	0.0
20 ^b	2.0	2.1	105	0.0
0 ^c	0	0	NA	NA
5/2.5 ^c	0.5	0.493	98.6	0.29
10/5 ^c	1.0	0.991	99.1	0.71
20/10/8 ^c	2.0	1.969	98.45	0.93

^a – samples taken prior to initiation of dosing
^b – samples taken from the preparations conducted for Week 1
^c – samples taken from the preparations conducted for Week 4
^dAverage % recovery was calculated from the nominal concentration.
RSD - Relative Standard Deviation

Study title: Lofexidine: Sub-Acute (90 Day) Oral Toxicity Study in Rats

Study no.: USWM-LX0-TOX-0006
Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\uswm-lx0-tox-0006\uswm-lx0-tox-0006-pre-clinical-study-report.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: July 15, 1975
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: Lofexidine, Unknown, Unknown

Key Study Findings

- Lofexidine was administered via oral gavage to Sprague-Dawley rats at 0, 1, 3, or 8 mg/kg lofexidine HCl (0, 0.88, 2.6 or 7.0 mg/kg/day lofexidine free base) for 90 days.
- Prominent clinical signs observed were slight depression (MD and HD) and yellow/wet abdomen (HD).
- Body weight gains were dose-dependently decreased compared to controls (up to 37% in males and up to 23% in females). Food consumption was also dose-dependently decreased in both sexes but with greater effect in females.
- Oculopathy was observed via both clinical sign and ophthalmological examination with slightly dose-dependently increasing incidence in 1 LD (male), 2 MD (1 male and 1 female), and 3 HD (1 male and 2 females). Keratitis and/or corneal epithelial scarring was also observed histopathologically at comparable incidence with some but not complete correlation with the findings reported as clinical signs and/or ophthalmological examinations.
- BUN levels were dose-dependently increased compared to controls by approximately 2-fold in both sexes.
- Cytoplasmic swelling was observed in the liver of 9/10 rats at the HD in both sexes. Dose-dependent increased in incidence of myocarditis in the heart, hydronephrosis in the kidneys, tracheitis in the trachea, and sinus histiocytosis as well as lymphoid depletion (in HD females only) in the mesenteric lymph nodes.

- The study NOAEL was the LD of 1.0 mg/kg (0.88 mg/kg/day of the base) based on higher incidences of myocarditis in MD and HD animals compared to control, providing a 3-fold safety margin to the MRHD of 2.88 mg/day based on body surface area allometric scaling. However, the exposure margin based AUC is only 0.2x.

Methods

Doses:	0, 0.88, 2.6, 7.0 mg/kg/day lofexidine (0, 1, 3, 8 mg/kg/day lofexidine HCl salt)
Frequency of dosing:	Once Daily
Route of administration:	Oral Gavage
Dose volume:	Unknown
Formulation/Vehicle:	Distilled Water
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	10 (only 5 for clinical pathology assessments)
Age:	PND 22-24
Weight:	111-154 g (males) 107-154 g (females)
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None Reported

Mortality

Rats were observed daily for appearance and behavior.

There were a total of three unscheduled deaths: one MD male and one HD female, were found dead and one MD male rat was sacrificed moribund. All unscheduled deaths were determined by the Sponsor to be unrelated to lofexidine-treatment. The MD male rat that was found dead was determined to be the result of impacted feces in the large intestines whereas acute bronchopneumonia was determined to be the cause of death of the HD female rat, although this rat was also found to have impacted feces. The other MD male rat was sacrificed moribund due to poor weight gain resulting from malalignment of lower incisors. Clonidine has been reported to reduce water intake in rats and given the findings of reduced urine output, the impacted feces may be the result of dehydration (Atkinson et al., 1978).

Clinical Signs

Rats were observed daily for appearance and behavior.

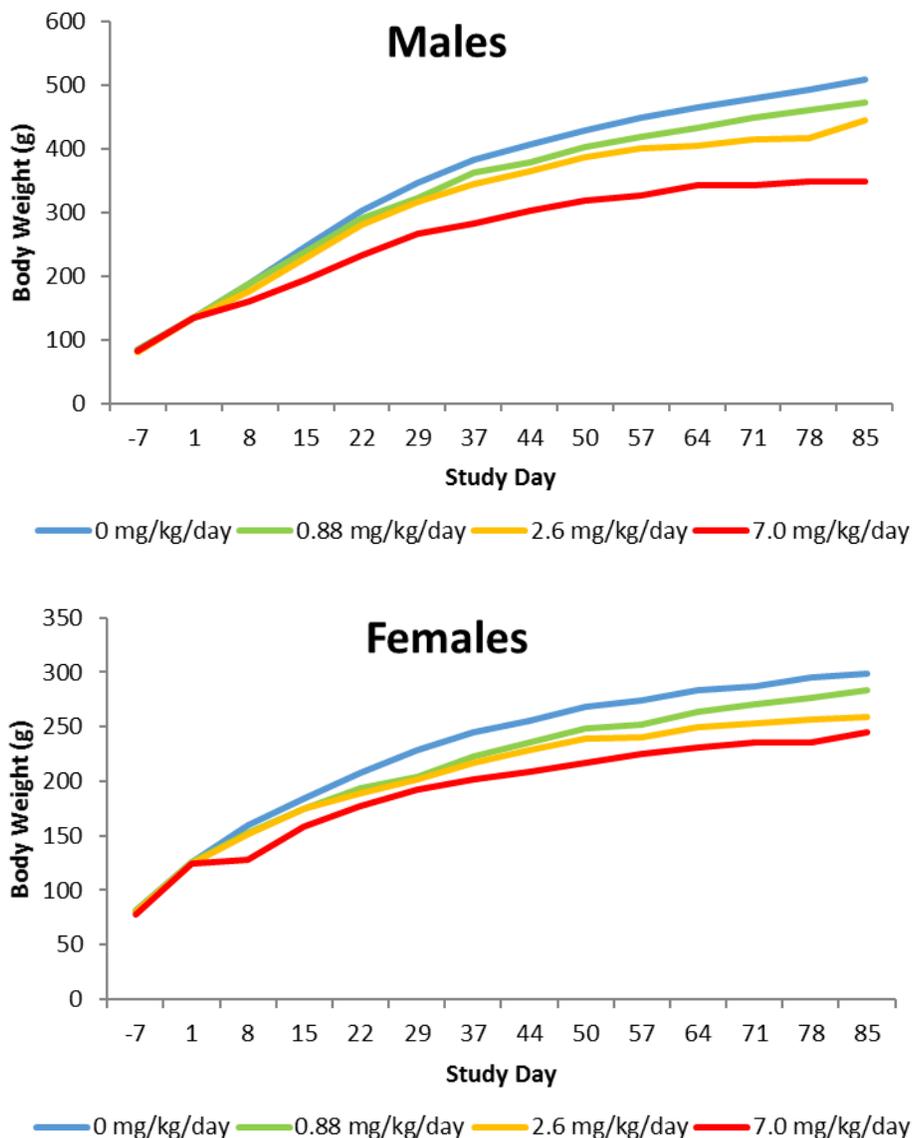
All rats of both sexes in the MD and HD treatment groups exhibited slight depression. Oculopathy was observed with low but dose-dependently increasing incidence: 1 LD (male), 2 MD (1 male and 1 female), and 3 HD (1 male and 2 females). Yellow hair and wet abdomen was observed in 7 HD females and 1 HD male with 1 HD female also exhibiting a distended abdomen. One HD female rats exhibited tremors on Day 4.

Body Weights

Body weights were recorded weekly.

Dose-dependent decreases in body weight gain were observed in both sexes. By the end of the treatment period, body weight gains in males were 9%, 14%, and 37% lower in the LD, MD, and HD treatment groups than controls and 7%, 18%, and 23% lower than controls in females, respectively (Figure 25).

Figure 25: Impact of 90-Day Lofexidine Treatment on Body Weight in Rats

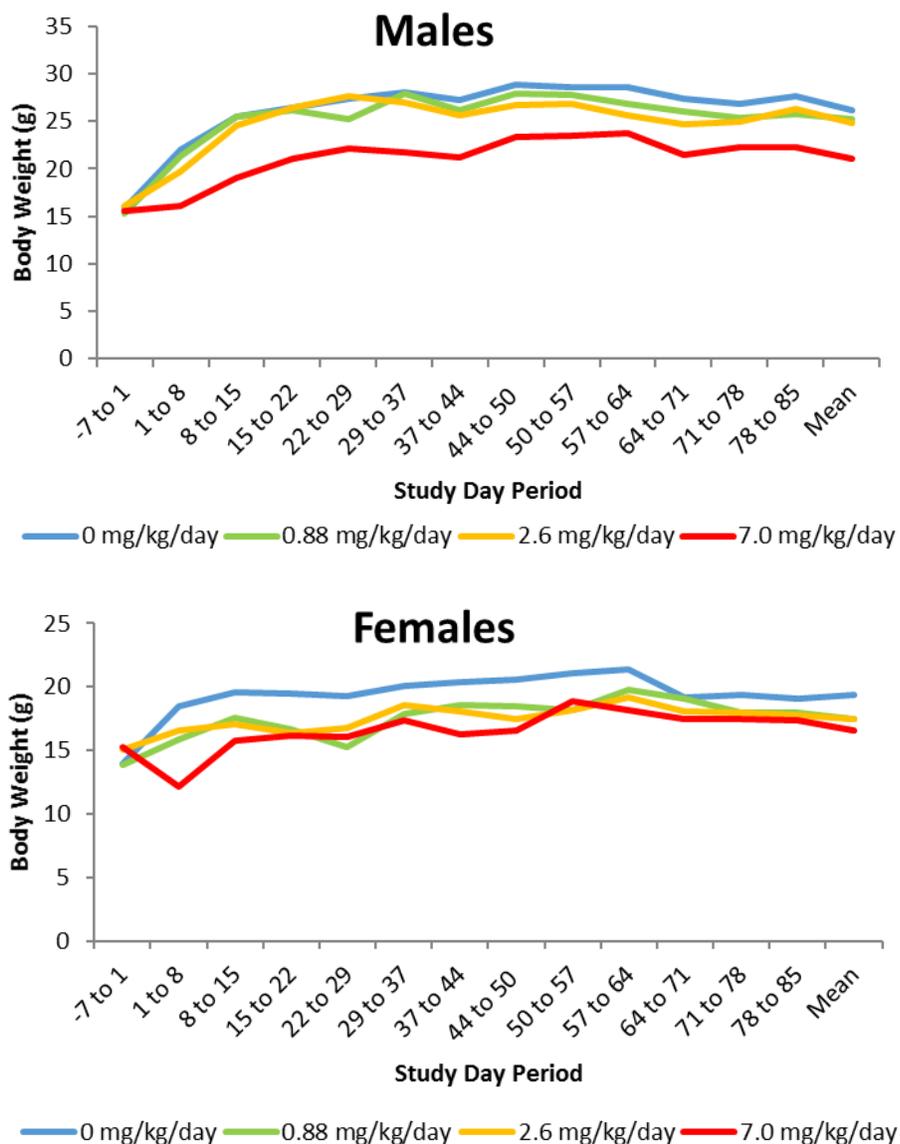


Food Consumption

Food consumption was recorded weekly.

Food consumption was decreased dose-dependently in both sexes, by 4%, 6%, and 21% in males and by 10%, 17%, and 43% in females (Figure 26).

Figure 26: Impact of 90-Day Lofexidine Treatment on Rat Food Consumption



Ophthalmoscopy

Ophthalmoscopic examination was performed on Days -2 and 90.

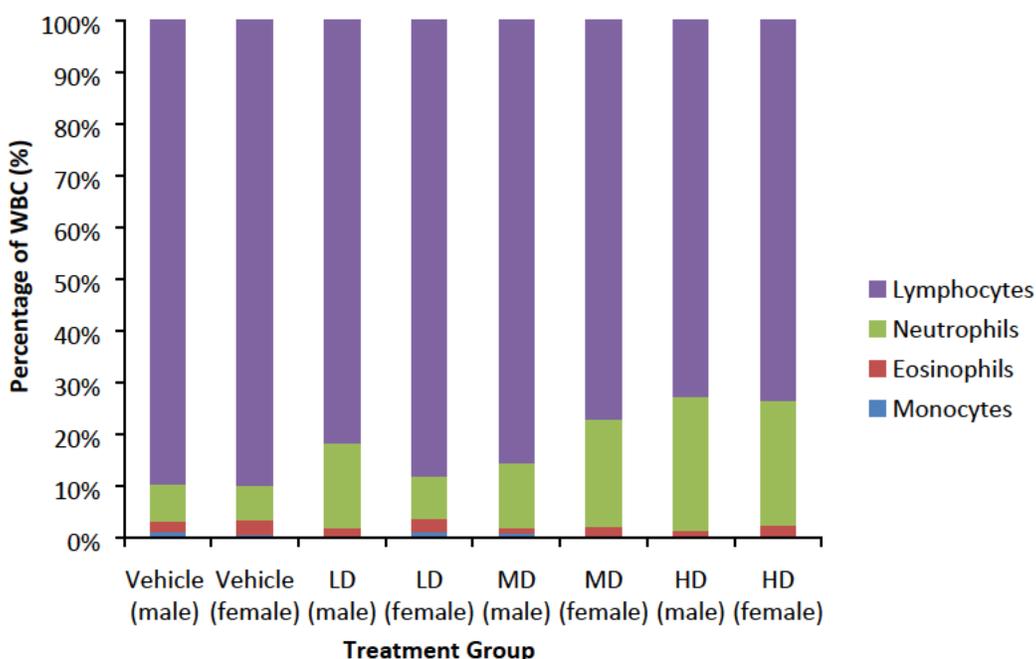
Dose dependent incidences of corneal scratches or defects were observed in 1 LD male, 2 MD (1 male and 1 female), and 3 HD (2 females and 1 male) rats.

Hematology

Blood samples for hematologic examination were obtained by cardiocentesis from 5 rats/sex/group on Days 92 and 93. Values for hemoglobin, hematocrit, white blood cell count, differential white cell count, and partial prothrombin time were recorded.

There were no clear treatment-related changes in absolute cell counts; however, analysis of the differential leukocyte counts revealed a dose-dependent increase in the relative abundance of neutrophils along with a corresponding decrease in relative abundance of lymphocytes. Statistical analysis was not reported by the sponsor and could not be performed in review due to the lack of raw data listings.

Figure 27: Impact of 90-Day Lofexidine Treatment on Differential Leukocyte Counts in Rats



Clinical Chemistry

Blood samples were obtained by cardiocentesis from 5 rats/sex/group on Days 92 and 93. Values for fasting blood glucose, blood urea nitrogen, blood total bilirubin, and serum glutamic pyruvic transaminase were recorded.

Blood urea nitrogen (BUN) levels were dose-dependently increased by up to 114% in males and 94% in females (Figure 28). Alanine aminotransferase (ALT) levels were also increased; however, with less clear dose-dependence up to 19% in males and 29% in females (Figure 29). Statistical analysis was not reported by the Sponsor and could not be performed in review due to the lack of raw data listings.

Figure 28: Impact of 90-Day Lofexidine Treatment on Rat BUN Levels

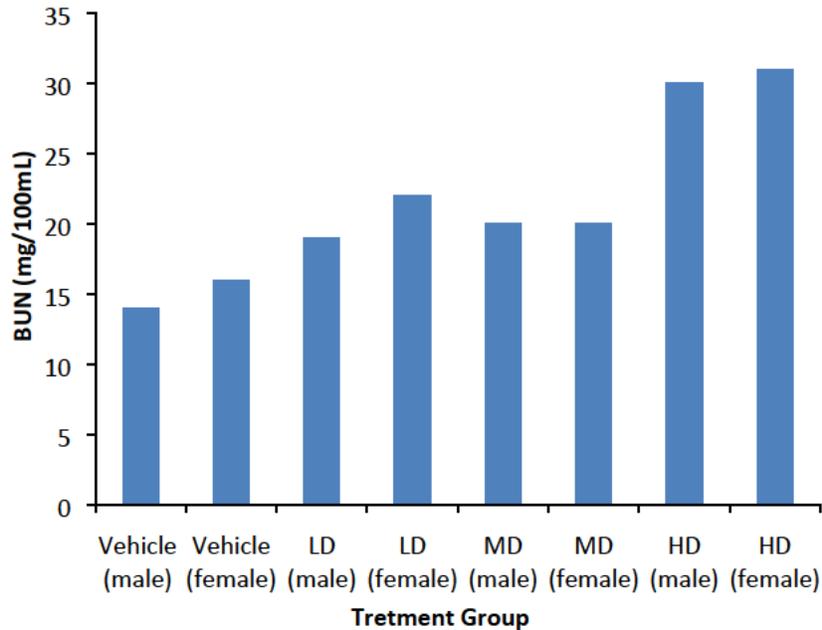
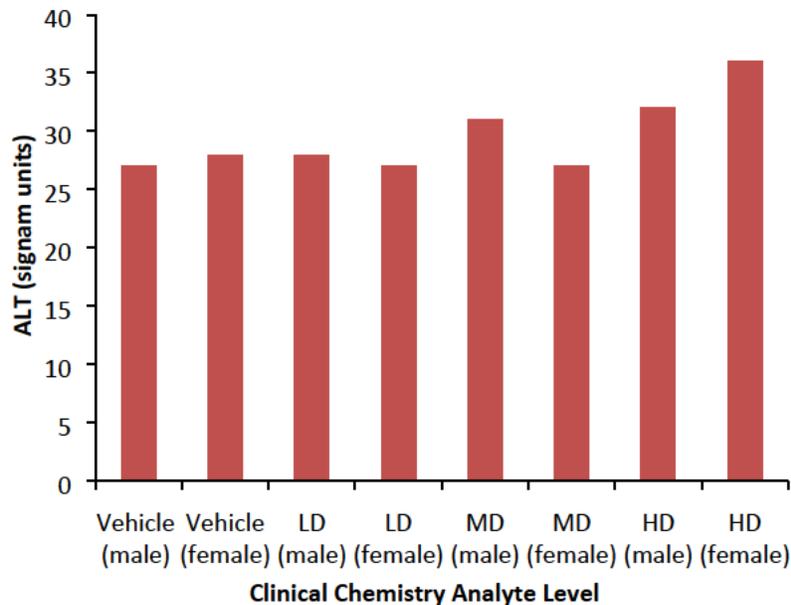


Figure 29: Impact of 90-Day Lofexidine Treatment on Rat ALT Levels



Urinalysis

Urine samples for urinalysis were taken by free-flow from 5 rats/sex/group on Day 91. Urine was analyzed for occult blood, bilirubin, ketones, glucose, protein, pH, and specific gravity, and the urinary sediment was examined microscopically.

There was no evidence of treatment-related changes in urinalysis parameters.

Gross Pathology

Rats were killed by decapitation followed by exsanguination and a complete necropsy was performed on all rats including those that died during test or were sacrificed early.

Of the two rats that were found dead, both exhibited large intestines that were distended and impacted with feces. Additionally, two HD male rats exhibited kidney hydronephrosis, which was correlated with histopathological signs of hydronephrosis.

Organ Weights

The following organs were weighed at necropsy: pituitary, thyroids, liver, spleen, kidneys, adrenals, heart, thymus, ovary, and uterus or testes, seminal vesicles, and ventral prostate.

Absolute weights of several organs were dose-dependently decreased whereas the relative organ-to-body-weight ratios of several organs were dose-dependently increased (Table 19). These changes in absolute and relative organ weights were confounded by the dose-dependent decrease in body weights in both sexes, making it difficult to distinguish an organ-specific treatment-related effect from a coincidental decrease in absolute organ weights due to a correlation of organ weight with dose-dependently decreasing body weight or a coincidental increase in relative organ weight due to a lack of correlation of organ weight with dose-dependently decreasing body weight. Changes in organ weights were assessed as absolute or relative changes based upon the historical data and analyses of the relationship between organ weights and body weights reported by Scharer (1977) and Bailey et al. (2004). A more robust statistical analysis of organ weight changes using ANCOVA, recommended for most organs by Bailey et al. (2004), could not be performed due to the lack of raw data listings.

No organ weight changes were consistently reported in both sexes. In males, significant changes were only observed at the HD. Relative pituitary and thyroid weights were significantly increased by 42% and 34%, respectively, whereas absolute thymus weights and relative prostate weights were both significantly decreased by 31% and 36%, respectively. In females, relative liver weights were significantly increased at all dose levels by up to 21%, and relative kidney weights were significantly increased at the MD and HD by up to 19%. At the HD only, relative heart and uterus weights were significantly increased by 18% and 49%, respectively, whereas adrenal and ovary weights were significantly decreased by 15% and 25%, respectively.

Table 19: Impact of 90-Day Lofexidine Treatment on Organ Weights in Rats

Organ	Organ Weight Comparison	Percent Change from Control					
		LD		MD		HD	
		Male	Female	Male	Female	Male	Female
Adrenals	Absolute Weight	-3%	-4%	+10%	-12%	-5%	-15%*
Heart	Body Weight Ratio	-4%	-2%	+2%	+9%	+13%	+18%**
Kidneys	Body Weight Ratio	0%	+9%	-2%	+19%**	+5%	+17%**
Liver	Body Weight Ratio	-3%	+10%*	+6%	+16%**	+1%	+21%**
Pituitary	Body Weight Ratio	+16%	-12%	+16%	-8%	+42%**	-9%
Spleen	Body Weight Ratio	-3%	+4%	-8%	+8%	+6%	+3%
Thymus	Absolute Weight	+3%	+4%	+2%	-7%	-31%*	-21%
Thyroid	Body Weight Ratio	+13%	+4%	6%	-4%	+34%*	+11%
Prostate	Body Weight Ratio	-2%	-	-17%	-	-36%**	-
Seminal Vesicles	Body Weight Ratio	0%	-	+2%	-	+3%	-
Testes	Neither Appropriate	-	-	-	-	-	-
Ovaries	Absolute Weight	-	-20%*	-	-14%	-	-25%**
Uterus	Body Weight Ratio	-	+29%	-	+46%*	-	+49%**

* p < 0.05; ** p < 0.01

Histopathology

The following organs/tissues were fixed in 10% phosphate buffered formalin, embedded in paraffin, sectioned at 6 microns and stained with hematoxylin and eosin: pituitary, thyroids, liver, spleen, kidneys, adrenals, heart, thymus, ovary, uterus or testes, seminal vesicles, and ventral prostate, brain, sciatic nerve, parathyroids, salivary glands, intra-orbital and exorbital lacrimal glands, external and internal lymph nodes, lung, diaphragm, esophagus, trachea, aorta, tongue, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, urinary bladder, mammary gland, skeletal muscle, skin, sternbrae, and vagina or epididymis. A smear of bone marrow was made also but was not examined microscopically. The eyes were fixed in Davidson's solution and these were handled in the same fashion as other tissues.

Adequate Battery: Yes**Peer Review: No****Histological Findings**

Select histopathological findings of potential toxicological relevance are displayed below in Table 20. The most prominent histopathological finding was cytoplasmic swelling of liver hepatocytes at the HD in both sexes, which correlated with the dose-dependent increase in liver-to-body-weight ratios in females. This finding was interpreted by the Sponsor as representing an increased metabolic burden, rather than as a manifestation of toxicity. Histopathological findings in the eye did not correlate perfectly with those of the ophthalmological examination, but corneal epithelial scars and/or keratitis were observed at least one rat at all lofexidine dose levels. Gross pathology findings of hydronephrosis in 2 HD male rats were confirmed histopathologically along with an additional finding of hydronephrosis in 1 LD female rat. Myocarditis in the heart was observed at slightly higher incidence at the MD and HD, particularly in males, which may be toxicologically relevant given that the heart is a primary pharmacological target of lofexidine. Dose-dependently increasing incidence of sinus histiocytosis in both sexes as well as lymphoid depletion in 2 HD females were observed in the mesenteric lymph nodes. These findings may be attributable to stress due to decreased food consumption and body weights. Chronic tracheitis was observed with low but dose-dependently increasing incidence, with necrotizing tracheitis observed at the HD in 1 female rat. This finding may be related to the gavage but the lack of findings in vehicle-treated rats suggests that it may be related to lofexidine treatment.

Table 20: Selected Histopathological Findings in Rats following 90-Day Treatment with Lofexidine

Organ	Finding	0 mg/kg/day		0.88 mg/kg/day		2.6 mg/kg/day		7.0 mg/kg/day	
		M	F	M	F	M	F	M	F
Eye	Corneal Epithelial Scar	-	-	1*	-	-	1*	-	-
	Keratitis	-	-	-	-	1	-	-	1*
Heart	Myocarditis	2	-	1	-	3	3	4	1
Kidney	Hydronephrosis	-	-	-	1	-	-	2**	-
Liver	Cytoplasmic Swelling	-	-	-	-	-	-	9	9
Mesenteric Lymph Node	Sinus Histiocytosis	-	1	3	3	3	6	7	4
	Lymphoid Depletion	-	-	-	-	-	-	-	2
Trachea	Chronic Tracheitis	-	-	1	-	1	2	2	-
	Necrotizing Tracheitis	-	-	-	-	-	-	-	1

* Finding correlated with findings from ophthalmological examination

** Finding correlated with findings from gross pathology examination

Toxicokinetics

Toxicokinetics evaluations were not performed.

Dosing Solution Analysis

Dosing solution analysis was not performed.

Study title: Chronic Toxicity and Carcinogenicity Study of Lofexidine in Rats

Study no.: USWM-LX0-TOX-0014

Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\uswm-lx0-tox-0014\uswm-lx0-tox-0014-pre-clinical-study-report.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: March 28, 1978

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: Lofexidine, Unknown, Unknown

Key Study Findings

- Lofexidine was administered via diet to Long Evans rats at 0, 2.6 or 7.0 mg/kg/day for 1 year.
- The mortality rate was slightly increased from 0% in controls to 4-8% at 2.6 mg/kg/day and markedly increased to 36-40% at 7.0 mg/kg/day.
- Abdominal distention, hyperexcitability, and self-mutilation were observed primarily at 7.0 mg/kg/day in both sexes.
- Body weight and food consumption were dose-dependently decreased in both lofexidine treatment groups for both sexes.
- Treatment-related histopathological findings at 7.0 mg/kg/day included: cytoplasmic vacuolation in the liver, erosion/ulceration/necrosis in the stomach, and myocardial degeneration (in males only). Erosion/ulceration/necrosis of the stomach was also observed in females at the LD, 2.6 mg/kg/day.
- No treatment-related effects on the incidence of neoplastic lesions was observed.
- A NOAEL was not identified due to increased mortality, decreased body weights, increased incidence of mortality, and stomach findings of erosion/ulceration/necrosis at all doses tested.

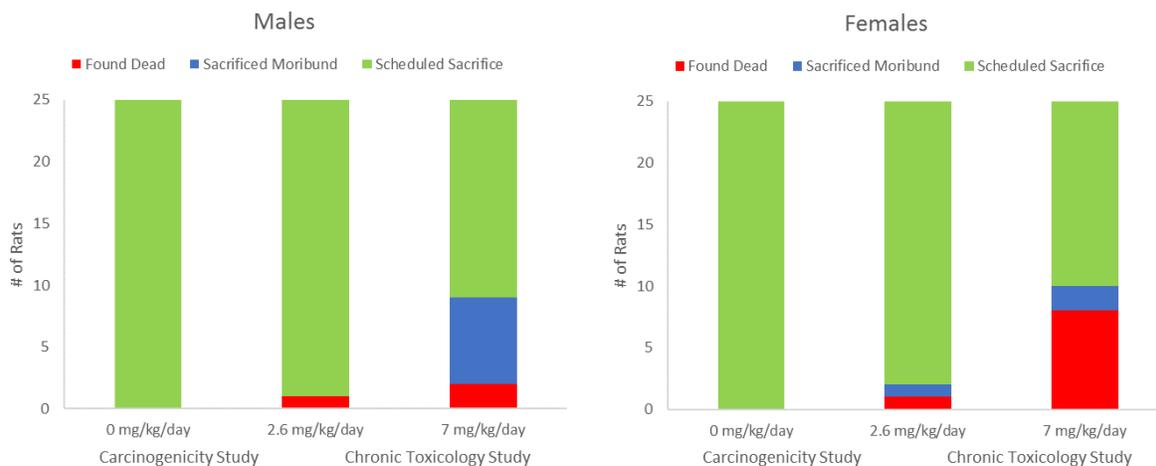
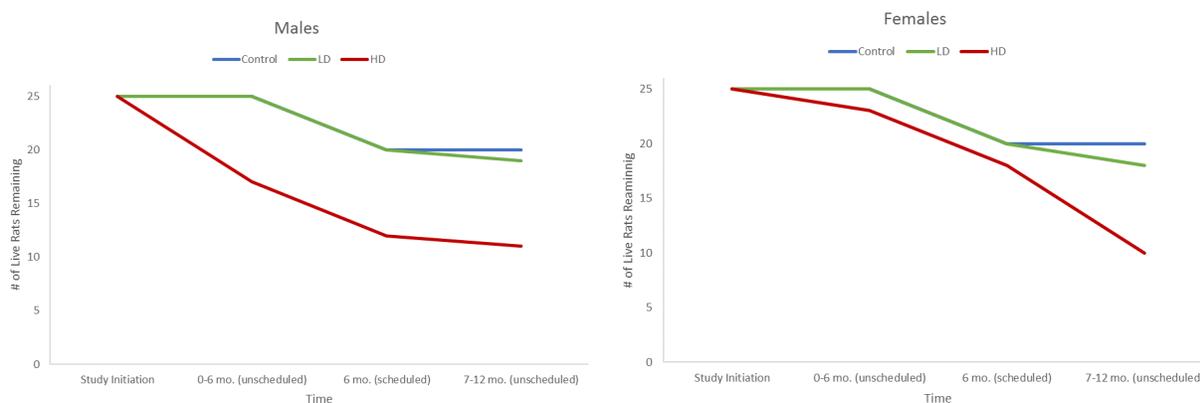
Methods

Doses: 0, 2.6, 7.0 mg/kg/day lofexidine
(0, 3, 8 mg/kg/day lofexidine HCl salt)
Frequency of dosing: Continuous
Route of administration: Diet
Dose volume: NA
Formulation/Vehicle: Formulation: Lofexidine (1%), Lactose (87.4%),
Citric Acid (11.6%)
Vehicle: Purina Lab Chow Meal
Species/Strain: Rat/Long Evans
Number/Sex/Group: 25
Age: PND 36-38
Weight: 121-171 g (males)
100-145 g (females)
Satellite groups: None
Unique study design: Interim sacrifice of 5 rats/sex/group after 6
months. Only two dose groups were evaluated.
Deviation from study protocol: None Reported

Mortality

Five rats/sex were sacrificed from all treatment groups at 6 months for toxicologic evaluation including assessments of clinical pathology (i.e., hematology, clinical chemistry, and urinalysis), gross pathology, organ weights, and histopathology. At 12 months, all surviving rats were sacrificed evaluation except clinical pathology was not assessed.

A significant increase in mortality, 36% in males and 40% in females, was observed at the HD in the chronic toxicology study. This increase in total mortality was primarily due an increase in moribund sacrifices in males and an increased number of rats found dead in females. These unscheduled deaths were more likely to occur during the first 6 months of the study in males than in females (Figure 41). Notably, five HD females died after abrupt withdrawal of lofexidine prior to terminal sacrifice at one year.

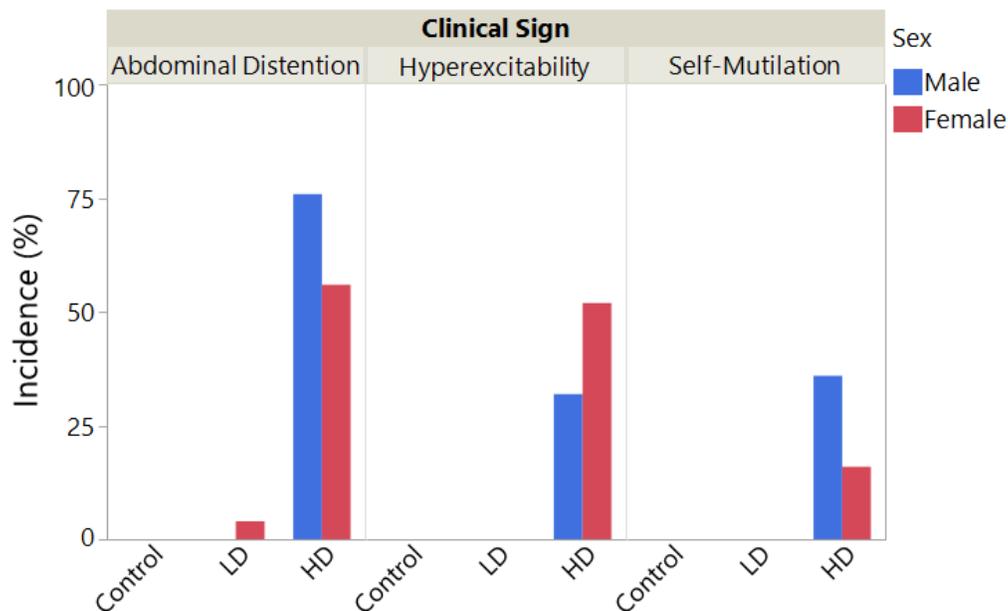
Figure 30: Mortality in Carcinogenicity and Chronic Toxicology Studies**Figure 31: Survival Curves in Carcinogenicity and Chronic Toxicology Studies**

Clinical Signs

Rats were observed daily for appearance and behavior.

There were no clinical signs reliably associated with lofexidine treatment at the LD but at the HD, abdominal distention, hyperexcitability, and self-mutilation were consistently observed in both sexes (Figure 32). The incidences of abdominal distention and self-mutilation were higher in males whereas hyperexcitability was observed more often in females. Abdominal distention was first observed during the 3rd month of the study and persisted in rats until termination. Hyperexcitability was episodic beginning on Day 5 and occurred as late as Day 183 but did not usually persist for more than several days. The earliest onset of self-mutilation occurred on Day 15 and was observed in other rats up to Day 170.

Figure 32: Clinical Signs Associated with Lofexidine Treatment in Chronic Toxicology Study

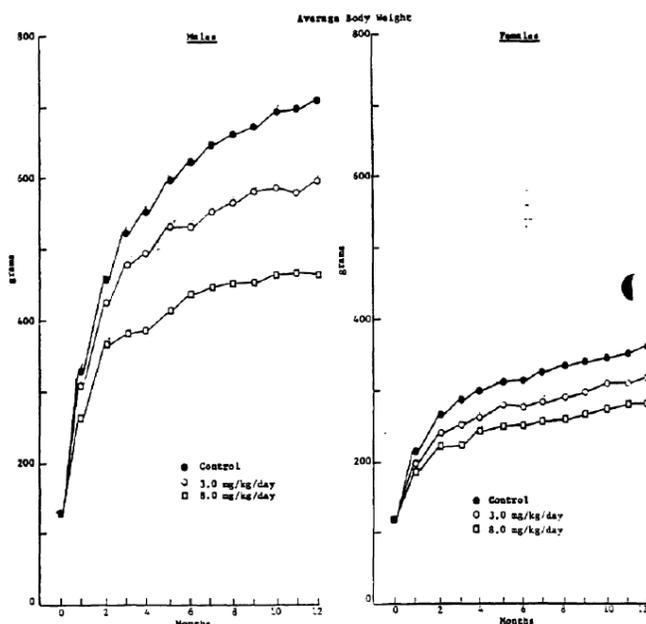


Body Weights

Body weights were recorded weekly and reported monthly.

Body weights were dose-dependently decreased throughout the entire study in both male and female rats (Figure 33). By the 12th month of the study, body weights were approximately 20% and 40% lower than controls at the LD and HD, respectively, across both sexes.

Figure 33: Impact of Lofexidine Treatment on Body Weight in Chronic Toxicology Study

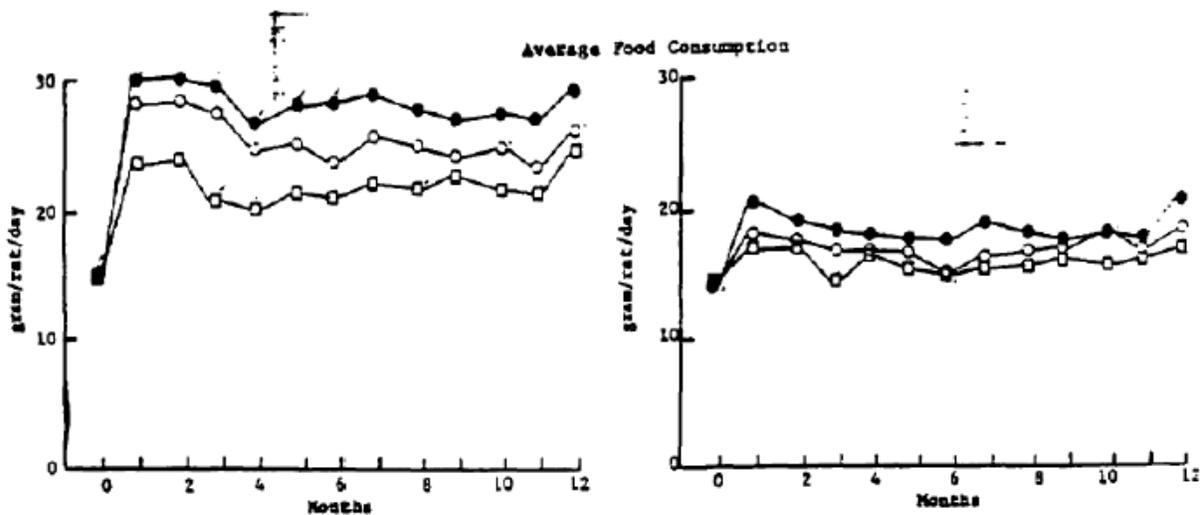


Food Consumption

Food consumption was recorded weekly.

Food consumption was dose-dependently decreased by approximately 15% and 30% at the LD and HD, respectively, in both male and female rats (Figure 34).

Figure 34: Impact of Lofexidine Treatment on Food Consumption in Chronic Toxicology Study



Ophthalmoscopy

Ophthalmic examinations were performed with the indirect ophthalmoscope following instillation in the eyes of 1% Mydriacyl prior to start of the test and prior to all scheduled sacrifices.

The results of the ophthalmic examinations were not explicitly mentioned in the study report.

Hematology

Blood samples for hematologic determinations were obtained by cardiocentesis from 5 rats/sex/group approximately 17 to 24 hours after drug/diet was withdrawn prior to scheduled sacrifices after 6 months and 12 months.

Absolute white blood cell count was not impacted by lofexidine treatment, but a dose-dependent increase in neutrophil-to-lymphocyte ratio was observed in both sexes (Figure 35; Figure 36). This effect was attributable to increases in absolute neutrophil count as well as decreases in absolute lymphocyte count and was present after 180 days and persisted until the end of the study. There were no additional significant effects of lofexidine treatment observed with respect to red blood cell, white blood cell, or coagulation parameters.

Figure 35: Impact of 1-Year Lofexidine Treatment on Absolute Differential White Blood Cell Count in Rats

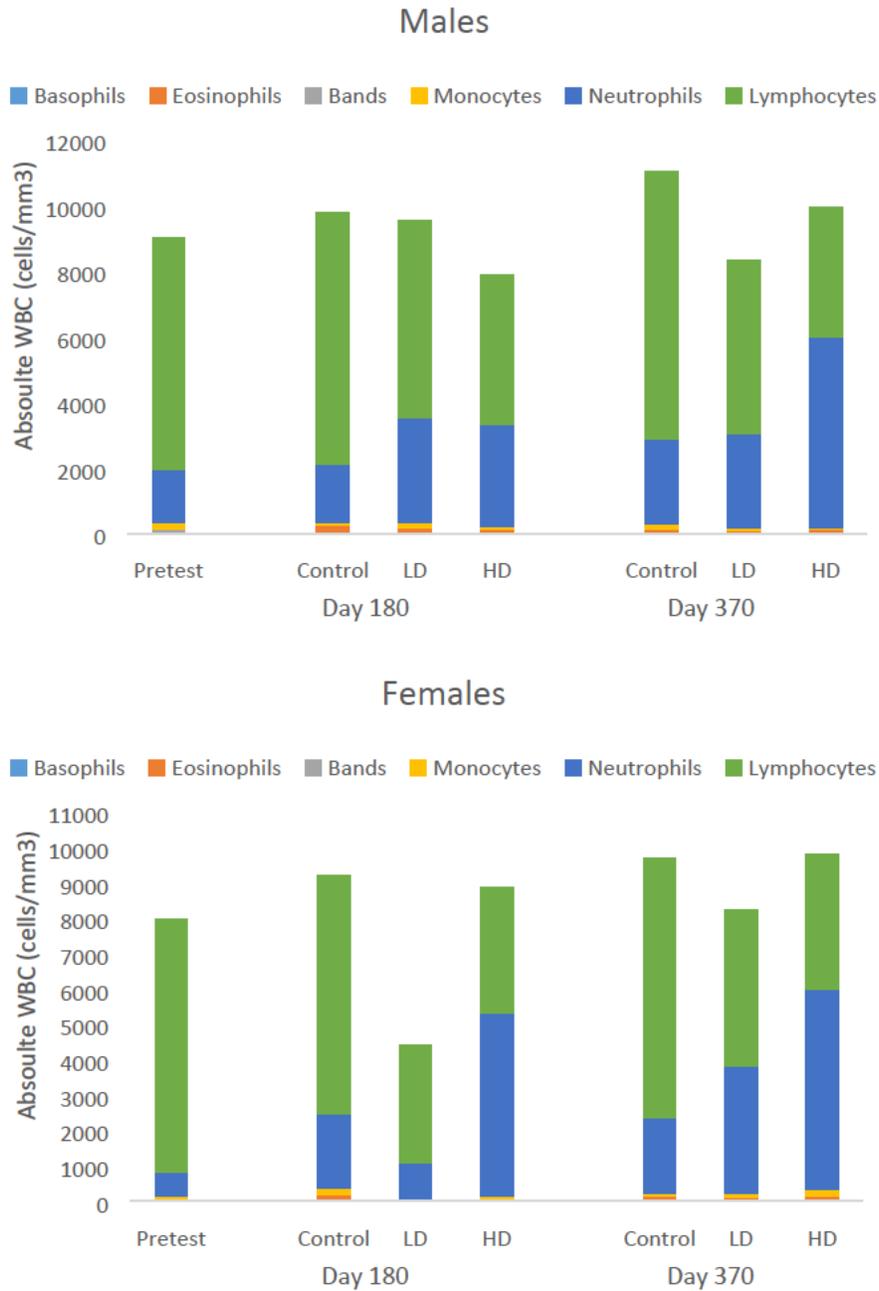
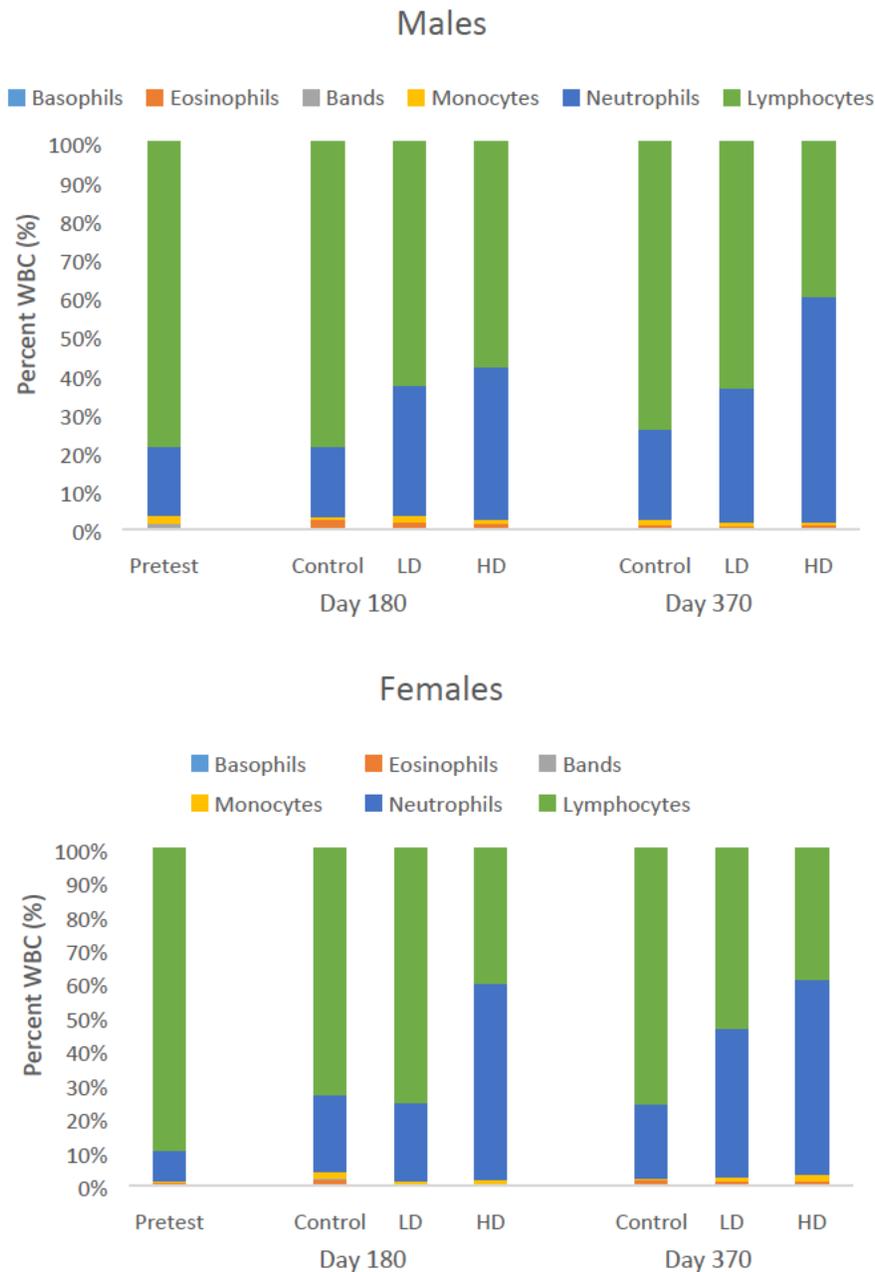


Figure 36: Impact of 1-Year Lofexidine Treatment on Percent Differential White Blood Cell Count in Rats



Clinical Chemistry

Blood samples for clinical chemistry determinations were obtained by cardiocentesis from 5 rats/sex/group approximately 17 to 24 hours after drug/diet was withdrawn prior to scheduled sacrifices after 6 months and 12 months.

Less than 2-fold increases in the liver enzyme aspartate aminotransferase (AST) were observed in lofexidine treated rats at both doses compared to control rats in males at 6

months and in females at 6 months and 12 months. A 2.6-fold increase in urea nitrogen was observed in HD females compared to controls at 6 months but only a 1.5-fold increase was observed at 12 months. Dose-dependent slight reductions in total protein, albumin, calcium, and glucose observed in both sexes were also observed and could be attributed to dose-dependent reductions in food consumption.

Urinalysis

Voided samples of urine were collected from the 5 rats/sex/group approximately 17 to 24 hours after drug/diet was withdrawn prior to scheduled sacrifices after 6 months and 12 months.

There were no treatment-related effects observed in any urinalysis parameters.

Gross Pathology

A complete necropsy was performed on all rats.

As shown in Table 21, a dose-dependent increase in incidence of gross lesions in the liver and stomach were observed during the first year of the study. Lesions in the liver were characterized as alterations of the color, size, or consistency and were sometimes correlated with histopathologically identified cytoplasmic vacuoles (Table 23). The dose-dependency of the incidence of these lesions was most apparent at the 12-month sacrifice. Lesions in the stomach, characterized as erosion, ulceration, hemorrhage, or red foci, were observed in approximately half of the rats at 7.0 mg/kg/day in both sexes and at 2.6 mg/kg/day in females only. Neither of these lesions were associated with unscheduled mortality. Lesions associated with unscheduled mortality were observed primarily at the highest dose evaluated, 7.0 mg/kg/day, and included: enlarged spleen, enlarged lymph nodes, small/atrophic prostate/seminal vesicles, small testis, enlarged/flabby heart, and self-mutilation lesions of the tail/flank.

Table 21: Macroscopic Findings Observed in First 12 Months of Study

Organ: Finding	Timing of Sacrifice	Dose Group (mg/kg/day)					
		0		2.6		7.0	
		Male	Female	Male	Female	Male	Female
Liver: Altered Color, Size, or Consistency	Scheduled 6-Month	1/10	-	-	-	1/5	3/5
	Scheduled 12-Month	1/30	1/30	3/19	3/18	6/11	9/10
	Unscheduled	-	1/3	-	1/2	-	-
	Total	2/25 (8%)	2/25 (8%)	3/25 (12%)	4/25 (16%)	7/25 (28%)	12/25 (48%)
Stomach: Erosion, Ulceration, Hemorrhage, or Red Foci	Scheduled 6-Month	-	-	-	4/5	5/5	5/5
	Scheduled 12-Month	-	-	-	5/10	7/11	
	Unscheduled	-	-	-	1/2	2/9	1/10
	Total	1/25 (4%)	0/25 (0%)	0/25 (0%)	10/25 (40%)	14/25 (56%)	16/25 (64%)

Organ Weights

Weights of the following organs were recorded from 5 rats/sex/group sacrificed at 6 months and all surviving rats sacrificed at 12 months: pituitary, thyroids, liver, spleen, kidneys, adrenals, heart, thymus, ovaries and uterus, or testes, seminal vesicles, and ventral prostate.

Changes in absolute and relative organ weights were confounded by the dose-dependent decrease in body weights in both sexes, making it difficult to distinguish an organ-specific treatment-related effect from a coincidental decrease in absolute organ weights due to a correlation of organ weight with dose-dependently decreasing body weight or a coincidental increase in relative organ weight due to a lack of correlation of organ weight with dose-dependently decreasing body weight. Changes in organ weights were assessed as absolute or relative changes based upon the historical data and analyses of the relationship between organ weights and body weights reported by Scharer (1977) and Bailey et al. (2004). A more robust statistical analysis of organ weight changes using ANCOVA, recommended for most organs by Bailey et al. (2004), could not be performed due to the lack of raw data listings.

At the 6-month sacrifice, absolute thymus weights were significantly decreased in males at the HD and relative spleen-to-body weight ratios were significantly decreased at the HD in males and females. At the 12-month sacrifice, thymus weights were not recorded but statistically significant changes in relative organ-to-body weight ratios were observed in the spleen, heart, liver, pituitary, thyroid, and seminal vesicles. Relative spleen weights remained decreased at the HD in males and females whereas relative thyroid weights were increased in these same groups. Relative heart weights were notably dose-dependently increased at the MD and HD in both sexes. Relative liver weights were increased at the HD in females but a decrease was observed at the MD in males. Relative pituitary and seminal vesicle weights were increased in males at the HD.

Table 22: Statistically Significant Differences in Organs Weights Compared to Controls after Oral Lofexidine Administration in Rats

Timing of Sacrifice	Organ	Organ Weight Comparison	Dose Group (mg/kg/day)			
			2.6		7.0	
			Male	Female	Male	Female
6 Months	Thymus	Absolute	-	-	-10%	-
	Spleen	Relative	-	-	-17%	-45%
12 Months	Spleen	Relative	-	-	-25%	-28%
	Heart	Relative	+14%	+15%	+26%	+23%
	Thyroid	Relative	-	-	+27%	+35%
	Liver	Relative	-9%	-	-	+9%
	Pituitary	Relative	-	-	+41%	-
	Seminal Vesicles	Relative	-	-	+30%	-

Histopathology

For the chronic toxicology study, histopathological examination was performed on all rats from the 7.0 mg/kg/day group and 10 rats/sex/group from the 0 and 2.6 mg/kg/day groups, sacrificed after 12 months. Tissues to be examined were fixed in 10% phosphate buffered formalin (except Davidson's solution was used to fix some eyes), embedded in paraffin, sectioned at 6 microns and stained with hematoxylin and eosin. The pituitary, thyroids, liver, spleen, kidneys, adrenals, heart, thymus, ovaries and uterus, or testes, seminal vesicles, ventral prostate, brain, sciatic nerve, parathyroids, salivary gland, intra- and exorbital lacrimal glands, external and internal lymph nodes, lung, sternbra, diaphragm, esophagus, trachea, aorta, tongue, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, urinary bladder, mammary gland, skeletal muscle, skin, vagina or epididymis were prepared and examined microscopically.

Adequate Battery: Yes

Peer Review: No

Histological Findings

The primary target organs with treatment-related non-neoplastic histopathological findings were the liver, stomach, and heart (Table 23). The incidence of cytoplasmic vacuoles in the liver was increased at the 7.0 mg/kg/day dose, particularly in females. Erosion, ulceration, and/or necrosis was observed in the stomach of females at 2.6 mg/kg/day and in both sexes at 7.0 mg/kg/day. Notably, these stomach findings were not attributable as the cause of death for any of the unscheduled deaths and were observed only in the MD and HD groups. Myocardial degeneration and/or necrosis was observed only in male rats at 7.0 mg/kg/day (HD). These findings were all approximately just as likely to occur during the first 6 months as the second 6 months of the first year of the study. Additional potentially treatment-related findings of relatively low incidence included dacryoadenitis in the lacrimal gland, lymphoid depletion and siderosis in the spleen, hematopoiesis in the spleen and liver, and bit wounds in the flank, abdominal skin, and tail.

Table 23: Histopathology Lesions Observed in 12-Month Chronic Study

Organ	Finding	Sex	Dose (mg/kg/day)	Incidence
Liver	Cytoplasmic Vacuoles	Male	0	1/15 (7%)
			7.0	3/25 (12%)
			7.0	15/25 (60%)
Stomach	Erosion / Ulceration / Necrosis	Male	7.0	5/25 (20%)
		Female	2.6	2/10 (20%)
			7.0	14/25 (56%)
Heart	Myocardial Necrosis / Degeneration	Male	0	1/15 (7%)
			7.0	5/25 (20%)

Toxicokinetics

Toxicokinetics evaluations were not performed.

Dosing Solution Analysis

Dosing solution analysis was not performed.

Study title: Subacute Oral Toxicity Study with RMI 14,042A in Dogs

Study no.: USWM-LX0-TOX-0019
Study report location: <\\cdsesub1\levsprod\nda209229\0002\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\uswm-lx0-tox-0019\uswm-lx0-tox-0019-pre-clinical-study-report.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: July 25, 1975
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: Lofexidine, unknown, unknown

Key Study Findings

- Lofexidine was administered orally via capsule to Beagle dogs at 0, 0.88, or 2.6 mg/kg/day for 90 days.
- Slight depression was observed in all lofexidine-treated dogs.
- Bradycardia was observed in most lofexidine-treated dogs at the HD in both sexes.
- Increases in liver enzymes, i.e., ALT and ALP, ranging from 50% to 250% were observed in lofexidine-treated dogs of both sexes, primarily at the HD.
- Centrilobular scarring/inflammation was observed in one male HD dog. Mild chronic interstitial nephritis was observed in 1 HD male and 1 HD female.
- A NOAEL was established at the LD, 0.88 mg/kg/day providing a 10-fold safety margin to the MRHD of 2.88 mg/day based on body surface area allometric scaling. However, the exposure margin based AUC is only 1.8x.

Methods

Doses: 0, 0.88, 2.6 mg/kg/day lofexidine
(0, 1, 3 mg/kg/day lofexidine HCl salt)
Frequency of dosing: Once daily
Route of administration: Oral
Dose volume: NA
Formulation/Vehicle: Gelatin capsule
Species/Strain: Dog/Beagle
Number/Sex/Group: 3
Age: 10 to 13 months
Weight: 7.5 to 15.0 kg
Satellite groups: None
Unique study design: None
Deviation from study protocol: None Reported

Mortality

Dogs were observed daily for appearance and department.

All dogs survived until their scheduled sacrifice at the end of the study.

Clinical Signs

Dogs were observed daily for appearance and behavior/clinical signs. A physical examination was performed on each dog on Day -9, 34, and 90.

Slight depression was observed in all lofexidine-treated dogs on Day 1 and most males on Day 2. Occasional emesis was also observed in most dosed dogs in both sexes. One HD male dog displayed difficulty standing on Day 3. Slow heartbeat was observed in all HD dogs of both sexes on Day 90.

Body Weights

Body weights were recorded weekly.

There were no treatment-related effects on body weight.

Food Consumption

Food consumption was recorded weekly.

There were no treatment-related effects on food consumption.

Ophthalmoscopy

An ophthalmoscopic examination was performed on each dog on Days -9, 34, and 90.

None of the dogs had detectable ocular abnormalities on ophthalmoscopic examination.

ECG

Electrocardiographic (ECG) tracings utilizing leads I, AVL, AVF, CV6LL, VIO, and CV5RL were obtained on Days -2, 15, and 87.

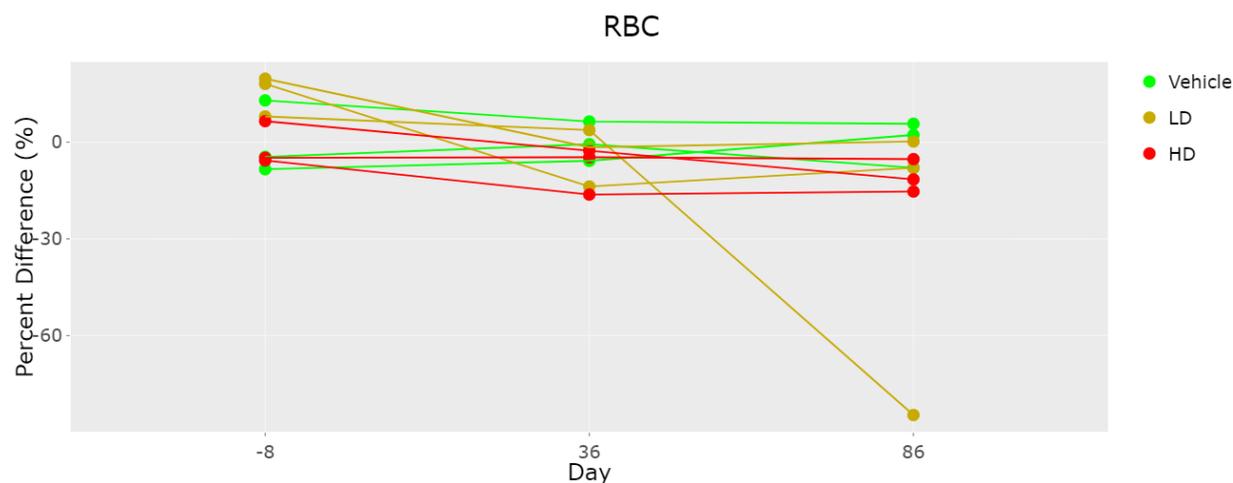
Bradycardia was observed at the HD in 5/6 dogs across both sexes on Day 15 and Day 87 and in one LD male dog only on Day 15.

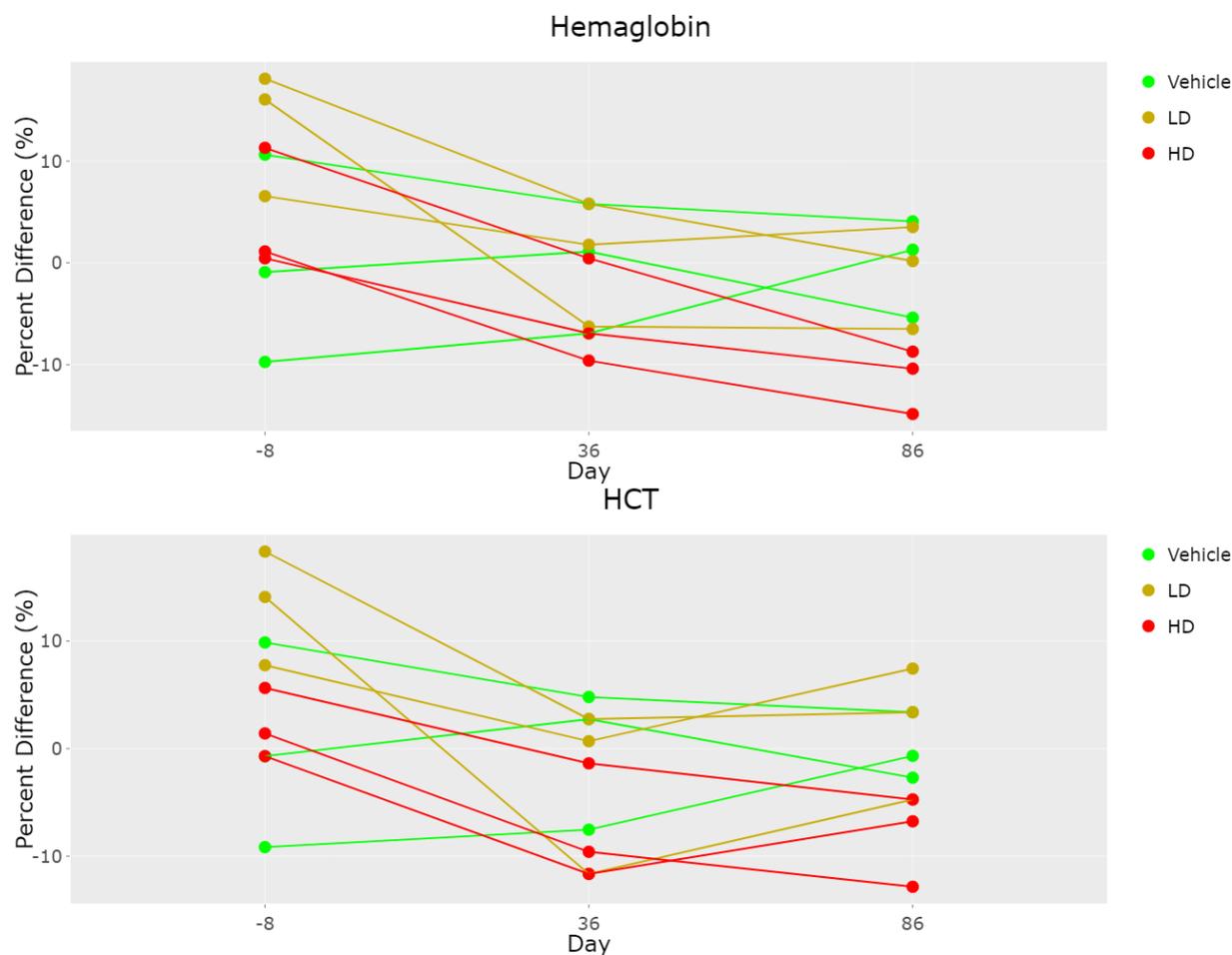
Hematology

Hematological procedures were performed on fasted blood samples obtained by puncture of the jugular vein on Day -8, 36, and 86. These procedures included hemoglobin, hematocrit (HCT), total erythrocyte count (RBC), total and differential leukocyte counts, estimation of platelets, prothrombin time, and partial thromboplastin time.

An approximately 10% decrease compared to controls was observed in HD males on Day 36 and Day 86 in the following red blood cell parameters: RBC, hemoglobin, and HCT, (Figure 37). There were no additional noteworthy effects of lofexidine treatment on the other hematology parameters.

Figure 37: Impact of 90-Day Lofexidine Treatment on Red Blood Cell Parameters in Male Dogs

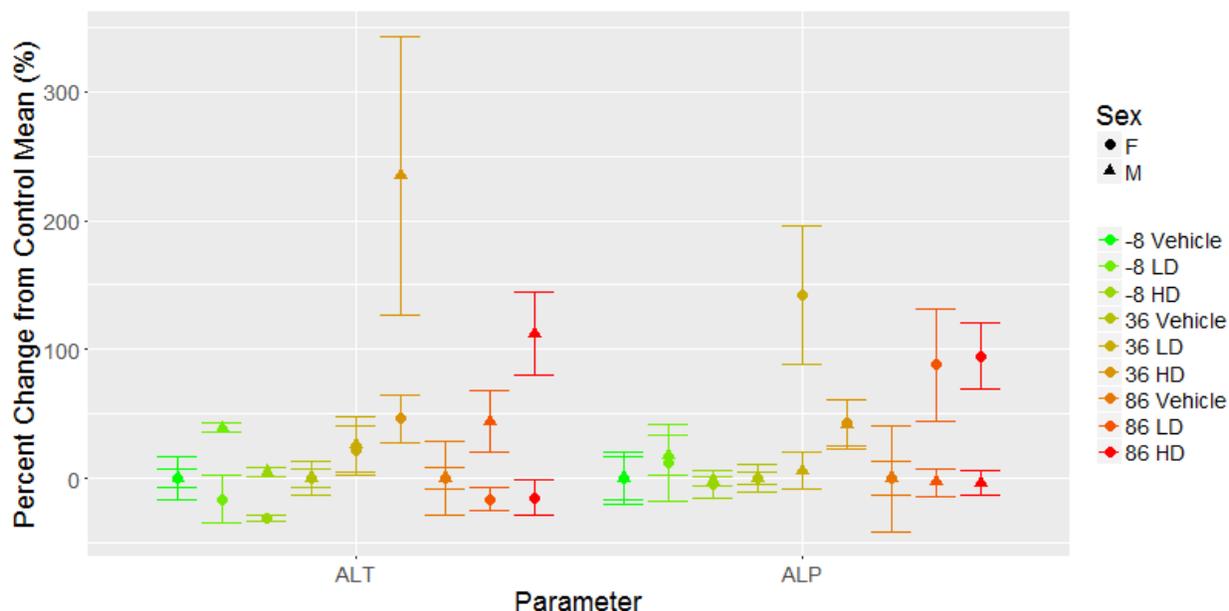




Clinical Chemistry

Blood chemical procedures were performed on fasted blood samples obtained by puncture of the jugular vein on Day -8, 36, and 86. These procedures included glucose, urea nitrogen, total bilirubin, alkaline phosphatase (ALP), total protein, albumin, albumin-globulin ratio, chloride, sodium, potassium, aspartate transaminase (AST), and alanine transaminase (ALT).

Increased levels of the liver enzymes, ALT and ALP, were observed in lofexidine-treated dogs of both sexes on Day 36, with ALT increased by 234% in males and 46% in females at the HD and ALP increased by 142% in females at the LD and 43% in males and 42% in females at the HD, compared to vehicle-treated dogs (Figure 38). On Day 86, ALT was increased by 112% only in males, whereas ALP was only increased by 88% and 95% in LD and HD females, respectively. These changes in liver enzyme levels reported here with respect to levels in vehicle-treated dogs at the same time point are also relatively consistent with changes from baseline (Day -8) within each treatment group as there was little variation among the levels recorded at baseline across treatment groups. There were no additional noteworthy effects of lofexidine treatment on other clinical chemistry parameters.

Figure 38: Impact of Lofexidine Treatment on Liver Enzymes, ALT and ALP

Urinalysis

Urinalyses were performed on samples taken by catheterization on Day -5, 31, and 90.

A slight, but statistically significant, 2% decrease in specific gravity was observed in female dogs at the LD on Day 86. As this effect was not dose-dependent and of low magnitude, it is unlikely to be truly treatment-related. There were no additional noteworthy effects of lofexidine treatment observed with respect to urinalysis parameters.

Gross Pathology

Twenty-four hours after the last dose, dogs were anesthetized with sodium thiamylal, exsanguinated, and necropsied.

No treatment-related gross abnormalities were observed.

Organ Weights

The weight of the pituitary, thyroids, liver, spleen, kidneys, adrenals, gonads, uterus, prostate, and heart (total heart weight and outer wall of the left and the right ventricles) were recorded.

Absolute adrenal weights were statistically significantly increased by 35% in males at the HD. This finding was less significant with respect to adrenal-to-body-weight ratio; however, there was not a strong correlation between adrenal weight and terminal body weight in these dogs and the effect was stronger, not weaker, when analyzed by ANCOVA with terminal body weight as a covariate.

One HD female had high liver weight (74-168). This dog had a 57% increase in ALT on Day 36 and 49% and 106% increases in ALP on Day 86.

Histopathology

The following organs were fixed in 10% phosphate-buffered formalin, embedded in paraffin, sectioned at 6 microns, and stained with hematoxylin and eosin: pituitary, thyroids, liver, spleen, kidneys, adrenals, gonads, uterus, prostate, heart, parathyroids, tonsils, thymus, mandibular salivary gland and lymph node, tongue, esophagus, sternebra, lung, hilar lymph nodes, aorta, diaphragm, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, cholecyst, urocyst, mesenteric lymph node, lumbar muscle and skin, mammary gland, epididymis, vagina, and costochondral junction. Specimens of brain (cerebrum, cerebellum), lumbar cord, sciatic nerve, and pituitary were fixed in 20% buffered formalin and the eyes in Davidson's solution and processed in a similar manner. A bone marrow smear was prepared but not examined microscopically.

Adequate Battery: Yes

Peer Review: No

Histological Findings

Potentially treatment-related histopathological findings were limited to the liver and kidneys in 1 HD male and 1 HD female. Liver findings included scarring of several centrilobular areas with pigment-bearing macrophages and scattered myelin bodies in the male dog, and a few clusters of pigment-laden Kupffer cells in the female dog. Additionally, mild chronic interstitial nephritis was observed in both of these dogs but no other dogs in the study. Both of these dogs exhibited the highest liver weights for their sex and the male dog exhibited the highest kidney weight in the study.

Toxicokinetics

Toxicokinetics evaluations were not performed.

Dosing Solution Analysis

Dosing solution analysis was not performed.

Study title: Chronic Oral Toxicity Study with Lofexidine in Dogs

Study no.: USWM-LX0-TOX-0020
Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\uswm-lx0-tox-0020\uswm-lx0-tox-0020.pdf>

Conducting laboratory and location:  (b) (4)

Date of study initiation: November 30, 1977
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: Lofexidine, Unknown, Unknown

Key Study Findings

- Lofexidine was administered orally via capsule to Beagle dogs at 0, 0.09, 0.26, 0.88, 2.6, or 4.4/8.8* mg/kg/day for 1 year (*The HD was increased from 4.4 mg/kg/day to 8.8 mg/kg/day after 6 months).
- 1/4 female dogs at 2.6 mg/kg/day was sacrificed moribund within the first month and 2/4 female dogs at 4.4/8.8 mg/kg/day were found dead after the first 6 months.
- Dose-dependent depression, ataxia, and bradycardia were observed at doses \geq 0.88 mg/kg/day in males and \geq 2.6 mg/kg/day in females. Additional clinical signs observed at doses \geq 2.6 mg/kg/day included: tremors, lethargic/listless, Cheyne-Stokes respiration, weak pulse, piloerection, coughing, limping, hyperthermia, spasticity, convulsions, ptyalism, weakness, and hyperactivity.
- Dose-dependent hepatopathy characterized by increased liver weights at doses \geq 0.26 mg/kg/day, elevated liver enzymes (ALT and ALP) at doses \geq 0.88 mg/kg/day, gross and microscopic lesions, e.g., centrilobular fibroplasia with bile stasis, intracytoplasmic hyaline bodies, fibrinofibrous capsulitis, congestion and hemorrhage, hepatocellular necrosis, cytoplasmic vacuolization, and hepatocellular degeneration, at doses \geq 2.6 mg/kg/day was observed.
- Nephropathy characterized by microscopic lesions, e.g., cortical calcinosis, new tubule formation, tubular degeneration, scars and/or casts, was observed at doses \geq 2.6 mg/kg/day.
- Cardiovascular toxicity characterized by ECG alterations, e.g., bradycardia and/or second degree A-V block, at doses \geq 2.6 mg/kg/day and both

macroscopic and microscopic evidence of cardiac hemorrhage in females at the 4.4/8.8 mg/kg/day dose was observed.

- A NOAEL was established at 0.88 mg/kg/day based on ECG changes as well as histopathological signs of hepatopathy and nephropathy at doses ≥ 2.6 mg/kg/day providing a 10-fold safety margin to the MRHD of 2.88 mg/day based on body surface area allometric scaling. However, the exposure margin based AUC is only 1.8x.

Methods

Doses:	0, 0.09, 0.26, 0.88, 2.6, 4.4/8.8 ^b mg/kg/day lofexidine base (0, 0.1, 0.3, 1.0, 3.0, 5.0/10 mg/kg/day lofexidine HCl salt)
Frequency of dosing:	Once Daily
Route of administration:	Oral
Dose volume:	NA
Formulation/Vehicle:	Gelatin Capsule ^c
Species/Strain:	Dog/Beagle
Number/Sex/Group:	4 (with an interim sacrifice of 1 dog/sex/group after 6 months)
Age:	9 to 27 months
Weight:	Males: 8.5 to 14.3 kg Females: 6.8 to 14.0 kg
Satellite groups:	None
Unique study design:	Five dose groups were evaluated.
Deviation from study protocol:	None Reported

Mortality

Dogs were observed daily to check for morbidity/mortality.

There were three unscheduled deaths in this study. One female in the 2.6 mg/kg/day treatment group was sacrificed moribund on Day 28. This dog has exhibited bloody emesis one day prior and Cheyne-Stokes respiration and blood from the anus on the day of sacrifice. Two females at the HD died at least one month after the dose was increased from 4.6 mg/kg/day to 8.8 mg/kg/day on Day 190. One died on Day 239 after exhibiting mydriasis and hematemesis. The other died on Day 286 after exhibiting weakness and terminal convulsions.

^b The 4.4 mg/kg/day lofexidine (5.0 mg/kg/day lofexidine HCl) dose was increased to 8.8 mg/kg/day lofexidine (10 mg/kg/day lofexidine HCl) after 6 months in an attempt to precipitate toxic effects.

^c In order to increase the accuracy of drug administration at the lowest dosages (≤ 0.88 mg/kg/day), the compound was expanded according to the following ratio: 1.0% test article, 87.4% lactose, and 11.6% citric acid.

Clinical Signs

Dogs were observed daily for appearance and behavior.

Except for transient drug-related depression observed during the first 3 days of treatment in 3 male dogs, along with ataxia and bradycardia in one of these dogs on Day 1, there were no treatment-related clinical signs at doses less than or equal to 0.88 mg/kg/day (Table 24). There were several treatment-related clinical signs observed in the 2.6 mg/kg/day and 4.4/8.8 mg/kg/day groups. Additional treatment-related signs observed at doses greater than or equal to 2.6 mg/kg/day were tremors, lethargic/listless, Cheyne-Stokes respiration, weak pulse, piloerection, coughing, and limping. Hyperthermia, spasticity, convulsions, ptyalism, weakness, and hyperactivity were observed only in the 4.4/8.8 mg/kg/day treatment group. These effects were slightly more frequent in females at the HD.

Table 24: Treatment-Related Clinical Signs Associated with Oral Lofexidine Administration in Dogs

	Dose Group (mg/kg/day)											
	Control		0.1		0.3		1.0		3.0		5.0/10.0	
	4M	4F	4M	4F	4M	4F	4M	4F	4M	4F	4M	4F
Depression							3		4	4	3	3
Ataxia, staggering							1		1	2	2	2
Tremors									1		1	3
Lethargic, listless										2		1
Bradycardia							1		3	2	1	2
Hyperpnea, hyperventilating, Cheyne-Stokes										1	1	3
Hyperthermia											1	2
Spasticity											1	1
Convulsions												1
Ptyalism											1	
Weak											2	1
Pulse slow and weak										1		
Hyperactive												1
Piloerection of dorsum										1	1	3
Coughing										1	1	3
Limping, lameness										1	1	1

Body Weights

Body weight was recorded weekly.

Except for one female dog in the 2.6 mg/kg/day treatment group that had lost 4 kg and was sacrificed moribund on Day 28, lofexidine treatment did not reliably impact body weights in this study.

Food Consumption

Food consumption was not recorded.

Ophthalmoscopy

The eyes were examined with an ophthalmoscope and biomicroscope prior to dosing and at 6, 9, and 12 months after the initiation of dosing. Dogs in the 2.6 mg/kg/day and 4.4/8.8 mg/kg/day treatment groups were not examined with the biomicroscope prior to dosing.

Examination of the eyes revealed no drug induced changes.

ECG

Electrocardiographic tracings were made utilizing leads AVL, AVF, CV₅RL, Lead I, CV₆11 and V₁₀ prior to dosing, approximately 6 months after the initiation of dosing, and terminally.

Treatment-related ECG abnormalities, consisting of bradycardia and/or second degree A-V block (Mobitz Type II), were observed in the 2.6 mg/kg/day and 4.4/8.8 mg/kg/day treatment groups. These alterations were indicative of vagal stimulation, either direct or indirect, and possible conduction blocks.

Hematology

Hematological determinations were executed on samples from fasted dogs obtained by jugular venicentesis prior to initiation of dosing, at selected times during the test, and terminally. All samples were collected 20 to 23 hours after the previous day's dosing.

A dose-dependent decrease in hemoglobin, hematocrit, and red blood cell count was particularly apparent in both sexes at the 2.6 and 4.4/8.8 mg/kg/day dose levels yet these reduced values were not outside the normal limits of these parameters.

Clinical Chemistry

Blood samples were collected from fasted dogs obtained by jugular venicentesis prior to initiation of dosing, at selected times during the test, and terminally. All samples were collected 20 to 23 hours after the previous day's dosing.

Dose-dependent increases plasma levels of the liver enzymes alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were observed in lofexidine-treated dogs starting at 0.88 mg/kg/day. These liver enzyme elevations were only correlated with histopathological evidence of liver pathology in the 2.6 mg/kg/day and 4.4/8.8 mg/kg/day treatment groups.

Urinalysis

Pretest and terminal urine samples were taken by catheterization from fasted dogs 21 to 23 hours after the previous day's dose.

Isolated incidences of slight bilirubinuria and glucosuria as well as granular and/or hyaline casts were observed in lofexidine-treated dogs without a clear dose relationship.

Gross Pathology

A complete necropsy was conducted on each dog whether it died, was sacrificed moribund, or was sacrificed on schedule. Dogs were sacrificed by exsanguination following anesthetization with sodium thiamylal.

No treatment-related gross lesions were observed in the 0.09, 0.26, or 0.88 mg/kg/day treatment groups. Treatment-related lesions were most prominently observed in the liver at the 2.6 mg/kg/day and 4.4/8.8 mg/kg/day dose levels (Table 25). In addition to these findings, purplish foci in the gall bladder, hemorrhagic/swollen adrenals, and discolored/red areas in the gastrointestinal tract were observed in the female dog from the 2.6 mg/kg/day treatment group that was sacrificed moribund. Additional gross lesions were also observed in the two HD females that were found dead during the study. The hearts of both of these dogs contained hemorrhages. In one of these dogs the stomach was reddened with hemorrhages and there was excessive mucus in the intestinal tract. The other dog had subcutaneous hemorrhages in thoracolumbar area of the back. In addition, the HD female that was sacrificed at 6 months exhibited a hemorrhagic focus and linear red areas of the duodenal mucosa.

Table 25: Incidence of Gross Lesions Observed in the Liver of Lofexidine Treatment in Dogs

	Dose Group (mg/kg/day)											
	Control		0.1		0.3		1.0		3.0		5.0/10.0	
	4M	4F	4M	4F	4M	4F	4M	4F	4M	4F	4M	4F
Liver - firm/cuts with resistance/rubbery											1	3
- mottled/pale/yellowish									1	1	1	3
- lobes adherent									2	2	1	
- frosty area(s)									2	1	1	
- enlarged												2

Organ Weights

The weights of the following organs were recorded for all dogs sacrificed terminally: thyroids, liver, spleen, pituitary, kidneys, adrenals, gonads, uterus, prostate, and heart (total heart weight and outer wall of left and right ventricles).

Liver weights were increased in the 2.6 mg/kg/day and 4.4/8.8 mg/kg/day treatment groups (Table 26). As liver weights were correlated with body weights, liver-to-body weight ratio was a less variable and more reliable metric than absolute body weight. This effect was relatively dose-dependent with some increase in liver weights observed at 0.26 mg/kg/day but not 0.88 mg/kg/day.

Table 26: Impact of Lofexidine Treatment on Liver Weights in Dogs

Measurement		Dose of Lofexidine (mg/kg/day)											
		0		0.09		0.26		0.88		2.6		4.4/8.8	
		M	F	M	F	M	F	M	F	M	F	M	F
Absolute Liver Weight	Mean ± SE (g)	223 ± 15	166 ± 14	216 ± 20	301 ± 12	303 ± 20	187 ± 22	217 ± 6.5	190 ± 13	288 ± 17	238 ± 22	260 ± 11	236 ± 9
	Percent Change from Control (%)	-	-	-3	-7	+35	+12	-2.6	+14	+29	+43	+16	+42
Liver-to-Body Weight Ratio	Mean ± SE (g/kg)	20.0 ± 0.3	21.1 ± 1.6	19.3 ± 0.9	20.2 ± 1.0	22.4 ± 1.8	23.3 ± 1.9	20.6 ± 1.5	20.4 ± 0.4	25.0 ± 2.1	26.0 ± 2.4	28.3 ± 0.5	26.7 ± 3.8
	Percent Change from Control (%)	-	-	-4	-4	+12	+10	+3	-4	+25	+23	+41	+26

Histopathology

A full histopathological examination was conducted for each dog whether it died, was sacrificed moribund, or was sacrificed on schedule. The following organs were fixed in 10% phosphate-buffered formalin: thyroids, liver, spleen, pituitary, kidneys, adrenals, gonads, uterus, prostate, heart, parathyroids, tonsils, thymus, mandibular salivary gland and lymph node, tongue, esophagus, sternebra (bone marrow), lung, bronchial (hilar) lymph nodes, aorta, diaphragm, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, cholecyst, urocyt, mesenteric lymph node, lumbar muscle and skin, mammary gland, epididymis, and vagina. Specimens of the brain (cerebrum, cerebellum), lumbar cord, and sciatic nerve were fixed in 20% buffered formalin and the eyes in Davidson's solution. Specimens of the superior cervical ganglion were removed from selected dogs and fixed in 10% phosphate-buffered formalin. A bone marrow smear was prepared but not examined. For histologic examination, the tissues were paraffin embedded, sectioned 6 microns thick, and stained with hematoxylin and eosin. The liver from 3 HD dogs and appropriate controls were stained with Oil-red-O for fat and PAS-Luxol Fast Blue for lipoprotein. The study report suggests that the pathologic liver and kidney findings as well as the hemorrhages observed in the heart and a few other organs are consistent with hypoxia induced by chronic exposure to the hypotensive pharmacologic activity of lofexidine rather than direct toxic effects.

Adequate Battery: Yes

Peer Review: No

Histological Findings

Treatment related lesions of the liver and kidneys were observed in both sexes at the 2.6 mg/kg/day and 4.4/8.8 mg/kg/day dose levels. With the exception of one female dog in the 2.6 mg/kg/day group, all dogs at these dose levels exhibited hepatopathy characterized by at least one of the following findings: centrilobular fibroplasia with bile stasis, intracytoplasmic hyaline bodies, fibrinofibrous capsulitis, congestion and hemorrhage, hepatocellular necrosis, cytoplasmic vacuolization, and hepatocellular degeneration. Evidence of hepatopathy present in all dogs sacrificed at 6 months as well as in all dogs that died or were sacrificed moribund. Special staining applied to

sections of liver from HD dogs revealed that the hyaline bodies were composed of lipoprotein not neutral lipid. Similarly, all but 1 male in the 2.6 mg/kg/day group and 1 male in the 4.4/8.8 mg/kg/day group exhibited nephropathy represented by cortical calcinosis, new tubule formation, tubular degeneration, scars and/or casts. In addition to these hepatic and renal lesions, cardiac hemorrhage with focal necrosis or calcifying scar as well as gastric mucosal congestion were observed in both HD females that were found dead. Hemorrhage was also observed in the adrenals, thymus, and subcutaneous adipose tissue of one of these dogs. In the female dog sacrificed moribund from the 2.6 mg/kg/day group, hemorrhage with or without edema and congestion were also observed in the gall bladder, intestinal tract, and omentum.

Table 27: Incidence of Histopathological Lesions in the Liver and Kidney Associated with Oral Lofexidine Administration in Dogs

	Dose Group (mg/kg/day)											
	Control		0.1		0.3		1.0		3.0		5.0/10.0	
	4M	4F	1M ^a	1F ^a	1M ^a	1F ^a	4M	4F	4M	4F	4M	4F
Liver - granuloma(s)	4	1	1	1	1	1	2	3	3	1	4	2
- bile stasis	2						1	1	3	2	3	4
- necrobiosis	1							1				
- melanosis					1							
- "salt inclusions"									1		1	
- intracytoplasmic hyalin bodies									3	1	2	2
- centrilobular fibroplasia/endotheliosis									3		4	4
- fibrinofibrous capsulitis									1	1		
- hepatic acidophilia									1	1	1	
- hepatic swelling/granularity									2			
- hemorrhage(s)/congestion									1	1		
- necrotic hepatocytes									1		1	
- hepatic degeneration										1		
- cytoplasmic vacuoles										1		
- cholangitis									1			
- central phlebitis									1			
Kidney - medullary calcinosis		1	1	1	1	1	1	1		2		
- cortical calcinosis									3	3	2	4
- pyelitis			1									
- neotubules									1		3	3
- tubular degeneration										1		
- scar(s)											2	
- amorphous casts											1	
- interstitial nephritis									2	1	2	4

Toxicokinetics

Toxicokinetics evaluations were not performed.

Dosing Solution Analysis

Dosing solution analysis was not performed.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Assay

Study no.: USWM-LX0-TOX-0008

Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\uswm-lx0-tox-0008\uswm-lx0-tox-0008-pre-clinical-study-report.pdf>

Conducting laboratory and location:



Date of study initiation: March 12, 2009

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: Lofexidine HCl, 28003072, 100.5%

Key Study Findings

- Lofexidine HCl was not mutagenic in any strains tested, with or without metabolic activation.

Methods

Strains: *Salmonella typhimurium*: TA98, TA100, TA1535, and TA1537

Escherichia coli: WP2 *uvrA*

Concentrations in definitive study: 50, 150, 500, 1500, and 5000 mcg/plate (Concentrations were adjusted to compensate for the salt form of the test article using a correction factor of 1.14.

Basis of concentration selection: Maximum concentration of 5000 mcg/plate did not produce background lawn toxicity in dose-range finding study.

Negative control: Phosphate-Buffered Saline, pH 7.4

Positive control: Without S9 Activation:

TA98: 2-Nitrofluorene

TA100: Sodium azide

TA1535: Sodium azide

TA1537: 9-Aminoacridine

WP2 *uvrA*: Methyl methanesulfonate

With S9 Activation:

All Strains: 2-Aminoanthracene

Formulation/Vehicle: Phosphate-Buffered Saline, pH 7.4

Incubation & sampling time: 48 to 72 hours

Study Validity

Standard bacterial tester strains were evaluated. Positive and negative controls produced expected responses. Selection of the concentrations tested was adequate based upon use of a limit dose (i.e., 5000 mcg/plate). Taken together the study appears to be valid.

Results

Lofexidine HCl did not increase the number of revertant colonies at any of the concentrations evaluated (up to 5000 mcg/plate) in either the dose range-finding study (Table 28) or the confirmatory study (Table 29). Reductions in revertant counts were observed at 5000 mcg/plate with tester strain WP2 *uvrA* during the dose range-finding study, but no background lawn toxicity was observed. In addition, no precipitate was observed.

Table 28: Ames Assay Evaluation of the Mutagenicity of Lofexidine HCl (Dose-Range-Finding Study)

Metabolic Activation	Test Article	Dose Level (µg/plate)	Revertant Colony Counts (Mean ± SD)							
			TA98	TA100	TA1535	TA1537	WP2 <i>uvrA</i>			
Without Activation	PBS, pH 7.4 (Vehicle)	200 µL/plate	29 ± 4	175 ± 8	17 ± 5	6 ± 0	52 ± 1			
Activation	Lofexidine hydrochloride	1.5	17 ± 2	170 ± 1	16 ± 4	5 ± 2	53 ± 13			
		5.0	20 ± 5	162 ± 40	13 ± 1	8 ± 1	45 ± 1			
		15	21 ± 2	121 ± 25	13 ± 1	7 ± 1	48 ± 3			
		50	17 ± 1	172 ± 34	15 ± 3	10 ± 5	59 ± 5			
		150	18 ± 1	164 ± 2	15 ± 3	11 ± 1	48 ± 2			
		500	16 ± 5	135 ± 3	15 ± 1	7 ± 5	43 ± 6			
		1500	19 ± 4	145 ± 2	19 ± 1	7 ± 2	29 ± 5			
		5000	15 ± 2	139 ± 3	19 ± 3	11 ± 2	18 ± 3			
	2-nitrofluorene	1.0	248 ± 27							
	Sodium azide	1.0		687 ± 77	542 ± 88					
9-aminoacridine	75				2099 ± 360					
Methyl methanesulfonate	1000						440 ± 6			
With Activation	PBS, pH 7.4 (Vehicle)	200 µL/plate	27 ± 3	179 ± 7	16 ± 1	5 ± 4	46 ± 5			
Activation	Lofexidine hydrochloride	1.5	26 ± 8	174 ± 1	17 ± 4	6 ± 1	46 ± 9			
		5.0	30 ± 1	180 ± 6	19 ± 7	7 ± 2	41 ± 11			
		15	31 ± 7	180 ± 7	16 ± 4	6 ± 7	47 ± 8			
		50	29 ± 12	183 ± 9	16 ± 0	8 ± 2	56 ± 4			
		150	25 ± 11	172 ± 27	17 ± 4	9 ± 1	39 ± 5			
		500	25 ± 1	176 ± 11	16 ± 1	5 ± 1	43 ± 2			
		1500	34 ± 1	162 ± 25	16 ± 1	7 ± 1	34 ± 0			
		5000	24 ± 1	139 ± 11	15 ± 5	5 ± 5	20 ± 4			
	2-aminoanthracene	1.0	470 ± 22		167 ± 71	65 ± 6				
	2-aminoanthracene	2.0		1160 ± 1						
2-aminoanthracene	10					344 ± 52				

Table 29: Ames Assay Evaluation of the Mutagenicity of Lofexidine HCl (Confirmatory Study)

Metabolic Activation	Test Article	Dose Level (µg/plate)	Revertant Colony Counts (Mean ± SD)								
			TA98		TA100		TA1535		TA1537		WP2 <i>uvrA</i>
Without Activation	PBS, pH 7.4 (Vehicle)	200 µL/plate	11 ± 2	134 ± 13	12 ± 4	4 ± 2	28 ± 5				
	Lofexidine hydrochloride	50	12 ± 2	139 ± 13	16 ± 3	5 ± 2	34 ± 5				
		150	12 ± 3	121 ± 26	14 ± 1	6 ± 3	30 ± 6				
		500	11 ± 4	131 ± 25	14 ± 1	7 ± 1	30 ± 8				
		1500	8 ± 2	118 ± 4	13 ± 2	5 ± 1	29 ± 6				
		5000	7 ± 6	115 ± 16	13 ± 1	4 ± 1	14 ± 1				
	2-nitrofluorene	1.0	239 ± 127								
	Sodium azide	1.0		544 ± 34	425 ± 10						
	9-aminoacridine	75				2201 ± 199					
	Methyl methanesulfonate	1000							438 ± 19		
	With Activation	PBS, pH 7.4 (Vehicle)	200 µL/plate	14 ± 2	124 ± 22	10 ± 5	4 ± 2	27 ± 4			
		Lofexidine hydrochloride	50	16 ± 2	119 ± 6	15 ± 4	4 ± 3	40 ± 12			
150			12 ± 2	149 ± 10	14 ± 4	5 ± 4	31 ± 5				
500			13 ± 8	129 ± 20	13 ± 3	6 ± 2	36 ± 4				
1500			16 ± 3	121 ± 13	12 ± 4	4 ± 1	25 ± 3				
5000			8 ± 4	108 ± 14	9 ± 1	7 ± 2	25 ± 2				
2-aminoanthracene		1.0	478 ± 92		172 ± 40	75 ± 7					
2-aminoanthracene		2.0		800 ± 21							
2-aminoanthracene		10						264 ± 73			

Lofexidine tested negative in all strains in the presence or absence of metabolic activation and was concluded to be non-mutagenic under the conditions tested.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: *In Vitro* Mammalian Cell Gene Mutation Test (L5178Y/TK^{+/-} Mouse Lymphoma Assay)

Study no.: USWM-LX0-TOX-0001
 Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\uswm-lx0-tox-0001\uswm-lx0-tox-0001-pre-clinical-study-report.pdf>

Conducting laboratory and location: (b) (4)

Date of study initiation: April 15, 2009
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Lofexidine HCl, 21498-08-8, 100.07%

Key Study Findings

- A significant increase in induced mutant frequency was observed after 4-hour exposure to lofexidine HCl at 40 mcg/mL with metabolic activation.

- This effect could be primarily attributed to an increase in the number of small colonies, indicating a clastogenic mode of action.

Methods

Cell line:	L5178Y Mouse Lymphoma TK ^{+/-} Cells
Concentrations in definitive study:	4-hour exposure (without S9): 100, 150, 250, 400, 500, 600 mcg/mL 24-hour exposure (without S9): 25, 50, 75, 100, 125 mcg/mL 4-hour exposure (with S9): 2.5, 5, 10, 40, 60, 75 mcg/mL
Basis of concentration selection:	Concentrations were limited on the basis of decreased suspension growth observed in preliminary toxicity assays.
Negative control:	Phosphate Buffered Saline
Positive control:	Methyl methane sulfonate (without S9) 7,12-Dimethyl-benz(a)anthracene (with S9)
Formulation/Vehicle:	Phosphate Buffered Saline
Incubation & sampling time:	4-hour incubation with and without S9 (sampled at 48 hours) and 24-hour incubation without S9 (sampled at 72 hours).

Study Validity

The study was deemed valid for the following reasons: 1) cytotoxicity data, plating efficiency, colony counts, mutant frequencies for treated and control cultures and mutant colony sizes were within acceptable range; 2) positive controls exhibited an increase above background; 3) maximum concentrations with relative total growth values were achieved.

It is noted that the dosing formulation analysis revealed that the actual concentrations of the dosing solutions used for the 150 mcg/mL and 2,600 mcg/mL nominal concentrations in the preliminary toxicity assay were found to be only 73.3% of their respective theoretical levels, which is outside of the Sponsor's defined acceptable range of $\pm 15\%$ (Table 33). Additionally, the dosing solution used for the dilution of all final concentrations used in the mutagenesis assay was found to be only 74% theoretical and 70% upon testing of a backup sample (Table 34). Although these results were outside of the Sponsor's defined acceptable range, they were unlikely to impact the validity of the study as appropriate toxicity-inducing concentrations were successfully selected for the mutagenesis assay; however, an adjustment for the difference between the nominal and actual concentrations employed in the mutagenesis assay should be considered when interpreting the results. Overall, these deviations did not affect the results of the interpretation of the results.

Results

No evidence of genotoxicity was observed without metabolic activation after 4-hour or 24-hour exposure at concentrations of up to 500 mcg/mL and 100 mcg/mL, respectively (Table 30; Table 31). A significant increase in induced mutant frequency was observed after 4-hour exposure with metabolic activation at the highest evaluable concentration tested 40 mcg/mL (Table 32). Evaluation of the colony size distribution revealed that the increase in mutant frequency observed at 40 mcg/mL lofexidine HCl could be primarily attributed to an increase in small colonies, suggesting a clastogenic rather than mutagenic mode of action (Figure 39).

Table 30: Preliminary Toxicity and Mutagenesis Results for 4-Hour Treatment with Lofexidine HCl without S9 in Mouse Lymphoma Assay

DOSE LEVEL (µg/mL)	PRECIP	CELL CONCENTRATION (cells/mL x 10 ⁶)			SUSPENSION GROWTH	
		DAY 0	DAY 1	DAY 2	TOTAL	% OF CONTROL
4HR NON-ACTIVATED CULTURES						
SOLVENT 1			1.230	1.515	20.7	100
SOLVENT 2			1.203	1.552	20.7	
		Not applicable for 4-hour exposure				
0.5			1.294	1.471	21.1	102
1.5			1.398	1.541	23.9	116
5			1.364	1.380	20.9	101
15			1.361	1.398	21.2	102
50			1.266	1.458	20.5	99
150			1.051	1.397	16.3	79
500			0.430	1.246	6.0	29
1500			0.019	0.073	0.0	0
2600			0.108	0.221	0.0	0

**DATA SUMMARY FOR L5178Y/TK⁺ MOUSE LYMPHOMA CELLS
TREATED WITH Lofexidine hydrochloride
IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION
Initial Assay (4-hour exposure)**

DOSE LEVEL (µg/mL)	PRECIP.	TOTAL SUSP. GROWTH	% SUSP. GROWTH	TFT COLONIES				VC COLONIES				TOTAL MUTANT FREQUENCY (PER 10 ⁶ CELLS)	INDUCED MUTANT FREQUENCY (PER 10 ⁶ CELLS)	% TOTAL GROWTH
				PLATE COUNTS				PLATE COUNTS						
				1	2	3	MEAN	1	2	3	MEAN			
SOLVENT 1		17.2	100	21	47	29	32	197	197	187	194	33	N/A	100
SOLVENT 2		16.8		42	28	34	35	197	193	167	186	37		
100	A	17.0	100	43	51	43	46	241	214	199	218	42	7	114
100	B	15.3	90	43	37	62	47	179	155	175	170	56	20	80
150	A	12.6	74	46	41	39	42	195	171	163	176	48	12	69
150	B	13.5	79	30	54	59	48	166	179	166	170	56	21	71
250	A	8.2	48	67	49	46	54	229	226	254	236	46	10	60
250	B	9.6	56	*	51	58	55	217	205	184	202	54	19	60
400	A	12.2	72	37	29	51	39	208	196	175	193	40	5	73
400	B	11.3	66	49	39	46	45	170	208	203	194	46	11	67
500	A	4.8	28	*	*	*		228	167	235	210			31
500	B	5.1	30	50	43	71	55	204	167	178	183	60	24	29
600	A	0.3	0	+				+						
600	B	0.7	8	+				+						
POSITIVE CONTROL: Methyl methanesulfonate (MMS) (µg/mL)														
20		10.2	60	159	151	145	152	64	85	76	75	404	369	24
15		11.1	65	142	142	*	142	117	83	85	95	299	264	33
<p align="center">MEAN SOLVENT TOTAL SUSPENSION GROWTH: 17.0 MEAN SOLVENT CLONING EFFICIENCY: 95% MEAN SOLVENT MUTANT FREQUENCY: 35 (PER 10⁶ CELLS)</p>														

Solvent = PBS A and B or 1 and 2 are duplicate cultures
+ - Too toxic to clone * - Culture lost to contamination

Table 31: Preliminary Toxicity and Mutagenesis Results for 24-Hour Treatment with Lofexidine HCl without S9 in Mouse Lymphoma Assay

DOSE LEVEL (µg/mL)	PRECIP.	CELL CONCENTRATION (cells/mL x 10 ⁶)			SUSPENSION GROWTH	
		DAY 0	DAY 1	DAY 2	TOTAL	% OF CONTROL
24HR NON-ACTIVATED CULTURES						
SOLVENT 1		0.821	0.849	1.302	33.6	100
SOLVENT 2		0.814	0.892	1.294	34.8	
0.5		0.783	0.836	1.274	30.9	90
1.5		0.806	0.839	1.352	33.8	99
5		0.803	0.891	1.292	34.2	100
15		0.786	0.810	1.203	28.4	83
50		0.767	0.759	1.253	27.0	79
150		0.378	0.317	0.587	2.6	8
500		0.089	0.050	0.025	0.0	0
1500		0.290	0.157	0.066	0.0	0
2600		0.325	0.215	0.144	0.0	0

**DATA SUMMARY FOR L5178Y/TK⁺ MOUSE LYMPHOMA CELLS
TREATED WITH Lofexidine hydrochloride
IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION
Extended Treatment Assay (24-hour exposure)**

DOSE LEVEL (µg/mL)	PRECIP.	TOTAL SUSP. GROWTH	% SUSP. GROWTH	TFT COLONIES				VC COLONIES				TOTAL MUTANT FREQUENCY (PER 10 ⁶ CELLS)	INDUCED MUTANT FREQUENCY (PER 10 ⁶ CELLS)	% TOTAL GROWTH
				PLATE COUNTS				PLATE COUNTS						
				1	2	3	MEAN	1	2	3	MEAN			
SOLVENT 1		30.7	100	40	46	48	45	138	192	200	177	51	N/A	100
SOLVENT 2		27.2		27	23	36	29	180	*	165	173	33		
25	A	30.6	106	32	32	23	29	141	146	166	151	38	-3	91
25	B	25.3	87	38	40	37	38	162	158	154	158	49	7	79
50	A	23.3	80	60	37	36	44	151	203	215	190	47	5	87
50	B	25.4	88	41	29	*	35	218	141	131	163	43	1	82
75	A	16.7	58	45	34	34	38	158	176	176	170	44	2	56
75	B	15.7	54	33	49	40	41	150	137	147	145	56	14	45
100	A	8.1	28	50	36	44	43	198	158	179	178	49	7	29
100	B	11.6	40	44	36	57	46	118	176	163	152	60	18	35
125	A	2.2	9	+				+						
125	B	2.8	9	+				+						
POSITIVE CONTROL:				Methyl methanesulfonate (MMS)				(µg/mL)						
7.5		15.4	53	222	241	222	228	53	85	106	81	561	520	25
5		22.8	79	236	212	228	225	141	82	111	111	405	363	50
MEAN SOLVENT TOTAL SUSPENSION GROWTH: 29.0														
MEAN SOLVENT CLONING EFFICIENCY: 87%														
MEAN SOLVENT MUTANT FREQUENCY: 42 (PER 10⁶ CELLS)														

Solvent = PBS A and B or 1 and 2 are duplicate cultures
 + - Too toxic to clone * - Culture lost to contamination

Table 32: Preliminary Toxicity and Mutagenesis Results for 4-Hour Treatment with Lofexidine HCl with S9 in Mouse Lymphoma Assay

DOSE LEVEL (µg/mL)	PRECIP.	CELL CONCENTRATION (cells/mL x 10 ⁶)			SUSPENSION GROWTH	
		DAY 0	DAY 1	DAY 2	TOTAL	% OF CONTROL
4HR S9-ACTIVATED CULTURES (Induced Rat Liver S9)						
SOLVENT 1			0.994	1.570	17.3	100
SOLVENT 2			1.209	1.299	17.4	
0.5		Not applicable for 4-hour exposure	1.110	1.448	17.8	102
1.5			1.006	1.422	15.9	91
5			0.526	1.321	7.7	44
15			0.271	1.210	4.0	23
50			**	**		**
150			0.115	0.226	0.0	0
500			**	**		**
1500			0.020	0.022	0.0	0
2600			0.031	0.045	0.0	0

**DATA SUMMARY FOR L5178Y/TK⁺ MOUSE LYMPHOMA CELLS
TREATED WITH Lofexidine hydrochloride
IN THE PRESENCE OF EXOGENOUS METABOLIC ACTIVATION
Initial Assay (4-hour exposure)**

DOSE LEVEL (µg/mL)	PRECIP.	TOTAL SUSP. GROWTH	% SUSP. GROWTH	TFT COLONIES				VC COLONIES				TOTAL MUTANT FREQUENCY (PER 10 ⁶ CELLS)	INDUCED MUTANT FREQUENCY (PER 10 ⁶ CELLS)	% TOTAL GROWTH
				PLATE COUNTS				PLATE COUNTS						
				1	2	3	MEAN	1	2	3	MEAN			
SOLVENT 1		14.0	100	71	64	66	67	192	199	245	212	63	N/A	100
SOLVENT 2		14.6		38	58	66	54	218	197	*	208	52		
2.5 A		11.8	82	71	67	78	72	150	200	209	186	77	20	73
2.5 B		11.5	80	46	72	67	62	199	196	*	198	62	5	76
5 A		7.8	55	75	60	60	65	151	208	242	200	65	7	52
5 B		7.5	53	54	58	*	56	164	187	209	187	60	2	47
10 A		4.2	30	57	79	95	77	184	171	185	180	86	28	25
10 B		4.3	30	68	72	*	70	180	*	188	184	76	18	26
40 A		1.9	16	167	164	158	163	132	128	142	134	243	186	10
40 B		2.1	18	120	112	150	127	133	132	156	140	181	124	12
60 A		1.3	12	++				137	114	107	119			7
60 B		1.3	12	++				116	91	117	108			6
75 A		+	+	+				+						
75 B		+	+	+				+						
POSITIVE CONTROL:				7,12-dimethylbenz(a)anthracene (DMBA) (µg/mL)										
1.25		3.1	22	249	231	*	240	141	153	149	148	325	267	16
1		5.6	39	183	*	*	183	149	155	138	147	248	191	28
MEAN SOLVENT TOTAL SUSPENSION GROWTH: 14.3														
MEAN SOLVENT CLONING EFFICIENCY: 105%														
MEAN SOLVENT MUTANT FREQUENCY: 58 (PER 10⁶ CELLS)														

Solvent = PBS

A and B or 1 and 2 are duplicate cultures

* - Culture lost to contamination

+ - Too toxic to clone

++ - Too toxic to count, total growth <10%

Figure 39: Colony Size Distribution for 4-Hour Treatment with Lofexidine HCl with S9 in Mouse Lymphoma Assay

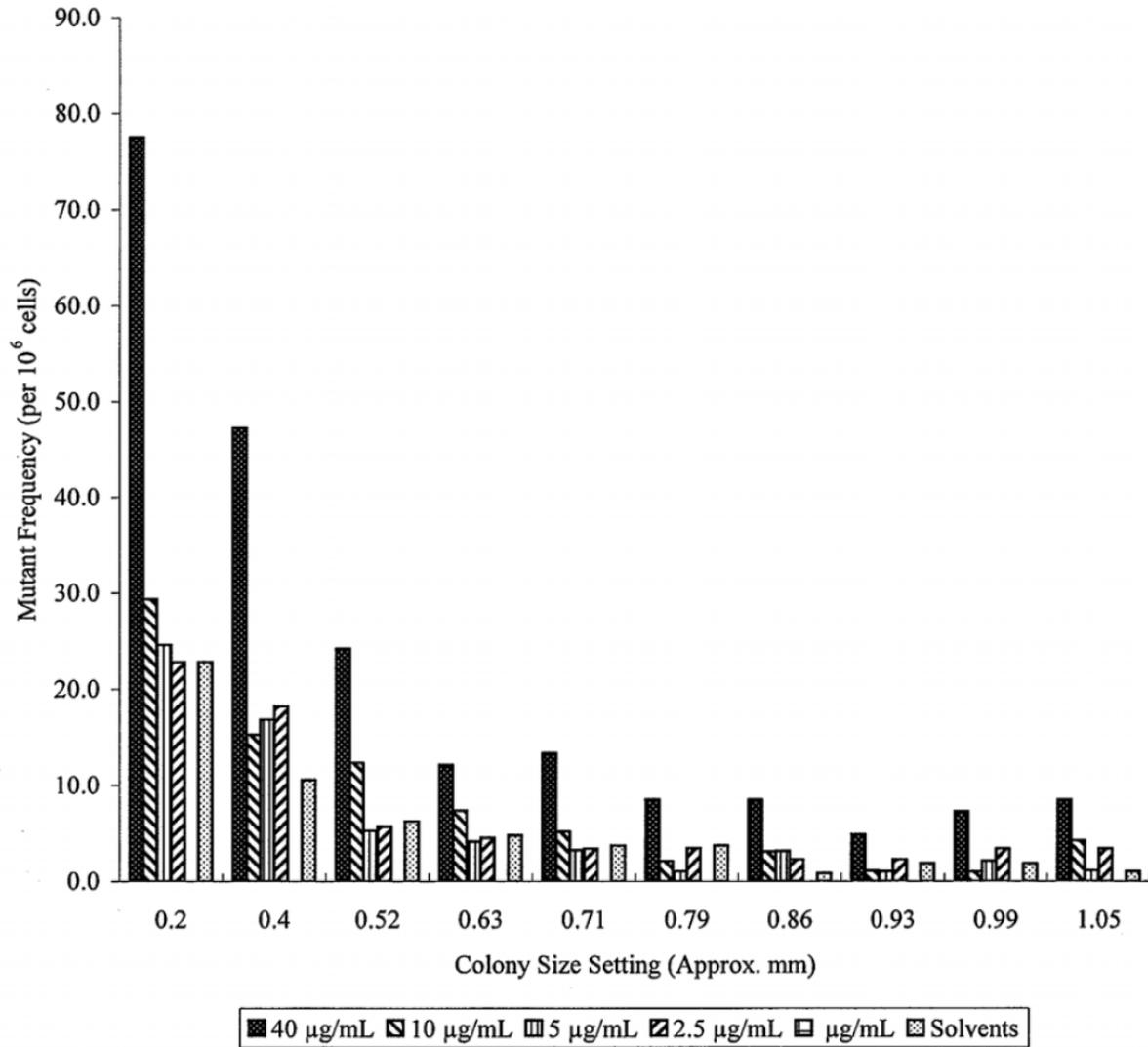


Table 33: Dosing Solution Analysis for Preliminary Toxicity Assay

Vial	Labeled Conc. (mg/mL)	Measured Conc. (mg/mL)	% Theoretical
1	0	0	--
2	0.005	0.005	100.0
3	0.015	0.015	100.0
4	0.05	0.05	100.0
5	0.15	0.14	93.3
6	0.5	0.5	100.0
7	1.5	1.1	73.3 *
8	5	5	100.0
9	15	11	73.3 *
10	26	24	90.4

Table 34: Dosing Solution Analysis for Mutagenesis Assay

Vial	Labeled Conc. (mg/mL)	Measured Conc. (mg/mL)	% Theoretical
1	0	0	--
2	10	7.4	74.0% *
Backup Samples			
1	0	0	--
2	10	7.0	70.0%

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Rat Bone Marrow Erythrocyte Micronucleus Test Following Oral Administration of Lofexidine hydrochloride

Study no: USWM-LX0-TOX-0002
 Study report location: <\\cdsesub1\levsprod\nda209229\0002\m4\42-stud-rep\423-tox\4233-genotox\42332-in-vivo\uswm-lx0-tox-0002\uswm-lx0-tox-0002.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: July 21, 2008
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Lofexidine HCl, 24004970, 100.07%

Key Study Findings

- Lofexidine HCL was not genotoxic in an in vivo rat bone marrow micronucleus assay when evaluated at doses up to 65 mg/kg.

Methods

Doses in definitive study:	25, 50, 65 mg/kg
Frequency of dosing:	Single dose
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	Phosphate buffered saline, pH 7.2
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	5
Satellite groups:	Toxicokinetics (3/sex/group)
Basis of dose selection:	Doses were selected on the basis of literature reports of the LD ₅₀ and LD ₀ of lofexidine.
Negative control:	Phosphate buffered saline, pH 7.2
Positive control:	Cyclophosphamide monohydrate

Study Validity

Rats were orally administered a single dose of 0, 25, 50, or 65 mg/kg lofexidine HCl (adjusted to compensate for the salt form of the test article) or 40 mg/kg cyclophosphamide monohydrate and sacrificed after 24 hours or 48 hours (vehicle and HD only). At all doses, all rats from all dose groups exhibited adverse clinical signs that included ataxia, lethargy, piloerection, and convulsions (see Sponsor's Table below). A maximum tolerated dose was evaluated. After sacrifice bone marrow was collected, adequate numbers of polychromatic erythrocytes (PCEs) were evaluated for the presence of micronuclei. Dose formulation analysis revealed that the actual concentrations of test article employed in this study were within the Sponsor's defined acceptance criteria of $\pm 15\%$. The positive control article produced a significant increase in number of micronucleated polychromatic erythrocytes as expected. The micronucleus assay appears to be a valid study.

Treatment (10 mL/kg)	Observation	Number of Animals With Observed Signs/Total Number of Animals Dosed		Number of Animals Died/Total Number of Animals Dosed	
		Males	Females	Males	Females
PBS	Normal	10/10	10/10	0/10	0/10
Lofexidine hydrochloride 25 mg/kg	Ataxia	5/5	5/5		
	Lethargy	5/5	5/5		
	Piloerection	5/5	5/5	0/5	0/5
	Crusty Eyes	5/5	5/5		
	Convulsions	5/5	5/5		
50 mg/kg	Ataxia	5/5	5/5		
	Lethargy	5/5	5/5		
	Piloerection	5/5	5/5	0/5	0/5
	Crusty Eyes	5/5	5/5		
	Convulsions	5/5	5/5		
65 mg/kg	Ataxia	15/15	15/15		
	Lethargy	15/15	15/15		
	Piloerection	15/15	15/15	0/15	0/15
	Crusty Eyes	15/15	15/15		
	Crusty Nose	10/15*	10/15*		
Convulsions	15/15	15/15			
Cyclophosphamide 40 mg/kg	Normal	5/5	5/5	0/5	0/5

* Crusty nose was observed in 48 hour treatment groups on Study Day 2 in all rats.

Results

No increase in the number of micronucleated polychromatic erythrocytes was observed in any of the lofexidine treatment groups (Table 35). Mild, dose-dependent reductions in the ratio of polychromatic erythrocytes to total of less than or equal to 20% compared to control were observed in bone marrow samples from lofexidine-treated rats. This effect was slightly more prominent in female rats, which was correlated with increased C_{max} and AUC values recorded in female rats from the toxicokinetics cohort (Table 36).

Table 35: Effect of Orally Administered Lofexidine HCl on Micronucleus Formation in Rat Bone Marrow Polychromatic Erythrocytes

Treatment (10 mL/kg)	Sex	Time (hr)	Number of Animals	PCE/Total Erythrocytes (Mean +/- SD)	Change from Control (%)	Number of MPCE/1000 PCE (Mean +/- SD)	Number of MPCE/PCE Scored
PBS	M	24	5	0.549 ± 0.05	---	0.2 ± 0.27	2 / 10000
	F	24	5	0.583 ± 0.03	---	0.0 ± 0.00	0 / 10000
Lofexidine hydrochloride 25 mg/kg	M	24	5	0.532 ± 0.04	-3	0.1 ± 0.22	1 / 10000
	F	24	5	0.477 ± 0.04	-18	0.3 ± 0.27	3 / 10000
50 mg/kg	M	24	5	0.488 ± 0.03	-11	0.1 ± 0.22	1 / 10000
	F	24	5	0.512 ± 0.06	-12	0.3 ± 0.27	3 / 10000
65 mg/kg	M	24	5	0.479 ± 0.06	-13	0.0 ± 0.00	0 / 10000
	F	24	5	0.464 ± 0.06	-20	0.6 ± 0.22	6 / 10000
Cyclophosphamide 40 mg/kg	M	24	5	0.443 ± 0.05	-19	10.5 ± 1.37	*105 / 10000
	F	24	5	0.410 ± 0.07	-30	10.0 ± 1.70	*100 / 10000
PBS	M	48	5	0.478 ± 0.07	---	0.4 ± 0.42	4 / 10000
	F	48	5	0.497 ± 0.05	---	0.2 ± 0.27	2 / 10000
Lofexidine hydrochloride 65 mg/kg	M	48	5	0.470 ± 0.09	-2	0.3 ± 0.27	3 / 10000
	F	48	5	0.432 ± 0.09	-13	0.2 ± 0.27	2 / 10000

*Statistically significant increase, $p \leq 0.05$ (Kastenbaum-Bowman Tables)

Table 36: Toxicokinetic Parameters in Rat Micronucleus Study

Dose (mg/kg)	Sex	AUC _{0-tlast} (hr•ng/mL)	AUC _{0-tlast} /Dose ((hr•ng/mL)/mg/kg)	C _{max} (ng/mL)	C _{max} /Dose ((ng/mL)/mg/kg)	T _{max} (hr)
25	M	231±39.1	9.25±1.56	214±59.8	8.55±2.39	0.500±0
	F	1910±2270	76.5±90.7	1360±1640	54.6±65.6	0.667±0.289
50	M	1250±1070	25.1±21.5	990±911	19.8±18.2	1.00±0.866
	F	3470±911	69.3±18.2	3180±1130	63.7±22.7	1.17±0.764
65	M	1140±862	17.6±13.3	910±707	14.0±10.9	1.17±0.764
	F	2350±102	36.1±1.57	1740±253	26.8±3.90	1.00±0.866

A single oral dose of lofexidine at doses up to 65 mg/kg did not induce an increase in the micronucleated polychromatic erythrocytes in rats and therefore lofexidine is concluded to be non-mutagenic under the test conditions of the assay.

8 Carcinogenicity

Study title: Chronic Toxicity and Carcinogenicity Study of Lofexidine in Rats

Study no.: USWM-LX0-TOX-0014
Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\uswm-lx0-tox-0014\uswm-lx0-tox-0014-pre-clinical-study-report.pdf>

Conducting laboratory and location:  (b) (4)

Date of study initiation: March 28, 1978
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: Lofexidine, Unknown, Unknown
CAC concurrence: No

Key Study Findings

- Lofexidine was administered via diet up at 0.09, 0.26, or 0.88 mg/kg/day for 2 years and produced no significant effects on mortality, clinical signs, body weight, food consumption, or non-neoplastic histopathology.
- A dose-response relationship was observed in skin/subcutis sebaceous cell neoplasms; however, the treatment-related increases in incidence of these tumors were not statistically significant when a pairwise comparison was applied.

Adequacy of Carcinogenicity Study

There are limitations to this study. A dose of 2.6 mg/kg/day, 3-fold higher than the HD in this study, appears to be a maximum tolerated dose, based on an approximately 10% decrease in body weight observed in the 1-year repeat-dose toxicology study in rats. The study was completed prior to the establishment of GLP. Drug purity was not included. Dosing solutions were not analyzed to confirm doses administered.

Collectively, given the limitations of the study design noted above, although study results were negative, the Division does not believe that including a statement  (b) (4) is warranted.

Executive CAC Conclusions

The Committee concurs with the Divisions conclusions.

- The Committee noted the lack of prior protocol and dose concurrence by CDER.

- Although no treatment-related tumors were observed, the Committee found that the study in both sexes was inadequate to assess the risk of carcinogenicity because the study was not conducted under GLP compliance, did not assess the concentration of the drug in the diet and did not evaluate an adequate high dose.

Appropriateness of Test Models

The Long Evans hooded rat was commonly used for carcinogenicity studies in the past, although rarely used today. The model is acceptable.

Evaluation of Tumor Findings

Methods

Doses:	0, 0.09, 0.26, 0.88 mg/kg/day (0, 0.1, 0.3, 1 mg/kg/day lofexidine HCl salt)
Frequency of dosing:	Continuous
Dose volume:	NA
Route of administration:	Diet
Formulation/Vehicle:	Formulation: Lofexidine (1%), Lactose (87.4%), Citric Acid (11.6%) Vehicle: Purina Lab Chow Meal
Basis of dose selection:	Not Described
Species/Strain:	Rat/Long Evans
Number/Sex/Group:	65
Age:	PND 36-38
Animal housing:	Individual
Paradigm for dietary restriction:	None
Dual control employed:	No
Interim sacrifice:	Yes: 5 rats/sex/group after 6 months and 10 rats/sex/group after 12 months
Satellite groups:	No
Deviation from study protocol:	None reported

Observations and Results

Mortality

Five rats/sex were sacrificed from all treatment groups at 6 months for toxicologic evaluation including assessments of clinical pathology (i.e. hematology, clinical chemistry, and urinalysis), gross pathology, organ weights, and histopathology. At 12 months, 10 rats/sex were sacrificed for the same toxicologic evaluation except clinical pathology was not assessed.

Lofexidine treatment was not associated with a consistent impact on mortality in male or female rats (Figure 40; Figure 31).

Figure 40: Mortality in Carcinogenicity and Chronic Toxicology Studies

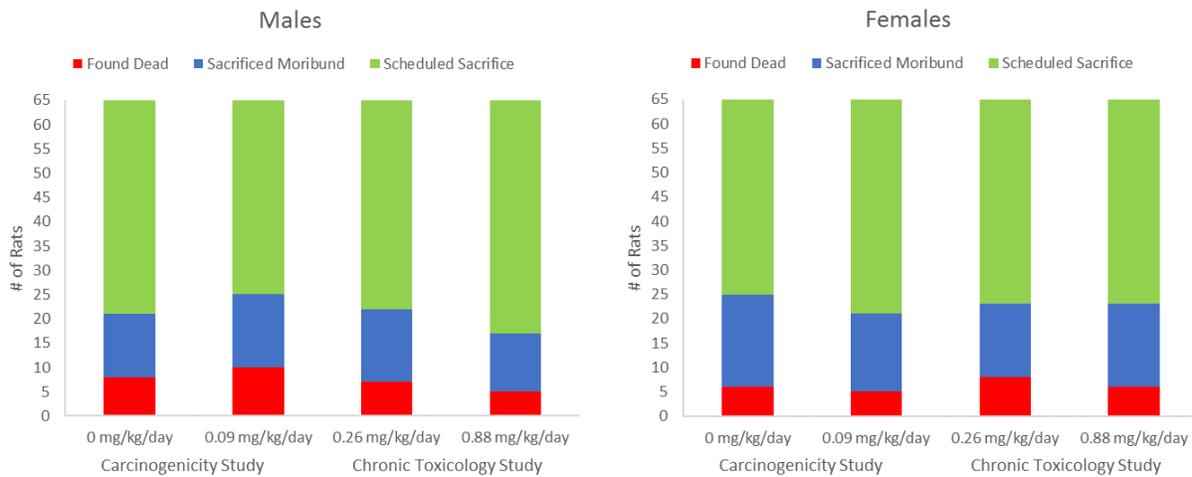
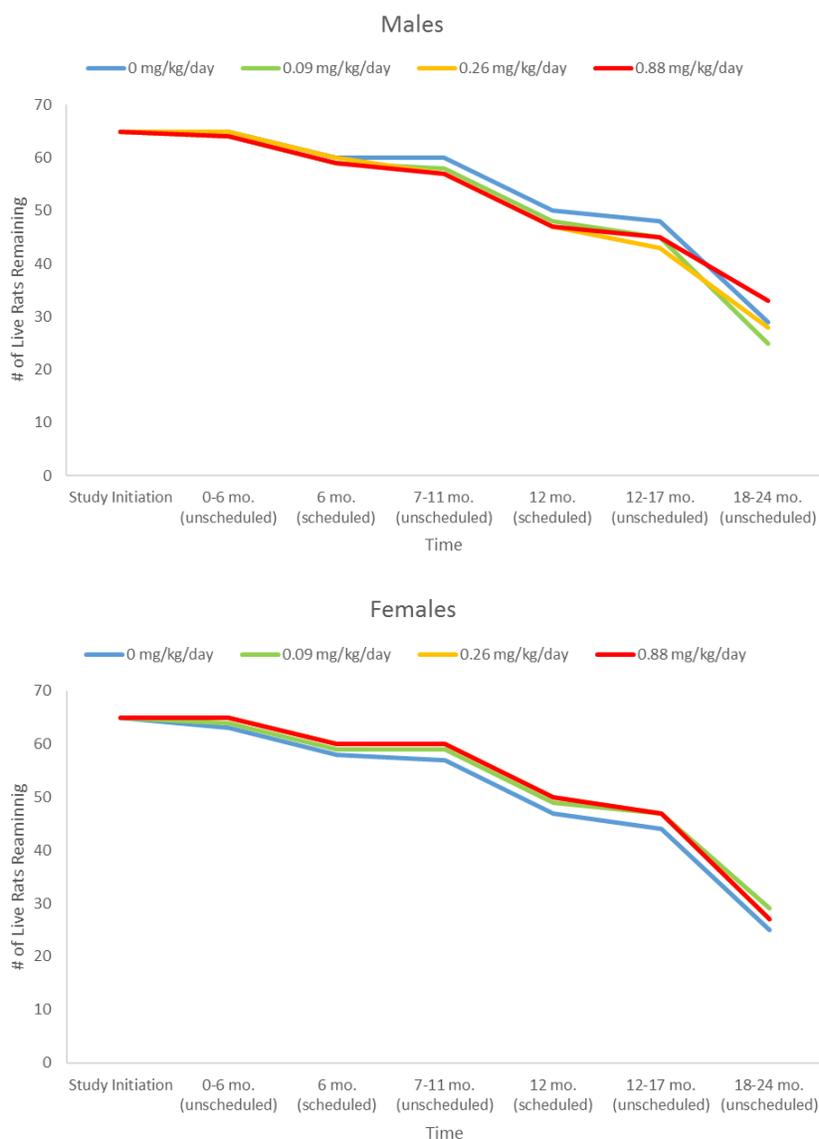


Figure 41: Survival Curves in Carcinogenicity and Chronic Toxicology Studies**Clinical Signs**

Rats were observed daily for appearance and behavior.

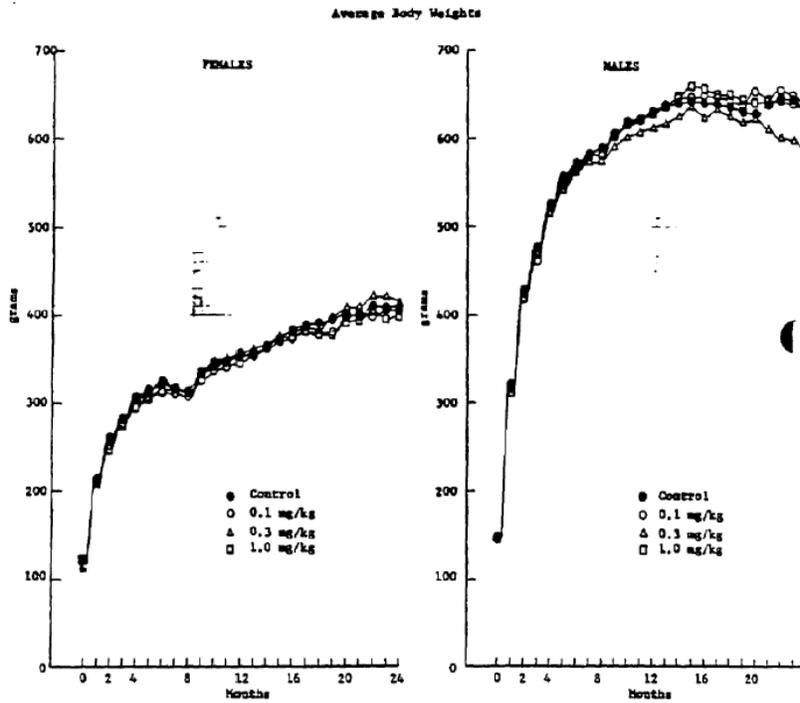
There were no clinical signs associated with lofexidine treatment.

Body Weights

Body weights were recorded weekly and reported monthly.

Body weights were not impacted by lofexidine treatment, apart from a decrease in body weights at the MD in males starting on Month 9 (Figure 42).

Figure 42: Impact of Lofexidine Treatment on Body Weight in Carcinogenicity Study

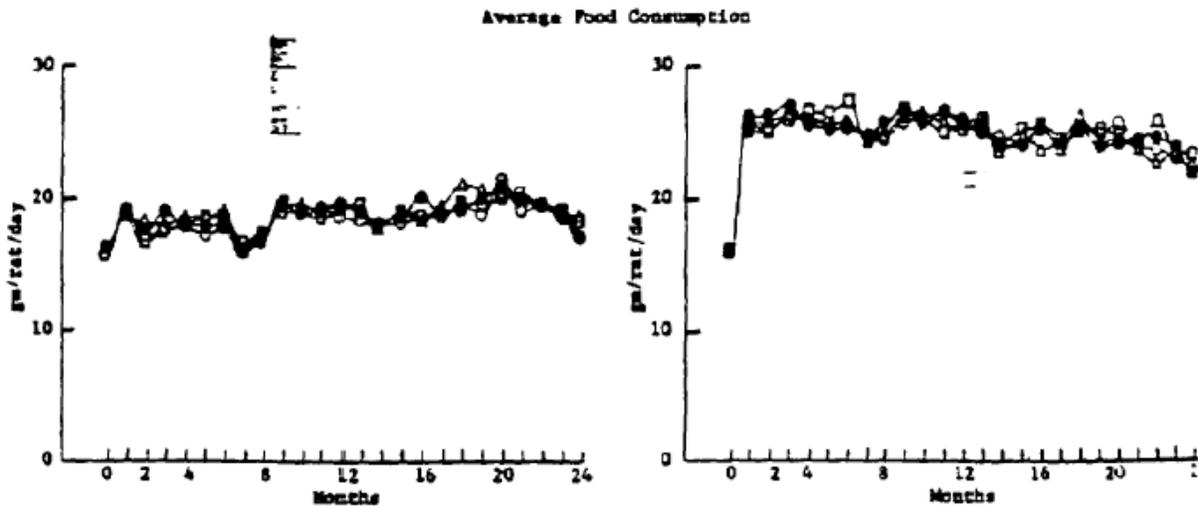


Food Consumption

Food consumption was recorded weekly.

Food consumption was not reliably impacted by lofexidine treatment in male or female rats (Figure 43).

Figure 43: Impact of Lofexidine Treatment on Food Consumption in Carcinogenicity Study



Gross Pathology

A complete necropsy was performed on all rats, including those that died or were sacrificed because of their poor physical condition. These results were only tabulated for rats sacrificed or found dead during the first year of the study, which included the scheduled sacrifice of 5 rats/sex/group after 6 months and 10 rats/sex/group after 12 months.

No gross necropsy findings were associated with lofexidine treatment.

Histopathology

Peer Review

Peer review of histopathology analysis/interpretation was not performed.

Neoplastic

For the carcinogenicity study, histomorphic evaluation was performed on the brain, kidneys, liver, lungs, gonads, spleen, stomach, urinary bladder, and any tissues with significant gross changes from representative rats sacrificed at one year and on all animals that died thereafter. This is not an adequate battery of tissues as per standard protocols.

As raw data in SAS transport file format was not included but only summary data was provided in the study report, an official statistical consult was not requested; however, the statistical analysis reported below was deemed adequate by Statistical Reviewer, Hepei Chen PhD (informal consult). Because there was no impact of lofexidine treatment on mortality, tumor incidence rates were not adjusted for survival. For each tumor or tumor combination of interest, the Cochran-Armitage linear trend test was applied across all doses employed in the study and Fisher's exact test was applied to evaluate pairwise comparisons between control and HD rats. A tumor finding was considered significantly associated with lofexidine treatment only if both the trend test and pairwise comparison were found to be statistically significant. In order to keep the overall false positive rate at the nominal level of approximately 10%, for both of the dose response relationship tests and the multiple pairwise comparisons of treated group with control group, the *Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals*, suggests the following thresholds for significance of common and rare tumors for trend tests and pairwise comparisons:

Table 37: p-Value Thresholds Applied in Statistical Analysis of Tumors

Tumor Type	p-Value Threshold	
	Trend Test	Pairwise Comparison
Common	0.005	0.01
Rare	0.025	0.05

Only one rare tumor type, sebaceous cell adenoma/carcinoma, exhibited a significant trend test result ($p < 0.025$), but the control-HD pairwise comparison did not achieve statistical significance ($p > 0.1$) so the finding was considered incidental. The study report listed several subtypes of sebaceous cell tumors individually (Table 38), such that they needed to be combined for statistical analysis (Table 39). No additional treatment-related trends were observed across any other tumor types.

Table 38: Line Listing of Incidence Sebaceous Cell Tumors

	Dose Group (mg/kg/day)							
	Control		0.1		0.3		1.0 ^a	
	60M	57F	58M	60F	57M	60F	57M	60F
<u>Skin/subcutis</u>								
epithelioma	-	-	-	-	-	1	-	-
papilloma	1	-	-	-	2	-	-	-
trichoepithelioma	5	2	3	3	3	1	8	4
keratoacanthoma	2	-	-	-	-	-	1	-
basal cell carcinoma (follicular), invasive and metastasizing	-	-	-	-	1	1	-	-
sebaceous adenoma	-	-	-	-	-	-	1	-
sebaceous carcinoma	-	-	-	-	-	1	-	-
sebaceous basal cell carcinoma	-	-	-	-	-	1	-	-
sebaceous basal cell carcinoma, invasive	-	-	-	-	-	-	1	-
sebaceous basal cell carcinoma, metastasizing	-	-	-	-	-	-	-	1
sebaceous basal cell carcinoma, invasive and metastasizing	-	-	-	-	-	-	1	-
fibroma	2	-	2	1	3	-	1	-
fibrosarcoma	-	-	1	1	-	-	-	-
malignant lymphoma, reticulum cell type	1	-	-	-	-	-	-	-

Table 39: Incidence of Combined Sebaceous Cell Tumors

Organ	Tumor Type	Dose Group (mg/kg/day)							
		0		0.09		0.26		0.88	
		M	F	M	F	M	F	M	F
Skin / Subcutis	Adenoma, sebaceous cell	-	-	-	-	-	-	1/57	-
	Carcinoma, sebaceous cell	-	-	-	-	-	2/60	2/57	2/60
	Adenoma/Carcinoma, sebaceous cell	-	-	-	-	-	2/60	3/57*	2/60

* $p < 0.025$ (Cochran Armitage Trend Test)

Non Neoplastic

Histopathological examination was performed on all rats that were sacrificed or died during the first six months as well as any rats with unscheduled deaths between 6 and 12 months and 10 rats from the 0.88 mg/kg/day group sacrificed after 12 months. Tissues to be examined were fixed in 10% phosphate buffered formalin (except Davidson’s solution was used to fix some eyes), embedded in paraffin, sectioned at 6 microns and stained with hematoxylin and eosin. The brain, sciatic nerve, parathyroids, salivary gland, intra- and exorbital lacrimal glands, external and internal lymph nodes, lung, sternebra, diaphragm, esophagus, trachea, aorta, tongue, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, urinary bladder, mammary gland, skeletal muscle, skin, vagina or epididymis were prepared and examined microscopically.

There were no notable non neoplastic lesions reported.

Toxicokinetics

Toxicokinetics evaluations were not performed.

Dosing Solution Analysis

Dosing solution analysis was not performed.

Study title: Carcinogenicity Evaluation of Lofexidine in Mice

Study no.: USWM-LX0-TOX-0015

Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4234-carcigen\42341-lt-stud\uswm-lx0-tox-0015\uswm-lx0-tox-0015-pre-clinical-study-report.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: November 16, 1977
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: Lofexidine, Unknown, Unknown
CAC concurrence: No

Key Study Findings

- Lofexidine was administered via diet up at 0.09, 0.26, or 0.88 mg/kg/day for 18 months and produced no significant effects on mortality, clinical signs, body weight, or food consumption; however, due to a dosing error male mice at the HD were sacrificed after 15 months.
- Clinical signs were observed in mice in all groups, but trauma inflicted in fighting was the cause of most these findings.
- A significant number of males died in the MD and HD either as a result of increased fighting or from the inadvertent 100-fold increase in dose levels during a 4-day period, approximately 15 months into the study.
- Potentially stress-related non-neoplastic histopathological findings were observed at the MD and HD in the spleen, kidney, and lymph nodes.
- No neoplastic lesions were observed with association to lofexidine treatment.

Adequacy of Carcinogenicity Study

There are limitations to this study. Although the Agency has historically accepted 18-month mouse studies, the males were sacrificed at approximately 15 months due to increased deaths that were the result of a 4-day dosing error resulting a 100-fold increase over the intended doses administered. Females were treated for the full 18 months. The study was also completed prior to the establishment of GLP. Drug purity was not included. Dosing solutions were not analyzed to confirm doses administered. A full set of standard tissues were not evaluated by histopathology; however, gross lesions were examined.

Collectively, given the limitations in the study design noted above, although negative, the Division does not believe that including a statement (b) (4) is warranted.

Executive CAC Conclusions

The Committee concurs with the Divisions conclusions.

- The Committee noted the lack of prior protocol and dose concurrence by CDER.
- Although no treatment-related tumors were observed, the Committee found that the study in both sexes was inadequate to assess the risk of carcinogenicity because the study was not conducted under GLP compliance, was of inadequate duration, had some animals terminated early due to a dosing error and had no basis for high dose selection.

Appropriateness of Test Models

The CD-1 mice is a common strain used for carcinogenicity studies. The model is acceptable.

Evaluation of Tumor Findings

Methods

Doses:	0, 0.09, 0.26, 0.88 mg/kg/day
Frequency of dosing:	Continuous
Dose volume:	NA
Route of administration:	Diet
Formulation/Vehicle:	Formulation: Lofexidine (1%), Lactose (87.4%), Citric Acid (11.6%) Vehicle: Purina Lab Chow Meal
Basis of dose selection:	Not Described
Species/Strain:	Mouse/CD-1
Number/Sex/Group:	50
Age:	PND 35-37
Animal housing:	Not Described
Paradigm for dietary restriction:	None
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	No
Deviation from study protocol:	An inadvertent 100-fold dose increase in the 0.26 and 0.88 mg/kg/day groups occurred over a period of 4 days (Days 442-446). The remaining males in the 0.88 mg/kg/day group were sacrificed on Day 447 (~ 15 months) in order to assure sufficient tissue for histopathological evaluation.

Observations and Results

Mortality

Mice were checked for mortality daily.

Increased mortality was associated with lofexidine treatment and was primarily attributable to an increase in the number of mice found dead (Figure 44). In males, increased mortality was apparent at the HD from Month 5 onward, and a slight increase in mortality was observed throughout the study at the MD as well (Figure 45). In Month 15, mortality spiked at the MD and HD, due to the 4-day, 100-fold increased dosing error that occurred. In females, mortality was less drastically and more consistently dose-dependently increased, with a bulk of the deaths occurring in Month 15 at the HD and in Month 18 at the LD and MD. The increased mortality observed in males compared to females, regardless of treatment group, was due to increased fighting.

Figure 44: Mortality Summary of Mouse Carcinogenicity Study

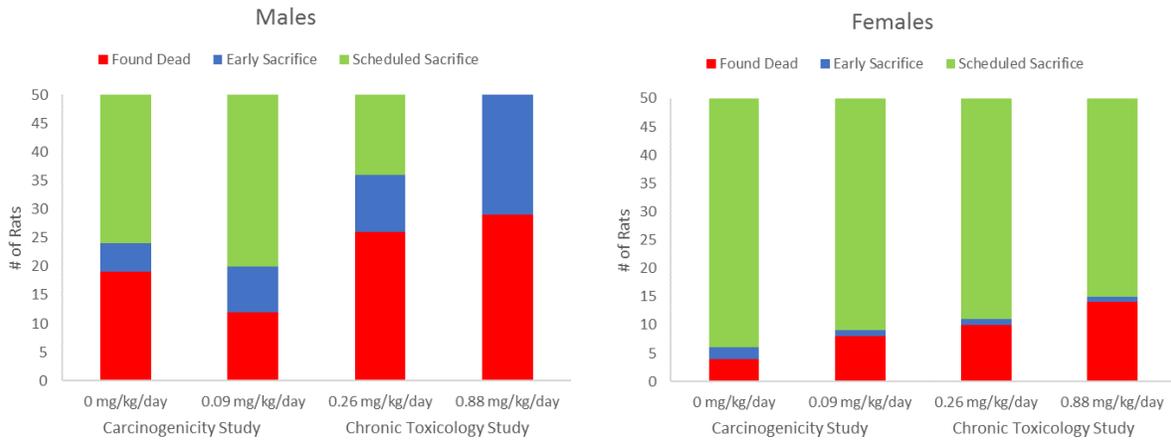
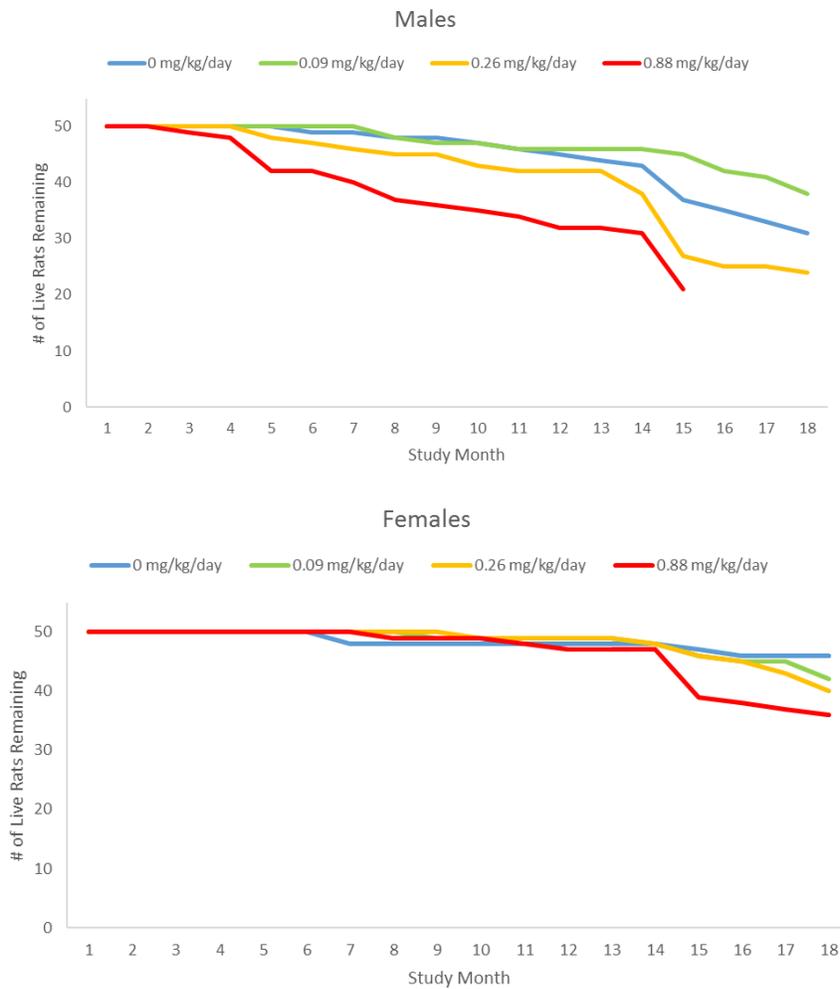


Figure 45: Survival Curves of Mouse Carcinogenicity Study



Clinical Signs

Mice were thoroughly checked weekly for clinical signs.

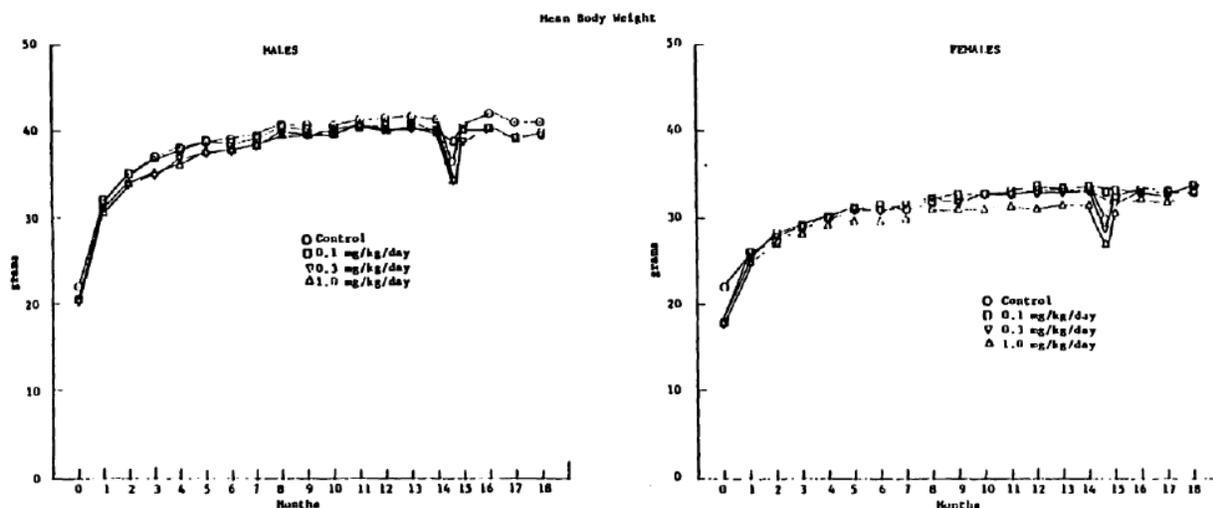
None of the clinical signs observed appeared to be related to lofexidine treatment. Prominent clinical signs observed across treatment groups included: lacerations/scabbing due to fighting (mostly in males), alopecia, and cornea opacity (mostly in females).

Body Weights

Body weights were recorded weekly and reported monthly.

Body weights of lofexidine-treated mice were consistently decreased from Month 3 onward at the HD in females and generally slightly less than controls at the LD and MD in both sexes and the HD in males throughout the study (Figure 46). In Month 15 there was an abrupt decrease in body weight for all mice at the MD and HD due to a 4-day, 100-fold increased dosing error, but the surviving mice appeared to recover from this effect in the final months of the study.

Figure 46: Impact of Lofexidine Treatment on Body Weight in Mice

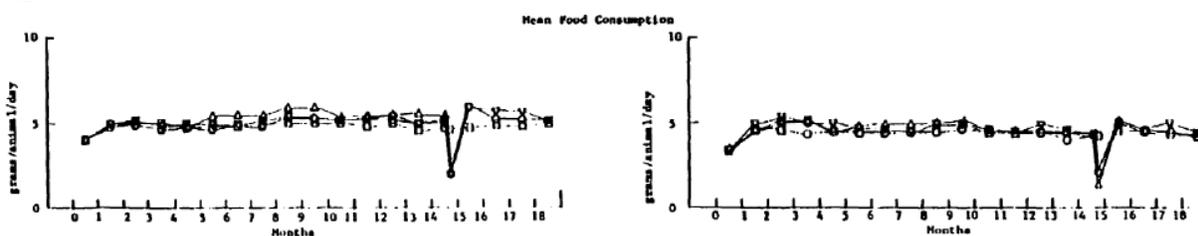


Food Consumption

Food consumption was recorded weekly and reported monthly.

Food consumption was not consistently impacted by lofexidine treatment in any group. In Month 15 there was an abrupt decrease in food consumption for all mice at the MD and HD due to a 4-day, 100-fold increased dosing error, but the surviving mice appeared to recover from this effect in the final months of the study.

Figure 47: Impact of Lofexidine Treatment on Food Consumption in Mice



Gross Pathology

Mice were sacrificed by decapitation and a necropsy was performed on all mice.

The only potentially dose-related gross necropsy findings were enlarged/red/nodular prostate and atrophic/small/flabby/cryptorchid testis at the MD and HD (). These macroscopic findings were not correlated with histopathological findings.

Table 40: Gross Necropsy Findings Associated with Lofexidine Treatment in Mice

	Dose Group (mg/kg/day)							
	0		0.1		0.3		1.0	
	45F	31M	42F	38M	40F	24M	36F	21M
Prostate - enlarged						2		1
- red						1		1
- nodular						1		
Testis - atrophic/small/flabby				1		2		
- cryptorchid						1		2

Histopathology

The following tissues were fixed in neutral-buffered 10% formalin, paraffin embedded, sectioned at 6 microns, stained with hematoxylin and eosin, and preserved for histopathological examination: brain, lung, liver, kidneys, bladder, spleen, stomach, gonads, and any abnormal organ or tissue identified in the gross necropsy examination. This is not an adequate battery of tissues per standard protocols.

Peer Review

Peer review of histopathology analysis/interpretation was not performed.

Neoplastic

The only neoplastic lesions observed with potentially dose-related incidence were a polyp of duodenum in 1/50 HD females, malignant lymphomas of lymph nodes in 1/49 MD males and 1/50 HD females, and leiomyoma of uterus in 1/48 MD females and 1/50 HD females. The low magnitude of incidence of these findings suggests that they are most likely incidental.

Non Neoplastic

Table 41 describes the potentially dose-related non-neoplastic histopathological findings associated with lofexidine treatment. Notably, the study report did not indicate the sex of mice displaying these lesions nor did it provide a denominator describing the total number of mice examined for each treatment group. Non-neoplastic histopathological findings associated with lofexidine treatment were limited to the spleen, kidney and lymph nodes. In the spleen, lymphoid depletion and hematopoiesis were observed with at least 2-fold greater incidence at the MD than in controls. The incidence of these findings declined at the HD, but this may be attributable to the earlier sacrifice time for HD males. Granulopoiesis was also observed in the spleen of 3-4 lofexidine treated mice per group but not in any control mice. Tubular dilation and atrophy were observed in the kidneys of 2-3 lofexidine-treated mice per group at the MD and HD with some dose-dependence and not at all in control mice. A dose-dependent increase in lymphadenitis was also observed in the lymph nodes. These findings were of relatively low magnitude and may have been stress-related.

Table 41: Histopathological Findings Associated with Lofexidine Treatment in Mice

	Dose Group (mg/kg/day)			
	0	0.1	0.3	1.0
<u>Spleen</u> - myelopoiesis	12	3		
- reticuloendothelial hyperplasia	1	4		
- hematopoiesis	2	4	14	5
- amyloidosis	1	2		1
- lymphoid hyperplasia	1		1	
- lymphoid depletion	4	8	16	7
- hemosiderosis		4	2	1
- erythropoiesis		3		
- hypervolemia		1		
- granulopoiesis		3	4	4
- scar		1		
- splenitis		1		
- leukemoid reaction			1	
- hemangiectasis			1	
- infarct with hemorrhage	1			

<u>Kidney</u> - nephritis/ nephrosis	36	40	22	21
- cyst-cystic	4	5	2	
- amyloidosis	20	33	4	3
- nephrosclerosis	3	9	5	3
- arteritis	1			
- infarct	1	1		
- fibrinoid degeneration	1			
- glomerular hyperplasia	1			
- mineralization	1			
- pyelonephritis/pyelitis	2	2	5	2
- degeneration		3	3	1
- casts		2		
- scar		2	1	1
- atrophy		2	2	3
- lymphoid hyperplasia			1	
- tubular dilation			2	2
<u>Lymph nodes</u> - reticuloendothelial hyperplasia	1			
- hemorrhage	1			
- pigment	1			
- reactive hyperplasia	1	1		
- lymphadenitis	1		2	5
- leukemoid reaction	1			
- histiocytosis	1	2		
- hemangiectasis		1		
- thrombus		1		
- hematopoiesis			1	
- lymphangiectasis			1	
- granulopoiesis				1

Toxicokinetics

Toxicokinetics evaluations were not performed.

Dosing Solution Analysis

Dosing solution analysis was not performed.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Testing the Fertility and Breeding Capacity of New Zealand Rabbits Given Ba 168 by Stomach Tube

Study no.: USWM-LX0-TOX-0017

Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42351-fert-embryo-dev\uswm-lx0-tox-0017\uswm-lx0-tox-0017-pre-clinical-study-report.pdf>

Conducting laboratory and location:



Date of study initiation: March 5, 1976

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: Lofexidine, Unknown, Unknown

Key Study Findings

- Lofexidine was orally administered to female rabbits starting 2 weeks prior to mating and through gestation and 4 weeks of lactation with an interim Cesarean section sacrifice of 10/group on GD 20.
- Six unscheduled deaths occurred at the HD during the pre-mating and mating periods, characterized by 5-30 hours of coma prior to death.
- Body weights were slightly reduced at the MD and dramatically reduced at the HD (>15%), and food consumption was also decreased at the HD.
- After Cesarean section and sacrifice on GD 20, post-implantation loss was increased at the MD and HD due to an increase in the number of resorptions per dam with little change in the number of implantations per dam.
- After spontaneous birth, litter size was reduced at the HD.
- Survival and body weight gains of kits were significantly reduced at the HD throughout the lactation period.
- The fertility NOAEL in females was the HD, 5.6 mg/kg/day, providing a 38-fold safety margin to the MRHD of 2.88 mg/day based on body surface area allometric scaling. However, the exposure margin based AUC is only 0.1x.
- The developmental NOAEL was the LD, 0.35 mg/kg/day, as there was increased post-implantation loss correlating with increased number of resorptions at the HD.
- This study provides data on early embryonic development but does not include standard female fertility assessments and males were not dosed to assess the impact of lofexidine on male fertility.

Methods

Doses: 0, 0.35, 1.4, 5.6 mg/kg/day
 Frequency of dosing: Once Daily
 Dose volume: 1 mL/kg
 Route of administration: Oral Gavage
 Formulation/Vehicle: 1% Aqueous methyl-hydroxyethylcellulose
 Species/Strain: Rabbit/New Zealand
 Number/Sex/Group: 20
 Satellite groups: None
 Study design: Only female rabbits were dosed starting 2 weeks prior to mating and ending on the day of sacrifice. 10 dams were sacrificed on GD 20 and 10 were sacrificed at the end of the 4th week of lactation. Males were not dosed with lofexidine.

Deviation from study protocol: None Reported

Group/ Sex	Dosage of Ba 168 in mg./kg. body weight/ day by stomach tube	No. of animals	Rabbits no.
(I) males	none	20	1 - 20
females	Controls: 1% aqueous methyl-hydroxy-ethyl- cellulose gel 300 P, 1 ml./kg. body weight	20	1 - 20
(II) males	none	20	1 - 20
females	0.4	20	1 - 20
(III) males	none	20	1 - 20
females	1.6	20	1 - 20
(IV) males	none	20	1 - 20
females	6.4	20	1 - 20

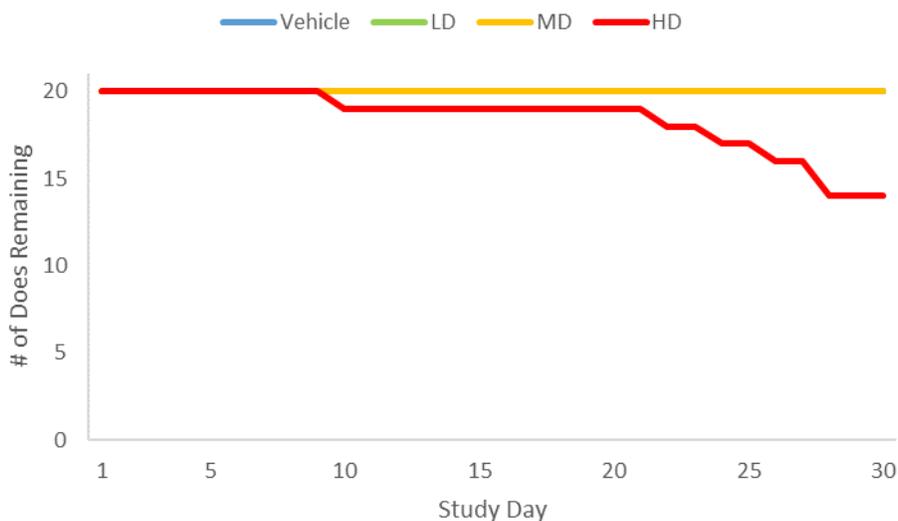
Observations and Results

Mortality

The behavior and general condition of the animals were checked daily.

As shown in Figure 48, six HD does died prior to scheduled sacrifice. Only one of these deaths occurred prior to mating on Study Day 10, and the remaining five occurred during the mating period. These deaths were preceded by 5-30 hours of coma and in one animal accompanied by agonal convulsions (Animal No. 12).

Figure 48: Survival of Lofexidine-Treated Does



Clinical Signs

The behavior and general condition of the animals were checked daily.

Mild to moderate sedation and fright were observed 5-10 minutes after dosing at the MD and HD, lasting approximately 3-5 hours at the MD and 4-12 hours at the HD. The intensity and duration of these findings increased throughout the study, by the end of the study lasting 5-24 hours at the MD and all day at the HD. Does in both of these treatment groups also displayed unkempt appearance and neglect of their fur. Soft feces and mild diarrhea was also observed throughout the entire study at the HD, starting between Study Day 10 and 20.

No treatment-related clinical signs were observed at the LD.

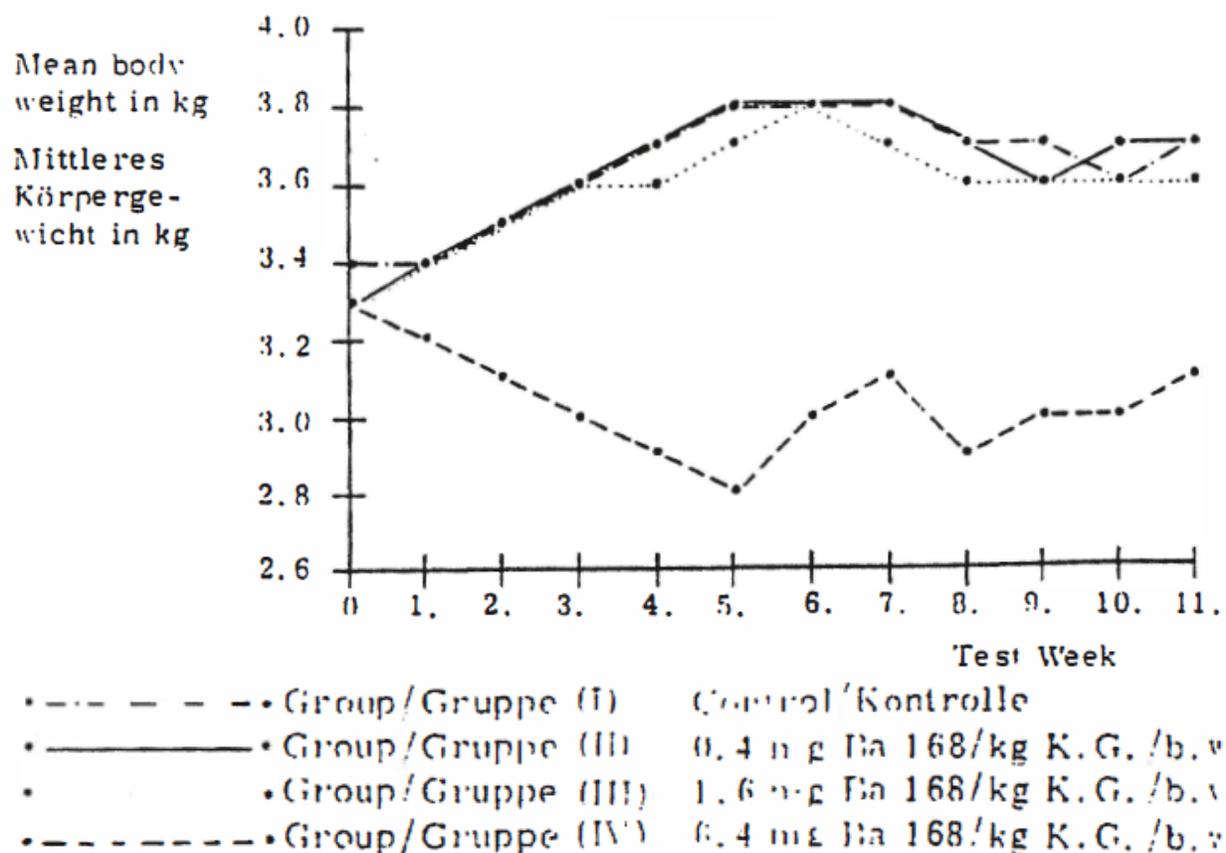
Body Weight

Once a week (on the same day and same time of day) the body weight was ascertained, and an unrecorded weighing was done every day to serve as a basis for calculating the daily dosage of the test article. Female animals were also weighed just before laparotomy or before delivery.

As shown in Figure 49, body weights of vehicle-treated, LD, and MD does increased during the pre-mating, mating, and early gestation periods and then plateaued and decreased slightly following parturition and during the lactation period. Weights of MD does were slightly decreased compared to controls throughout the gestation and

lactation periods. In contrast at the HD, body weights decreased during the pre-mating, mating, and early gestation periods, partially recovered during late gestation, decreased again after parturition, and partially recovered during lactation.

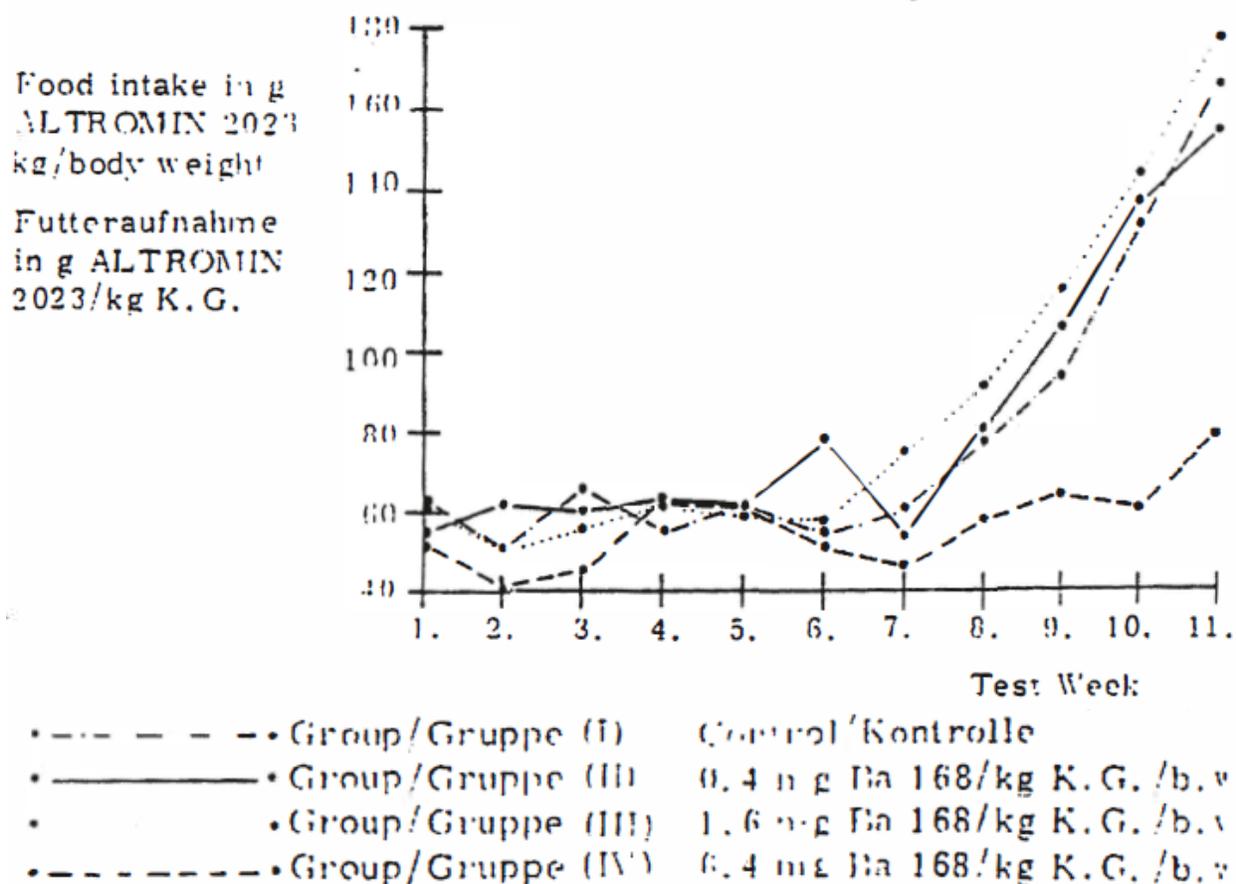
Figure 49: Impact of Lofexidine Treatment on Body Weight in Does



Food Consumption

Food consumption was determined daily (at the same time of day) by re-weighing the amounts not eaten.

As shown in Figure 50, food consumption was moderately decreased at the HD compared to vehicle-treated does during the 2nd and 3rd weeks of the study, corresponding to the pre-mating and mating phases of the study. During the gestation period, food consumption was not different between treatment groups, but food consumption increased dramatically in all but HD does during lactation, starting on Week 7.

Figure 50: Impact of Lofexidine Treatment on Food Consumption in Does**Toxicokinetics**

Toxicokinetics evaluations were not performed.

Dosing Solution Analysis

Dosing solution analysis was not performed.

Necropsy

At the time of scheduled sacrifice, parent animals were killed by a blow to the neck, exsanguinated, sectioned, and inspected macroscopically.

The only treatment-related macroscopic findings were pale, parenchymatous organs observed in the HD does that died prior to scheduled sacrifice.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

The following signs of fertility were evaluated after Cesarean section and sacrifice of dams on GD 20: number and distribution of corpora lutea, implantations, fetuses, and resorptions in the uterine horns. Resorptions were further categorized as those with embryonal attachments vs. fetuses and as early or late resorptions. Rate of resorption, pre-implantation loss, and post-implantation loss were also calculated.

Twice as many copulation attempts were required in HD does compared to vehicle-treated does resulting in a significant reduction in “breeding rate” as reported by the Applicant. The HD animals also demonstrated significant sedation and clinical signs including mortality, which may have impacted the outcome. After Cesarean section and sacrifice of dams on GD 20, the average number of corpora lutea and implantations per dam as well as the rate of pre-implantation loss were not impacted by lofexidine treatment; however, the average number of fetuses per dam was dose-dependently decreased by almost 2-fold at the HD, and the average number of resorptions per dam were increased compared to controls by 1.4-fold and 3-fold at the MD and HD, respectively (Table 42). Additionally, post-implantation loss was increased compared to controls by 1.5-fold and 3-fold at the MD and HD, respectively. Notably, in dams with at least one live fetus, no differences were observed across treatment groups with respect to the average number of fetuses or resorptions per dam. These data suggest that lofexidine treatment did not impair pre-implantation fertility, but embryo viability was dose-dependently decreased starting at the MD.

Table 42: Cesarean Section Results on GD 20

Treatment	Average Number of Observations per Dam ± SD				Rate of Embryo Loss	
	Corpora Lutea	Implantations	Fetuses	Resorptions	Pre-Implantation	Post-Implantation
Vehicle	10.2 ± 1.0	9.9 ± 1.5	8.2 ± 2.2	1.7 ± 1.7	3.4%	16.9%
LD	10.1 ± 1.2	9.5 ± 1.2	8.3 ± 1.8	1.3 ± 1.3	6.6%	13.2%
MD	9.8 ± 1.0	9.2 ± 1.3	6.8 ± 3.6	2.4 ± 2.7	6.0%	26.5%
HD	10.1 ± 0.8	9.6 ± 1.0	4.6 ± 4.6	5.0 ± 4.6	4.5%	52.2%

The following signs of fertility were evaluated in dams and offspring after spontaneous delivery and observation during the 4-week lactation period: average duration of pregnancy, number and birthweight of kits, malformations and morphological findings in the kits at dissection, behavior, kit survival rate, and weight development throughout the lactation period.

In dams with spontaneous deliveries and their offspring, there were no treatment-related changes in the duration of pregnancy, the average weight of kits at birth, or the number of runts or deformed offspring; however, the average litter size was decreased at the HD by approximately 2-fold, and the rate of stillborn births per litter was increased at the HD by 3-fold (Table 43). Although the average weight of kits at birth was not different across treatment groups, the average weights of kits at the HD were decreased by 40% compared to controls in all subsequent weeks, until sacrifice at the end of the 4th week of the lactation period (Figure 51). The survival rate of kits was decreased at the HD

with only 30% surviving by the end of Week 4 compared to 83% in controls (Figure 52). These data indicate that maternal treatment with lofexidine at the HD adversely impacted litter size and kit growth and survival during the lactation period. Effects observed during the lactation period may be due to exposure of kits via milk or effects of lofexidine-treatment on maternal care.

Table 43: Spontaneous Delivery Results

Treatment	Pregnancy Duration (\pm SD)	Litter Size (\pm SD)	Number of Stillborn Births	
			Total	Per Litter (\pm SD)
Vehicle	32.4 \pm 1.1	7.9 \pm 1.8	3	0.4 \pm 0.8
LD	32.5 \pm 1.3	8.0 \pm 3.0	0	0
MD	30.9 \pm 0.9	8.0 \pm 1.7	1	0.1 \pm 0.3
HD	31.0 \pm 0.7	4.1 \pm 3.9	6	1.2 \pm 1.3

Figure 51: Impact of Maternal Lofexidine Treatment on Kit Body Weights

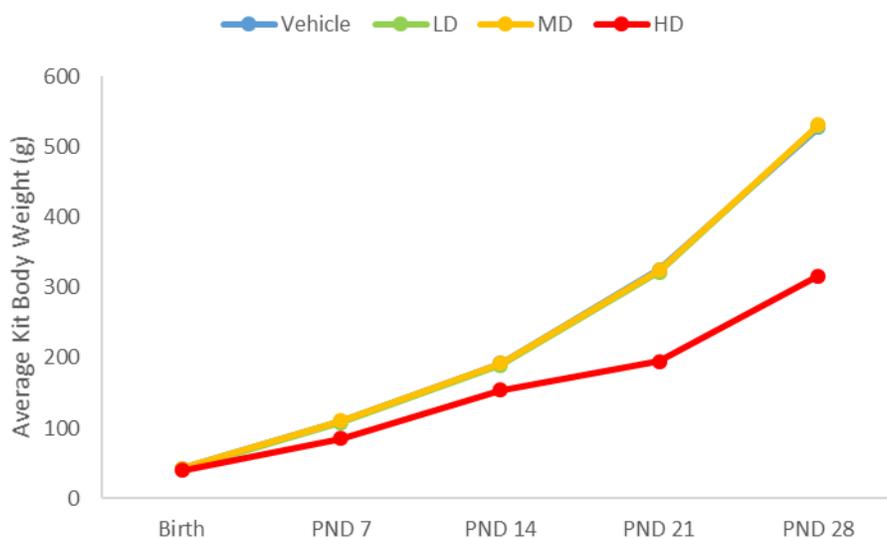
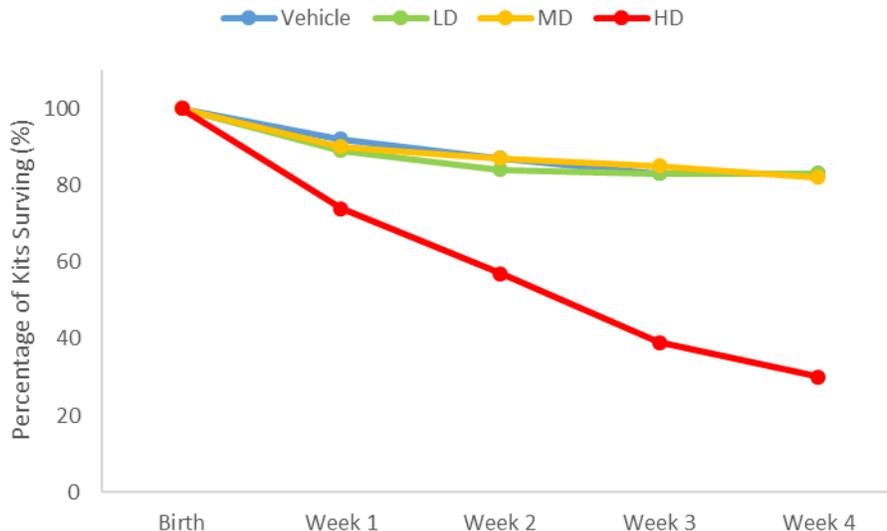


Figure 52: Kit Survival Rate during Lactation Period



Study title: Reproduction Study with Lofexidine in Rats

Study no.: USWM-LX0-TOX-0016
 Study report location: <\\cdsesub1\levsprod\nda209229\0002\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42353-pre-postnatal-dev\uswm-lx0-tox-0016\uswm-lx0-tox-0016.pdf>

Conducting laboratory and location: (b) (4)

Date of study initiation: December 12, 1977
 GLP compliance: No
 QA statement: No
 Drug, lot #, and % purity: Lofexidine, Unknown, Unknown

Key Study Findings

- Lofexidine was administered in diet to male and female rats for prior to mating and to the dams through gestation and 3 weeks of lactation with an interim Cesarean section sacrifice of 12/30/group on GD 15. Fertility of F1 offspring was also assessed.
- Lofexidine treatment at the HD mildly decreased body weight (mean of up to 2.5%) and food consumption in dams.
- No treatment-related effects were observed with respect to the results of Cesarean sections on GD 15.
- The average number of live pups per litter was slightly decreased at the HD in dams that were allowed to deliver spontaneously. Pups from these litters also

showed slightly decreased survival rates after 48 hours and after three weeks of lactation.

- A slight increase in the incidence of resorptions was observed after mating in F₁ dams.
- The NOAEL for this study with respect to fertility was the HD, 0.88 mg/kg/day providing a 3-fold safety margin to the MRHD of 2.88 mg/day based on body surface area allometric scaling. However, the exposure margin based AUC is only 0.2x.

Methods

Doses: 0, 0.1, 0.3, and 1.0 mg/kg/day (lofexidine HCl)
0, 0.09, 0.26, 0.88 mg/kg/day (lofexidine free base)

Frequency of dosing: Daily via diet
Dose volume: NA

Route of administration: Diet
Formulation/Vehicle: Purina Lab Chow
Species/Strain: Rat/Long Evans
Number/Sex/Group: 30
Satellite groups: None
Study design: Female rats were dosed starting 2 weeks prior to mating with male rats that had been dosed for 87 days. Male rats were removed from the study after successful copulation (up to a maximum of 14 attempts), and dams continued to be dosed throughout gestation until sacrifice. 12 dams/group were sacrificed and examined on GD 15 and the remaining 18 dams/group were allowed to deliver and were sacrificed at the end of the 3rd week of lactation. Two male and 2 female F₁ offspring were selected from each litter and were mated on PND 110. F₁ females were sacrificed and examined on GD 16.

Deviation from study protocol: None Reported

Observations and Results

Mortality

No unscheduled deaths occurred during the study.

Clinical Signs

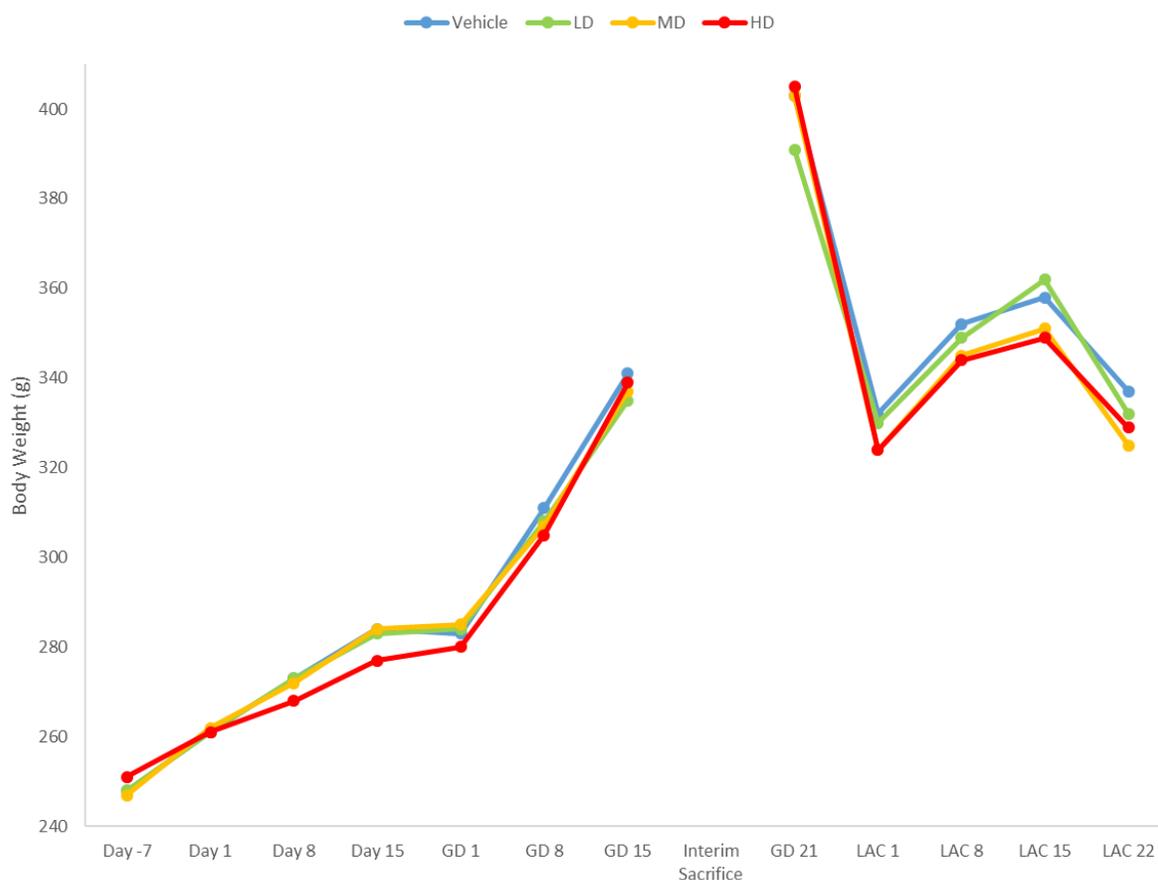
No adverse clinical signs were noted in lofexidine-treated male or female rats.

Body Weight

Body weights of F0 females were recorded at weekly intervals starting one week prior to dosing.

Body weight gains in HD dams were slightly decreased during the initial 2-week dosing period prior to mating (up to 2.5% of control), but appeared to recover during gestation (Figure 53). Immediately after parturition, MD and HD dams had slightly lower body weights than controls and this trend persisted throughout the lactation period.

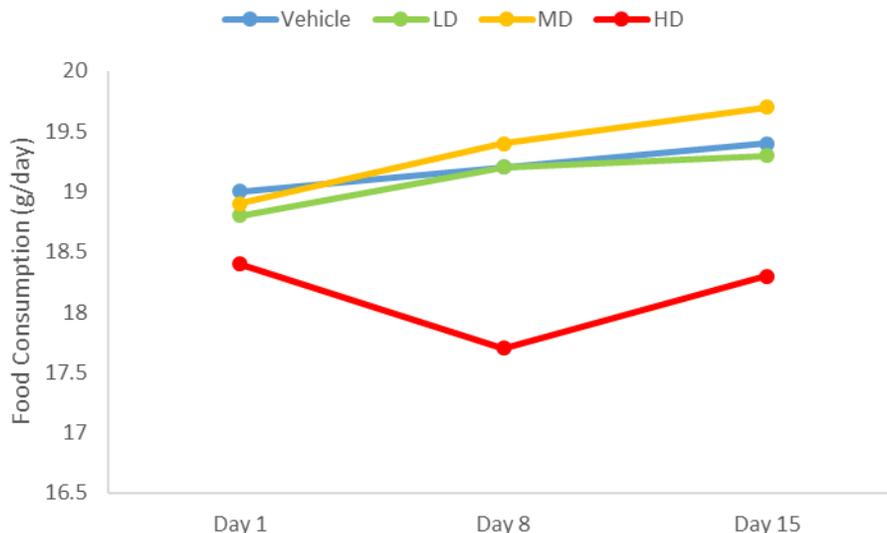
Figure 53: Impact of Lofexidine Treatment on Body Weights in Dams



Food Consumption

Food consumption was measured weekly during the first two weeks of dosing.

Food consumption was modestly decreased by approximately 5% during the first two weeks of dosing (Figure 54).

Figure 54: Impact of Lofexidine Treatment on Food Consumption in Dams**Toxicokinetics**

Toxicokinetics evaluations were not performed.

Dosing Solution Analysis

Dosing solution analysis was not performed.

Necropsy

No treatment-related macroscopic findings were observed in F₀ dams.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

All F₀ females, except for one at the LD, showed evidence of copulation during the first 14 days. Cesarean sections on GD 15 revealed that 10 rats in each treatment group were pregnant and no treatment-related effects were observed with respect to the incidence of live, dead, or resorbed fetuses (Table 44). With the exceptions of one vehicle-treated and 3 LD dams, all the remaining dams had normal spontaneous deliveries (Table 45). Average number of pups per litter was slightly decreased at the HD, and the number of dead pups was slightly higher than controls in all lofexidine treatment groups. Pup birthweights and sex ratio were not impacted by maternal lofexidine treatment. Pup 48-hour survival rates were slightly reduced in all lofexidine treatment groups compared to controls (Table 46). Litters were then reduced to 8 pups, if possible, and survival rates by Lactation Day 22 were higher than controls at the LD and MD but still slightly lower than controls at the HD. Two males and two females from each F₁ litter were allowed to mate on approximately PND 110 and were examined on GD 15. Apart from a slight increase in the incidence of resorptions at the HD which manifested as a slight decrease in the average number of viable fetuses per dam, there

were no treatment-related effects observed with respect to fertility in the F₁ offspring (Table 47). Male fertility parameters such as sperm counts and motility were not evaluated in this study. As designed, it is not clear if there are any effects on male fertility or not.

Table 44: Cesarean Section Results on GD 15

	<u>Females Sacrificed for Dominant Lethal Study</u>											
	Total	%	Avg.	Total	%	Avg.	Total	%	Avg.			
Number sacrificed	11			12			12			12		
Number pregnant	10	90.9		10	83.3		10	83.3		10	83.3	
Total implants	142	100	14.2	141	100	14.1	124	100	12.4	147	100	14.7
Viable fetuses	133	93.7	13.3	140	99.3	14.0	112	90.3	11.2	138	93.9	13.8
Dead fetuses	0			0			0			0		
Resorptions	9	6.3	0.9	1	0.7	0.1	12	9.7	1.2	9	6.1	0.9
Number litters with resorp.	6	60		1	10		4	40		5	50	

Table 45: Spontaneous Delivery Results

	<u>Females Allowed to Deliver</u>											
	Total	%	Avg.	Total	%	Avg.	Total	%	Avg.	Total	%	Avg.
Number retained	19 ^b			18			18			18		
Number delivered	18 ^b	94.7		14 ^c	77.8		18	100		18	100	
Length of gestation (days)			22.6			22.5			22.6			22.6
No. delivered - live pups	18	100		14	100		18	100		18	100	
- dead pups	1	5.6		4	28.6		2	11.1		5	27.8	
Total pups at birth	246	100	13.7	188	100	13.4	239	100	13.3	221	100	12.3
Live pups at birth	245	99.6	13.6	177	94.1	12.6	234	97.9	13.0	209	94.6	11.6
Dead pups at birth	.1	0.4	.06	11	5.9	0.8	5	2.1	0.3	12	5.4	0.7
Pup wt. (g) at birth			6.1			6.1			6.2			6.1
Ratio at birth (live pups)												
Male	132	53.9	7.3	85	48.0	6.1	114	48.7	6.3	107	51.2	5.9
Female	113	46.1	6.3	92	52.0	6.6	120	51.3	6.7	102	48.8	5.7

^a One female sacrificed day 33 - no evidence of copulation during first 14 days of cohabitation

^b One female sacrificed day 43 - not pregnant, no evidence of implantation

^c Three females sacrificed day 43 - 2 not pregnant, no evidence of implantation. One female (pregnant) did not deliver - one oversized dead pup found in uterus. None of these dams or pup included in data

Table 46: Survival and Weight Gain of F₁ Pups

	Dose Group (mg/kg/day)			
	Control	0.1	0.3	1.0
No. alive at 48 hours	241 (13.4)	168 (12.0)	224 (12.4)	196 (10.9)
% Survival birth to 48 hrs.	98	95	96	94
No. litters with dead pups, birth to 48 hrs.	4	3	4	6
Avg. body wt.(g) remaining pups	7.6	7.7	7.8	7.8
Total males remaining	129 (7.2)	84 (6.0)	110 (6.1)	98 (5.4)
Total females remaining	112 (6.2)	84 (6.0)	114 (6.3)	98 (5.4)
No. pups retained at 48 hrs. ^b	141 (7.8)	106 (7.6)	143 (7.9)	134 (7.4)
Avg. body wt.(g) retained pups	7.7	7.8	7.9	8.0
Total males retained	68 (3.8)	54 (3.9)	74 (4.1)	71 (3.9)
Total females retained	73 (4.1)	52 (3.7)	69 (3.8)	63 (3.5)
No. alive at day B22	136 (7.6)	104 (7.4)	142 (7.9)	124 (7.3)
% Survival 48 hr. to day B22	96	98	99	93
No. litters with dead pups, 48 hrs. to day B22	5	2	1	3 ^a
Avg. body wt.(g) at day B22	47.8	49.2	46.6	46.8
Total males day B22 ^c	62 (3.4)	50 (3.6)	69 (3.8)	62 (3.4)
Total females day B22 ^c	74 (4.1)	54 (3.9)	73 (4.1)	62 (3.4)

() = average values

^a All 8 pups died in one litter^b All litters reduced to 8 pups (4 males and 4 females) when possible^c Difference between 48 hrs. and B22 due to difficulty in sexing at 48 hrs.Table 47: Summary of F₁ Generation Breeding Results

	Dose Groups (mg/kg/day)											
	Control			0.1			0.3			1.0		
	Total	%	Avg.	Total	%	Avg.	Total	%	Avg.	Total	%	Avg.
No. females sacrificed	18			14			18			17		
No. pregnant	18	100		13	92.9		18	100		16	94.1	
Total implants	233	100	12.9	151	100	11.6	228	100	12.7	201	100	12.6
Viable fetuses	217	93.1	12.1	136	90.1	10.5	218	95.6	12.1	164	81.6	10.3
Dead fetuses	1	0.4	.06	1	0.7	.08	0			0		
No. resorptions	15	6.4	0.8	14	9.2	1.1	10	4.4	0.6	37	18.4	2.3
No. litters with resorptions	10	56		6	46		9	50		10	62.5	

9.2 Embryonic Fetal Development

Study title: Teratologic Study with RMI 14,042A in Rabbits

Study no.: USWM-LX0-TOX-0010
Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev\uswm-lx0-tox-0010\uswm-lx0-tox-0010-pre-clinical-study-report.pdf>
Conducting laboratory and location:  (b) (4)
Date of study initiation: December 28, 1976
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: Lofexidine hydrochloride, Unknown, Unknown

Key Study Findings

Maternal Toxicities

- Lofexidine treatment at the HD was associated with increased mortality during the study, particularly near the end of the dosing period.
- Body weights and food consumption were dose-dependently decreased during the dosing period and subsequently began to recover during the last week of gestation.
- The NOAEL for maternal toxicity was the MD of 5.0 mg/kg/day (4.4 mg/kg base), as the HD was associated with higher incidences of mortality.

Embryofetal Toxicities

- Rate of conception was decreased at the HD.
- The average number of resorptions per dam was increased at the MD and HD.
- The average number of implantations was decreased at the HD.
- Mean litter weights were reduced by 8.3 and 21% in the MD and HD group; however, there were no differences in mean fetal weights.
- There was an increase in the incidence of umbilical hernia and extra ribs in the MD and HD over controls.
- No overt teratogenic effects of lofexidine treatment were observed.
- The NOAEL for embryofetal toxicity was the LD, 1.5 mg/kg/day (1.3 mg/kg base), based on an increase in the average number of resorptions per dam at the MD, providing a 9-fold safety margin to the MRHD of 2.88 mg/day based on body surface area allometric scaling. However, the exposure margin based AUC is only 0.02x.

Methods

Doses: 0, 1.5, 5.0, 15.0 mg/kg/day (lofexidine HCl)
 0, 1.3, 4.4, 13.2 mg/kg/day (lofexidine free base)
 Frequency of dosing: Once Daily
 Dose volume: 3 mL/kg
 Route of administration: Oral Gavage
 Formulation/Vehicle: Distilled Water
 Species/Strain: Rabbit/New Zealand White
 Number/Sex/Group: 18
 Satellite groups: None
 Study design: Dosing of dams from GD 7 through GD 19 with sacrifice and uterine examination on GD 29
 Deviation from study protocol: None Reported

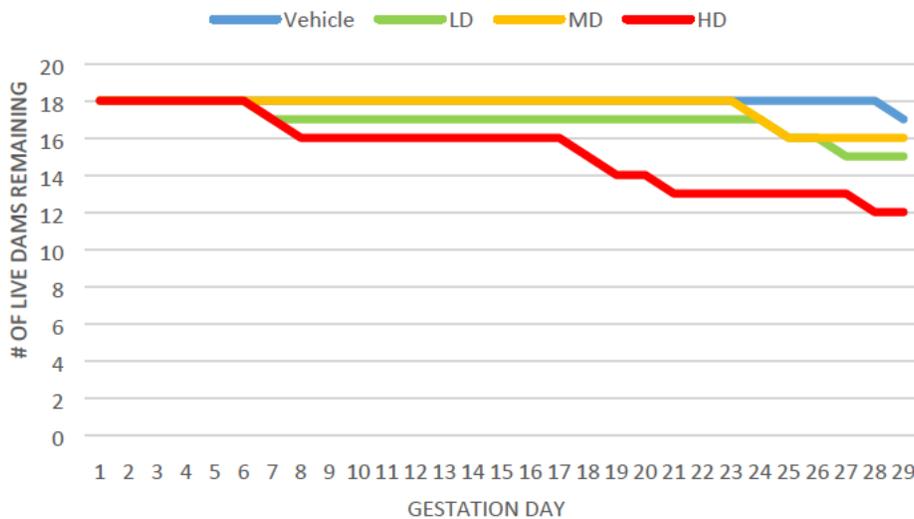
Observations and Results

Mortality

Animals were observed daily to check for morbidity/mortality.

Figure 55 displays the cumulative survival of dams across treatment groups. Three likely gavage-error-related unscheduled deaths occurred upon the initiation of dosing on GD 7 and 8 (1 at the LD and 2 at the HD). Three additional unscheduled deaths occurred at the HD around the end of the dosing period on GD 18, 19, and 21. During the final week of gestation, there one or two unscheduled deaths across all treatment groups. Except for the gavage-related deaths, a cause of death could not be identified based on the necropsy results.

Figure 55: Survival of Lofexidine-Treated Dams



Clinical Signs

Dams were observed daily for any changes in appearance or behavior.

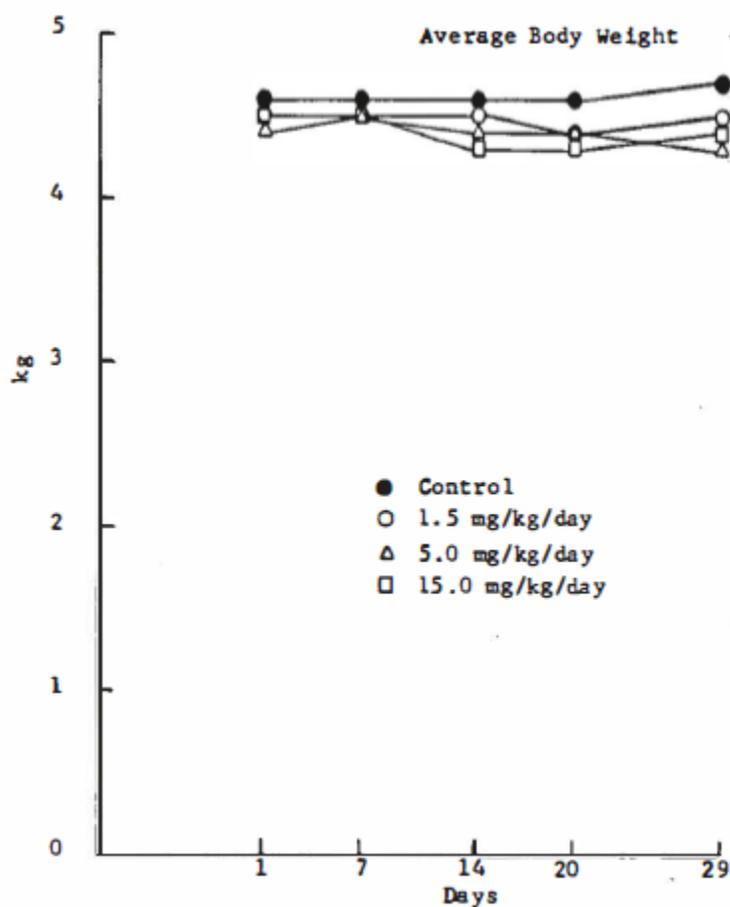
Lofexidine-treatment was not associated with the occurrence of any clinical signs recorded in this study.

Body Weight

Body weights of dams were measured at selected intervals throughout pregnancy.

Mean body weights were reduced in lofexidine-treated dams at all dose levels compared to controls, but this effect was most pronounced during the treatment period at the HD (Figure 56).

Figure 56: Impact of Lofexidine Treatment on Body Weights in Dams

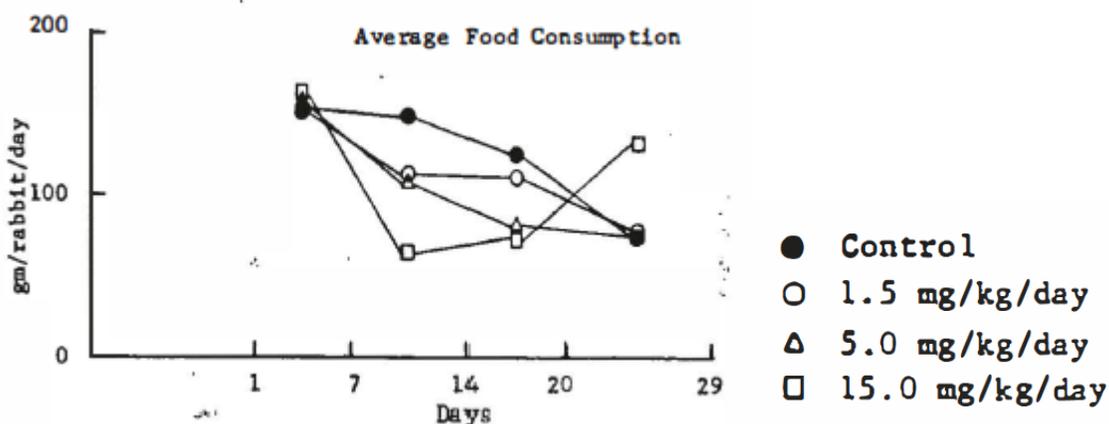


Food Consumption

Food consumption of dams was measured at selected intervals throughout pregnancy.

Food consumption was dose-dependently decreased during the dosing period (Figure 57). This effect was particularly pronounced at the HD, but rebounded back to almost pre-dose levels when dosing ceased.

Figure 57: Impact of Lofexidine Treatment on Food Consumption in Dams



Toxicokinetics

Toxicokinetics evaluations were not performed.

Dosing Solution Analysis

Dosing solution analysis was not performed.

Necropsy

Any animal that died during the test was necropsied to determine the cause of death and to assess the status of the reproductive organs. All surviving dams were sacrificed by decapitation and examined for gross lesions on GD 29.

Lofexidine treatment was not associated with the occurrence of any gross lesions.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

After sacrifice, uterine contents were examined, and the number of corpora lutea, as well as live, dead, or resorbed fetuses were recorded.

As shown in Table 48, conception rates at the LD and MD were greater than or equal to controls (94%) but markedly lower at the HD (72%). It is unclear whether this finding is truly test article related as dosing was initiated after implantation should have already occurred (Sivaraman et al., 2008). A dose-dependent reduction in the average number of live fetuses per dam was observed. This effect was primarily attributable to an increase in the average number of resorptions per dam and was further exacerbated at the HD by a decrease in the average number of implantations per dam.

Table 48: Impact of Lofexidine Treatment on Cesarean Section Results

	Dose Group (mg/kg/day)							
	Control	1.5	5.0	15				
CONCEPTION								
No. inseminated	18	18	18	18				
No. with corpora lutea	17	18	18	18				
No. died - not pregnant	0	0	0	2				
- pregnant	1	3	2	4				
No. delivered early	1	0	2	1				
No. pregnant at term	14	14	14	8				
FATE OF INDIVIDUAL IMPLANTATIONS								
	<u>Avg.</u>	<u>Z</u>	<u>Avg.</u>	<u>Z</u>	<u>Avg.</u>	<u>Z</u>	<u>Avg.</u>	<u>Z</u>
Live fetuses (avg/dam)	8.1	90	6.6	80	6.3	71	4.8	69
Dead fetuses (avg/dam)	0.1	1	0.6	8	0.1	2	0	0
Incomplete resorptions (avg/dam)	0.2	2	0.3	3	0.7	8	0	0
Complete resorptions (avg/dam)	0.6	7	0.7	9	1.7	19	2.1	31
Implant (avg/dam)	9.0		8.2		8.9		6.9	

Offspring (Malformations, Variations, etc.)

Live fetuses were weighted, examined grossly, and then sacrificed by decapitation. The heads were preserved in Boiun's fixative and then examined grossly by free-hand sectioning. Thoracic and abdominal viscera were examined by dissection. The fetuses were then skinned, eviscerated and fixed in 70% alcohol, cleared with potassium hydroxide, stained with alizarin-red-S and examined for any skeletal abnormalities.

A dose-dependent decrease in average litter weight was observed (Table 49); however, this finding was solely attributable to a dose-dependent decrease in pups per litter as no significant changes in average fetal weight were observed across treatment groups. Dose-dependent increases in the incidence rate of umbilical hernias and contracted rear foot tendons; however, both findings were of low incidence, up to 2/38 and 3/38 at the HD, respectively. Historical control data suggest the incidence of umbilical hernias can range from 0-8.3%^d. There are no historical control data for incidence of contracted tendons to our knowledge. The study report concluded that the finding was incidental as it was not discovered until the bones were evaluated. Additional findings of single incidence at the HD that were not present in controls included lateral spine curvature and incomplete vertebrae ossification. As the incidence rate of these few potentially treatment-related findings is quite low, lofexidine does not appear to be clearly teratogenic.

^d https://www.citoxlab.com/wp-content/uploads/2015/12/Pages-de-Poster_ETS_HDEF.pdf

Table 49: Impact of Lofexidine Treatment on Offspring

<u>FETAL OBSERVATIONS</u>				
Total fetuses examined	113	92	88	38
Avg. litter weight (gms)	255	231	234	202
Avg. fetal weight (gms)	32	33	35	32
<u>MALFORMATIONS</u>				
Spine - lateral curvature	0	0	0	1
Vertebrae - portions missing, misaligned and/or fused; some with ribs fused, forked or missing	3	2	1	0
Ribs - forked (cartilaginous portion)	0	1	0	0
Kit edematous, heart enlarged, subcutaneous hemorrhage	1	0	0	0
Clavicle - rudimentary	0	1	0	0
Spleen - forked	0	1	0	0
Hydrocephalus	1	1	0	1
Hernia - umbilical	0	0	1	2
<u>VARIATIONS</u>				
Ribs - extra 13th	63	48	48	18
- extra anterior to 1st	0	0	1	2
- soft	1	0	0	0
Sternaebrae - small	69	65	53	31
- missing	29	31	20	15
- bipartite or irregular	14	10	8	3
Vertebrae - incomplete ossification	0	0	1	1
Contracted tendons - front foot	1	0	0	0
- rear foot/feet*	0	2	3	3
Super adduction, pelvic limb	1	0	0	0
Hemorrhagic amnion	0	0	1	0
Maceration (artifact)	1	0	0	0

* Detected only after processing fetuses for examination of the skeleton

Study title: Lofexidine Hydrochloride: An Oral Toxicokinetic Study in Pregnant Rabbits (GLP)

Study no.: USWM-LX0-TOX-0004
Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev\uswm-lx0-tox-0004\uswm-lx0-tox-0004-pre-clinical-study-report.pdf>
Conducting laboratory and location:  (b) (4)
Date of study initiation: July 31, 2008
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Lofexidine HCl, 24004970, 100.07%

Key Study Findings

- Maternal toxicity was induced at the HD and to a lesser extent at the MD in the form of decreased body weight gain and decreased food consumption.
- Detailed analyses designed to detect embryofetal toxicity were not performed.
- Toxicokinetic parameters were evaluated on GD 6 and GD 19.

Methods

Doses: 0, 1.5, 5.0, 15 mg/kg/day
Frequency of dosing: Once Daily
Dose volume: 3 mL/kg
Route of administration: Oral Gavage
Formulation/Vehicle: Phosphate Buffered Saline (PBS), pH 7.2
Species/Strain: Rabbit/New Zealand White
Number/Sex/Group: 5
Satellite groups: None
Study design: As this study was designed to assess toxicokinetic parameters, dams were dosed from GD 6 through GD 19 with sacrifice and uterine examination on GD 21.
Deviation from study protocol: No blood sample was obtained at the 12-hour timepoint for Animal No. 4510 on GD 6. This deviation and other minor deviations noted did not impact the validity of the study.

		Dosage (once daily, oral gavage)			No. of TK Animals
		Dose ^a (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	
1	Control	0.0	0.00	3	5
2	Low	1.5	0.50	3	5
3	Intermediate	5.0	1.67	3	5
4	High	15.0	5.00	3	5

^aDoses represent active ingredient adjusted with a correction factor of 1.14, to account for the salt form.

Observations and Results

Mortality

Animals were observed in their cages twice daily for mortality, morbidity, and signs of severe toxicity. Animals in extremely poor health were identified for further monitoring.

There was no mortality during the study.

Clinical Signs

Each dam was observed cage-side for overt signs of toxicity prior to dosing and at a minimum approximately one hour after dosing and concurrent with the viability observations in the afternoon. Dams were also examined more closely on GD 4, 6, 9, 12, 14, 15, 18, and 21. Detailed examinations included observations of general condition, skin and fur, eyes, nose, oral cavity, abdomen and external genitalia, as well as evaluations of respiration. These evaluations were performed prior to dosing, during the treatment phase.

Except for decreased fecal volume in almost all lofexidine-treated dams on GD 8, there were no test article-related clinical signs post-dose during the study.

Body Weight

Dams were weighed on GD 4, 6, 9, 12, 14, 15, 18, and 21. Body weights were recorded and body weight changes were reported from GD 6 through GD 21 by three day intervals.

Lofexidine treatment was not associated with an obvious impact on absolute body weights (Figure 58); however, analysis of body weight changes revealed decreases in body weight gain between GD6 and GD 21 of 25% at the MD and 44% at the HD (Figure 59).

Figure 58: Impact of Lofexidine-Treatment on Body Weights in Dams

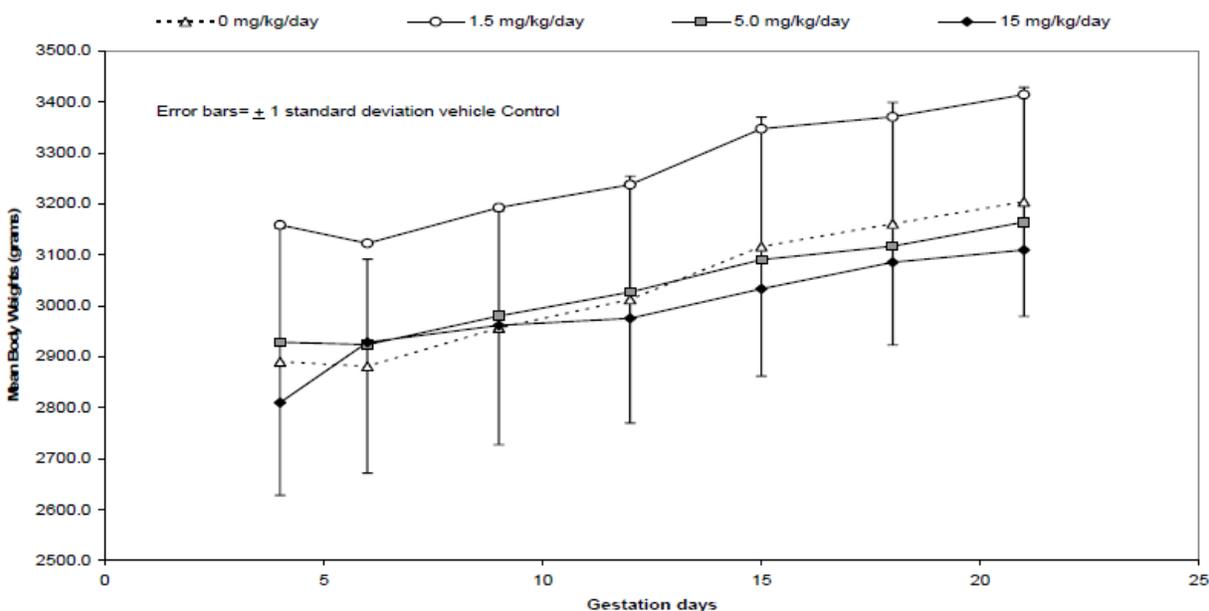
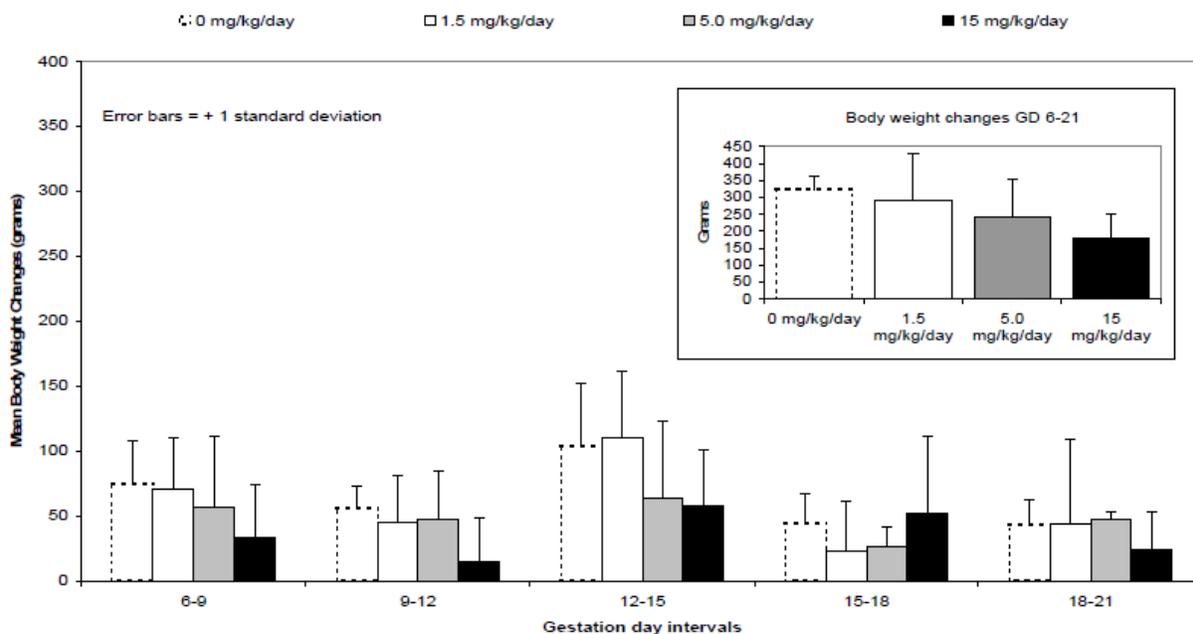


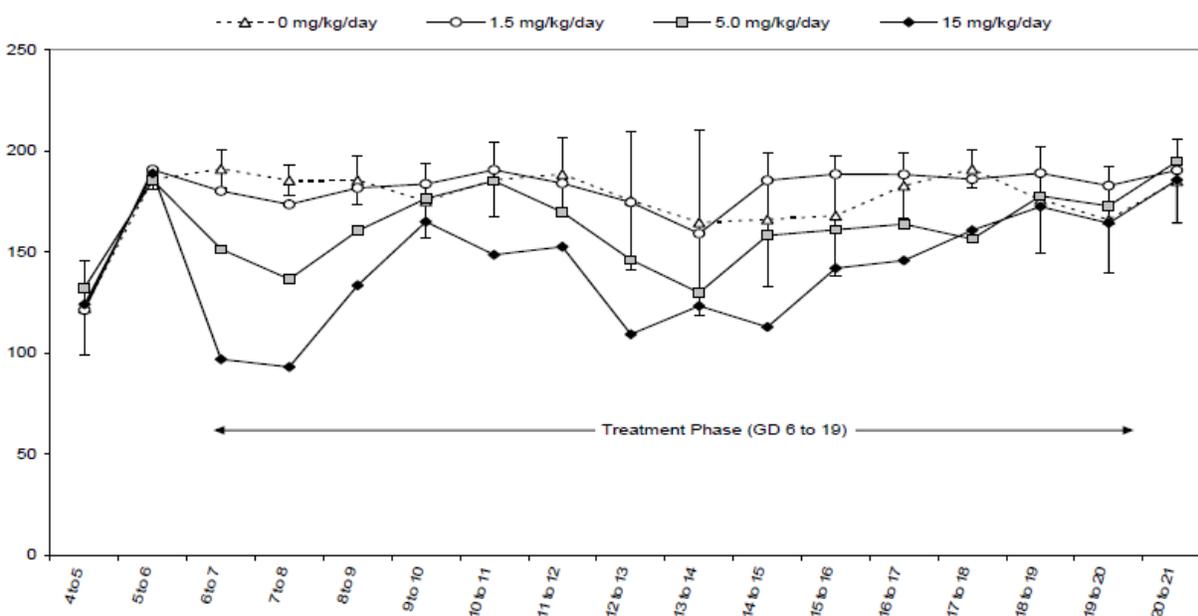
Figure 59: Impact of Lofexidine-Treatment on Body Weight Gains in Dams



Food Consumption

Food consumption was measured daily and reported for the same intervals as body weight changes.

Food consumption was significantly reduced at the HD by up to 49.8% from GD 7-8 and by 25% between GD 6 and GD 21 (Figure 60). Food consumption was also decreased at the MD by 5.2% to 26.4%, but this effect did not achieve statistical significance.

Figure 60: Impact of Lofexidine Treatment on Food Consumption in Dams

Toxicokinetics

Blood samples were collected from each lofexidine-treated dam on GD 6 and GD 19 at the following timepoints: predose, 0.5, 1, 2, 4, 8, 12, and 24 hours postdose. Only the 2-hour postdose timepoint was collected and analyzed for vehicle-treated dams.

The results of the toxicokinetics analysis are shown below in Table 50. No measurable lofexidine was recorded in vehicle-treated dams or at the LD on GD 6. Approximately 2 to 4-fold accumulation was observed on GD 19 at the MD and HD. C_{max} increased nearly dose-proportionally whereas AUC increased more than dose-proportionally at the HD.

Table 50: Toxicokinetics Parameters from GLP Rabbit Embryofetal Study

GD	Dose (mg/kg/day)	AUC _{0-last} (hr•ng/mL)	AUC _{0-last} /Dose ((hr•ng/mL)/mg/kg)	C _{max} (ng/mL)	C _{max} /Dose ((ng/mL)/mg/kg)	t _{1/2} (hr)	T _{max} (hr)
6	15	0±0	0±0	0±0	0±0	NC	NC
	5.0	196±1.65	0.391±0.331	1.06±0.337	0.211±0.0674	9.26	1.00±0
	15.0	14.7±2.72	0.980±0.181	2.89±0.897	0.192±0.0598	7.39±4.65	1.40±0.548
19	15	220±0.506	1.46±0.337	1.76±0.625	1.17±0.416	1.28±0.278	0.500±0
	5.0	752±1.22	1.50±0.245	2.41±0.737	0.482±0.147	2.71±0.988	0.875±0.250
	15.0	36.7±15.0	2.44±1.00	7.95±3.18	0.530±0.212	2.83±0.631	1.80±1.30

NC = not calculated; insufficient data

Dosing Solution Analysis

Stability and homogeneity analyses were not reported for this study. Dose confirmation analysis was performed on duplicate samples taken from the middle region of the dosing formulations at the beginning and near the end of the study.

One of the duplicate samples taken at the beginning of the study for the MD formulation was measured to be 21% below its nominal concentration (Table 51). This fell outside of the acceptable range of $\pm 10\%$; however, the other duplicate and a backup sample were both found to be within the acceptable range. Based on this dosing solution analysis, the test article formulations used in this study were acceptable.

Table 51: Dosing Solution Analysis for GLP Rabbit Embryofetal Study

Vial Group (sampling date)	Labeled Concentration	Measured Concentration	% Theoretical
1 (Aug 7)	0	0	0
1 (Aug 7)	0	0	0
1 (Aug 14)	0	0	0
1 (Aug 14)	0	0	0
2 (Aug 7)	0.5	0.475	95
2 (Aug 7)	0.5	0.468	93.6
2 (Aug 14)	0.5	0.476	95.4
2 (Aug 14)	0.5	0.462	92.4
3 (Aug 7) ^a	1.67	1.321	79 [±]
3 (Aug 7) ^a	1.67	1.563	93.6
3 (Aug 14) ^b	1.67	1.593	95.4
3 (Aug 14) ^b	1.67	1.58	94.6
4 (Aug 7)	5	4.66	93.2
4 (Aug 7)	5	4.665	93.3
4 (Aug 14)	5	4.872	97.4
4 (Aug 14)	5	4.734	94.7
Backup samples			
3 (Aug 7) ^a	1.67	1.71	102.40%
3 (Aug 14) ^b	1.67	1.49	89.3% [±]

Necropsy

A macroscopic evaluation was performed during necropsy to assess pregnancy status and total number of implantations only.

Necropsy revealed that 1 vehicle-treated doe and one MD doe were not pregnant. All pregnant dams had viable fetuses.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Detailed analysis of Cesarean section results were not performed.

Offspring (Malformations, Variations, etc.)

Detailed analysis of offspring malformation and variations was not performed.

Study title: Teratology Study with RMI 14,042A in Rats

Study no.: USWM-LX0-TOX-0018

Study report location: <\\cdsesub1\evsprod\nda209229\0002\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev\uswm-lx0-tox-0018\uswm-lx0-tox-0018-pre-clinical-study-report.pdf>

Conducting laboratory and location:



Date of study initiation: November 18, 1975

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: Lofexidine hydrochloride^e, Unknown, Unknown

Key Study FindingsMaternal Toxicities

- Maternal toxicity was evident at the HD, as evidenced by two unscheduled deaths, the emergence of clinical signs of distress, e.g., thin/weak appearance, nasal discharge, and urine staining of abdominal pelage, and significant decreases in body weight gains and food consumption.
- The maternal NOAEL was the MD of 0.88 mg/kg/day lofexidine base (1.0 mg/kg lofexidine HCl).

Embryofetal Toxicities

- Conception rates and the percentage of live fetuses were modestly decreased (15-20%) compared to controls at all dose levels of lofexidine.
- The average number of implantations per dam was dose-dependently decreased by lofexidine treatment.
- Average individual and litter weights of fetuses were significantly decreased at the HD.
- The incidence of extra vestigial ribs and sternal variations were increased compared to controls at the HD.

^e As per ChemIDPlus, RMI 14,042A is the hydrochloride salt of lofexidine

- The developmental NOAEL was the MD of 1.0 mg/kg (0.88 mg/kg base) providing a 3-fold safety margin to the MRHD of 2.88 mg/day based on body surface area allometric scaling. However, the exposure margin based AUC is only 0.2x.

Methods

Doses:	0, 0.26, 0.88, 2.6 mg/kg/day of the base Report describes doses of 0, 0.3, 1.0, or 3.0 mg/kg/day lofexidine, which appears to be the hydrochloride salt
Frequency of dosing:	Once Daily
Dose volume:	3 mL/kg
Route of administration:	Oral Gavage
Formulation/Vehicle:	Distilled Water
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	20
Satellite groups:	None
Study design:	Dosing of dams from GD 7 through GD 16 with sacrifice and uterine examination on GD 21
Deviation from study protocol:	None Reported

Observations and Results

Mortality

Two HD rats, #69 and #75, were found dead on GD 15. Rat #69 was not pregnant at the time of death and displayed no evidence of any implantations. This rat was found dead 23 hours postdose and necropsy revealed dehydration and red adrenals. Necropsy of Rat #75 revealed a distended intestinal tract, marked congestion of vessels, and 8 complete resorptions. Both rats exhibited the following clinical signs that were also observed in other HD rats: slight depression, urine staining of abdominal pelage, reddish nasal discharge, and thin/weak appearance.

Clinical Signs

Rats were observed daily after dosing was started to determine any changes in appearance or behavior.

Several adverse clinical signs were observed, primarily at the HD (Table 52). All HD rats exhibited slight depression approximately 1 hour after dosing throughout the entire dosing period. Signs of stress, e.g., urine staining of abdominal pelage and/or nasal discharge, were also noted in approximately half of the HD rats. Thin/weak appearance was also noted in 4 HD rats, two of which were found dead on GD 15, and 1 MD rat. No additional clinical signs were observed in any of the other treatment groups.

Table 52: Summary of Clinical Observations in Dams

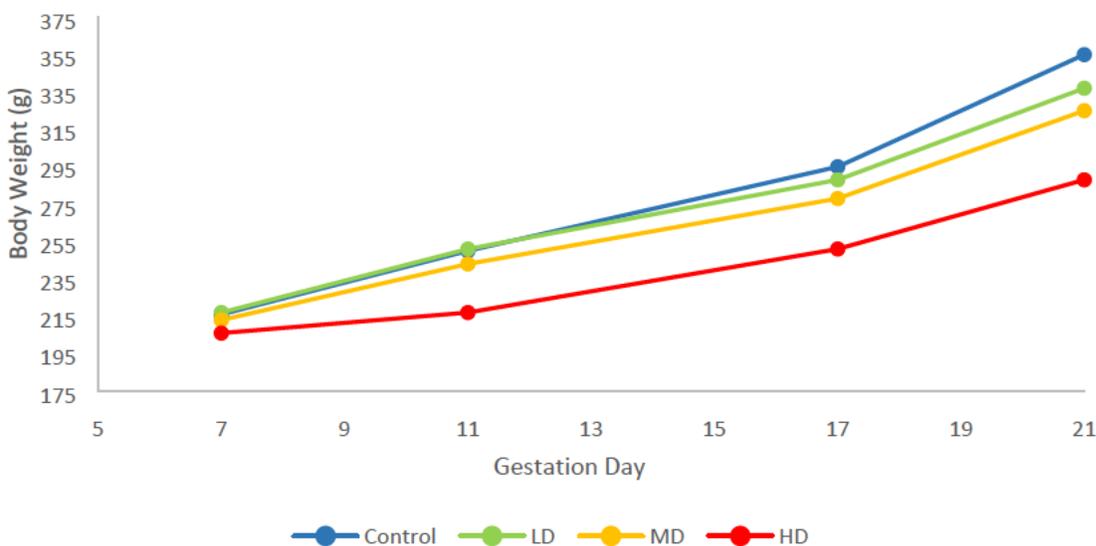
	Dose Group (mg/kg/day)			
	Control	0.3	1.0	3.0
	20F	20F	20F	20F
Appears thin/weak	-	-	1	4
Reddish nasal discharge	-	-	-	7
Slight depression	-	-	-	20
Urine staining of abdominal pelage	-	-	-	12
Red spots on tail	-	-	-	1
Appears moribund	-	-	-	1
Chromdacrystorrhea	-	-	-	1
Ocular proptosis, congested sclera, prominent protrusion of tissue at medial canthus, discoloration of fur between eyes	-	-	-	1
Found dead	-	-	-	2
Nothing significant	20	20	19	-

Body Weight

Body weight was measured at selected intervals on GD 7, 11, 17, and 21. Only group mean values were reported.

Body weights were dose-dependently decreased by up to 19% at the HD on GD 21, with the largest decrease in body weight gains occurring between GD 7 and GD 11. Body weights on GD 21 were decreased by only 5% and 8% at the LD and MD, respectively.

Figure 61: Impact of Lofexidine Treatment on Body Weight in Dams

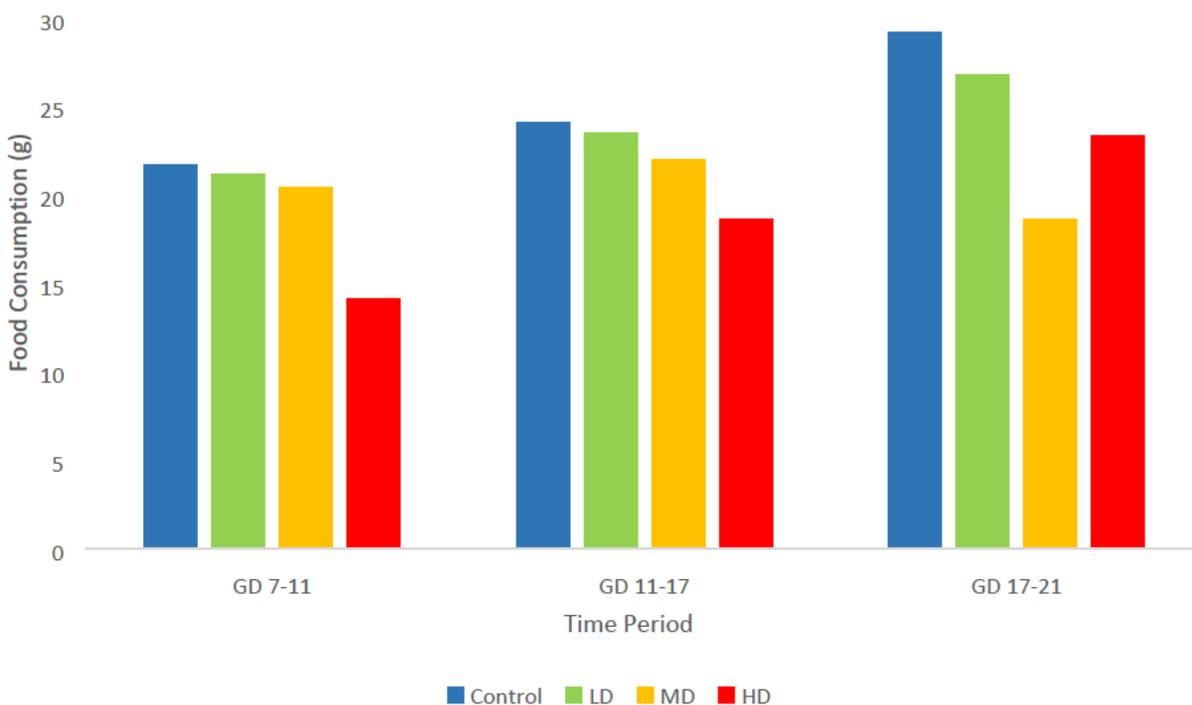


Food Consumption

Food consumption was measured at the following selected intervals: GD 7-11, 11-17, and 17-21. Only group mean values were reported.

Food consumption was decreased primarily at the HD by up to 35% between GD 7 and GD 11. Decreases in food consumption at the HD remained significant but were somewhat attenuated between GD 11 and GD 21. At the MD, food consumption was significantly decreased by 36% only between GD 17 and GD 21, just after dosing had ceased, potentially indicating a withdrawal effect.

Figure 62: Impact of Lofexidine Treatment on Food Consumption in Dams



Toxicokinetics

Toxicokinetics evaluations were not performed.

Dosing Solution Analysis

Dosing solution analysis was not performed.

Necropsy

Dams were examined for gross lesions during necropsy on GD 21.

Apart from the gross lesions reported above in the 2 HD rats that were found dead and eye proptosis (exophthalmos) observed in one HD rat, which was attributed to physical trauma, no gross lesions were observed.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

On GD 21, dams were sacrificed by decapitation and uterine contents were examined. The number and location of live, dead, and resorbed fetuses were recorded.

Cesarean section results are described in Table 53. Conception rates were decreased in lofexidine-treated dams by 15% at the LD and MD and by 25% at the HD. The average number of implantations per dam was dose-dependently decreased by up to 15% at the HD. The percentage of live fetuses decreased by up to 4% at the MD due to an increase in the number of complete resorptions; however, this effect did not appear to be dose dependent and may be coincidental. No dead or incompletely absorbed fetuses were observed in any of treatment groups.

Table 53: Impact of Lofexidine Treatment on Cesarean Section Results

	Dose group (mg/kg/day)											
	Control	0.3	1.0	3.0								
No. bred by supplier	20	20	20	20								
No. not pregnant (died)	-	-	-	1								
No. not pregnant (lived)	-	3	3	4								
No. pregnant (died)	-	-	-	1								
No. pregnant at term	20	17	17	14								
	<u>Total</u>	<u>%</u>	<u>Avg.</u>	<u>Total</u>	<u>%</u>	<u>Avg.</u>	<u>Total</u>	<u>%</u>	<u>Avg.</u>	<u>Total</u>	<u>%</u>	<u>Avg.</u>
Live fetuses	188	99	9.4	150	97	8.8	144	95	8.5	111	97	7.9
Dead fetuses	-	-	-	-	-	-	-	-	-	-	-	-
Incomplete resorptions	-	-	-	-	-	-	-	-	-	-	-	-
Complete resorptions	2	1	0.1	4	3	0.2	7	5	0.4	3	3	0.3
Implantations	190	-	9.5	154	-	9.1	151	-	8.9	114	-	8.1

Offspring (Malformations, Variations, et c.)

Live fetuses were weighed and given a thorough gross examination. Half of the live fetuses were fixed in Bouin's solution and transverse freehand sections of the head and thorax, as well as the dissected abdominal viscera, were examined grossly. The remaining pups were fixed in 70% alcohol, cleared, stained with Alizarin-red-S, and examined for skeletal abnormalities.

A summary of offspring observations is shown below in Table 54. Average individual fetal weights were decreased by 7% at the HD only, and litter weights were even more drastically decreased by 22% also only at the HD. The greater magnitude of the decrease in litter weights compared to individual fetal weights can be attributed to a decrease in average number of live fetuses at the HD. It is unclear whether the

observed decrease fetal weights at the HD was a direct effect of the test article or a secondary effect of maternal toxicity (i.e., reduced food consumption).

The only unusual gross fetal abnormality observed in the study was the lack of anterior portion of the head in a single LD fetus. Dilated renal pelvis was the only visceral abnormality to occur with greater incidence in lofexidine-treated groups than controls; however, dilated renal pelvis is a common background finding, and the overall incidence in all lofexidine-treated groups was low and did not exhibit dose-dependence. The incidence rate of vestigial extra ribs was increased compared to controls in all lofexidine treatment groups by up to 53% at the HD. Additional findings at the HD included an increase in the incidence rate of sternal variations by 18% and a single case of prognathia.

Table 54: Impact of Lofexidine Treatment on Offspring

	Dose group (mg/kg/day)					
	Control	0.3	1.0	3.0		
Avg. fetal wt. (live) gm.	4.03	4.25	4.20	3.73		
Avg. litter wt. (live) gm.	37.88	37.46	35.58	29.60		
No. fetuses cleared	94	75	72	55		
Total fetuses examined	188	150	144	111		
No. fetuses with:						
Gross	(Hematomas	3	2	1	2	
	(Lack of face	-	1	-	-	
Visceral	(Lung adhesions	2	1	-	-	
	(Dilated renal pelvis	-	2	1	1	
Skeletal	(Sternal variations	90 (85%)	65 (87%)	57 (79%)	55 (100%)	100%
	(Rib variations					
	(traumatized, irreg-					
	(ularly shaped, in-					
	(completely ossifi-					
	(cation, segmented,					
	(shortened)	13 (14%)	8 (11%)	3 (4%)	9 (16)	
(Vertebral variations	14 (15%)	12 (16%)	15 (21%)	6 (11)		
(Wide fontanelis	14 (15%)	10 (13%)	-	5 (9%)		
(Vestigial extra ribs	42 (45%)	45 (60%)	39 (54%)	38 (69)		
(Prognathia	-	-	-	1		

9.3 Prenatal and Postnatal Development

Study title: Lofexidine Hydrochloride: Pre- and Post-Natal Development Study in Rats, Including Maternal Function (GLP)

Study no.: USWM-LX0-TOX-0003

Study report location: <\\cdsesub1\levsprod\nda209229\0002\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42353-pre-postnatal-dev\uswm-lx0-tox-0003\uswm-lx0-tox-0003.pdf>

Conducting laboratory and location:



Date of study initiation: July 14, 2008

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: Lofexidine HCl, 24004970, 100.07%

Key Study Findings

- Pregnant dams (22/sex/group) were dosed with either vehicle (PBS) or lofexidine HCl at 0.3, 1.0, or 2.0 mg/kg/day from GD 6 through lactation

F₀ Maternal Toxicities

- Piloerection and decreased activity were observed in lofexidine-treated dams, primarily at the MD and HD, while lethargy and slow breathing observed were also observed, primarily at the HD. These findings tended to occur with higher incidence during the gestation period than during the lactation period.
- Maternal body weights were significantly decreased by 13% at the HD and 10% at the MD during the gestation period, and this effect persisted albeit without further increase in magnitude throughout the lactation period. Food consumption was also dose-dependently decreased at the MD and HD.
- The NOAEL for maternal toxicity was the LD.

Delivery/Litter Observations

- Delivery index was significantly decreased, and percentage of unaccounted implantation sites was significantly increased at the HD
- Total litter losses occurred for 5 dams at the HD and 1 dam at the MD.
- Percentage of litters with stillbirths was dose-dependently increased from 13.6% in the vehicle-treated group up to 36.4% at the HD.
- Viability and lactation indices were statistically significantly decreased at the HD. However, a dose related trend was evident across the doses.

F₁ Offspring Toxicities

- A dose dependent increase in pup mortality was noted at all doses both before and after culling.

- Body weights at birth were significantly decreased at birth in both sexes by 15% at the MD and 20% at the HD. This effect persisted throughout the study with slight exacerbation throughout the pre-weaning period and slight attenuation during the post-weaning period.
- Pre-weaning functional assessments indicated statistically significant developmental delays in surface righting at the MD and HD and dose-dependently increasing delays in acquisition of the auditory startle reflex at all dose levels. The LD response, per the Applicant, was within 75-90% of the concurrent control values and was dismissed by the Applicant.
- Sexual maturation was significantly delayed in males (preputial separation) at the HD and in females (vaginal opening) dose-dependently at the MD and HD.
- After mating, significant decreases were observed in the number of corpora lutea at the MD and HD and the number of implantations at the HD.
- F₁ males from the HD groups also had reduced testes, epididymis, and seminal vesicle weights. Seminal vesicle weights in the MD males were also statistically reduced compared to controls (10% at MD, 17% at HD).

NOAEL/Toxicokinetics

- The NOAEL in this study with respect maternal (F₀) and toxicities was the LD of 0.3 mg/kg/day, providing a 1-fold safety margin to the MRHD of 2.88 mg/day based on body surface area allometric scaling. This dose was associated with an average C_{max} of 1.76 ng/mL and an AUC of 3.67 ng*h/mL, providing a 0.04-fold exposure margin compared to human exposure at the MRHD, 89.24 ng/mL*h.
- No NOAEL was determined for pre- and post-natal (F1) toxicity (<0.04-fold exposure margin compared to human MRHD based on AUC).

Methods

Doses:	0, 0.3, 1.0, 2.0 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Phosphate buffered saline (PBS), pH 7.2
Species/Strain:	Rat/Crl: CD (SD) IGS BR
Number/Sex/Group:	22
Satellite groups:	None
Study design:	See Table 55
Deviation from study protocol:	Several minor protocol deviations were noted, but these deviations did not compromise the validity or integrity of the study.

Table 55: Rat Pre- and Post-Natal Development Study Design

Group	Group Designation	Doses ^a			Days of Treatment	Number of Animals	
		Dose (mg/kg/day)	Concentration (mg/mL)	Volume (mL/kg)		F ₀ Females	F ₁ Weanlings
1	Control	0	0	10	GD 6 – LAC 20	22	1 or more/sex/litter
2	Low	0.3	0.03	10	GD 6 – LAC 20	22	1 or more/sex/litter
3	Intermediate	1.0	0.10	10	GD 6 – LAC 20	22	1 or more/sex/litter
4	High	2.0	0.2	10	GD 6 – LAC 20	22	1 or more/sex/litter

^aDoses represent active ingredient adjusted with a correction factor = 1.14, to account for the salt form.

Study Design

Pregnant dams (22/sex/group) were dosed with either vehicle (PBS) or lofexidine HCl at 0.3, 1.0, or 2.0 mg/kg/day from Gestation Day 6 (GD 6) through lactation. F₀ dams were evaluated for viability, clinical observations, body weights, food consumption, littering, and necropsy findings. Litters pups were culled down to 5 pups/sex on Postnatal Day 4 (PND 4) if possible. Prior to weaning, pups were evaluated for viability, clinical observations, body weight, and pre-weaning functional development (surface and air righting reflexes, pupillary reflex, and startle response). At weaning on PND 21, one male and one female pup were retained and evaluated for viability, clinical observations, body weight, food consumption, post-weaning functional development (open field evaluations, locomotor activity, and learning and memory tests), sexual maturation, reproductive competence, gross necropsy findings, and selected organ weights.

Observations and Results

F₀ Dams

Mortality

F₀ dams were observed in their cages twice daily for mortality and signs of severe toxic or pharmacologic effects.

Five dams at the HD and one dam at the MD were sacrificed early due to total litter loss between Lactation Day 1 (LAC 1) and LAC 8. These dams did not have significantly different gestational body weights or food consumption than other dams in their respective treatment groups that did not suffer total litter loss.

Table 56: Number of F₀ Dams with Total Litter Loss

Dose level	Dam No.	No. Pups	Dam No.	No. Pups
2.0 mg/kg/day	4502	11	4510	15
	4507	12	4517	9
	4518	11		
1.0 mg/kg/day	3520	15		

Clinical Signs

Each F₀ dam was observed for overt signs of toxicity approximately one to two hours after dosing was completed. Physical examinations of general condition, skin and fur, eyes, nose, oral cavity, abdomen and external genitalia as well as evaluations of respiration were performed twice weekly.

Lofexidine treatment was associated with increasing incidence of piloerection, decreased activity, lethargy, and slow breathing in dams that was dose-dependent (Figure 63; Figure 64). The average daily incidence of decreased activity, lethargy, and slow breathing was significantly greater during the gestation period than during lactation. Incidence rates of piloerection and decreased activity at the HD fluctuated between 25% and 75% in a highly correlated manner throughout the entire study. Lethargy incidence rates at the HD peaked at approximately 25% at the end of the first week of treatment and reemerged in days surrounding parturition as well as in the last days of lactation. Slow breathing at the HD peaked at an incidence rate of approximately 75% during the final week of gestation and subsequently plateaued at approximately 25% leading up to parturition before tapering off after the first week of lactation. Irregular gait was also temporarily observed in approximately 20% of HD dams at the initiation of lofexidine treatment but tapered off by the end of the first week.

Figure 63: Average Daily Incidence of Clinical Signs Associated with Lofexidine Treatment in Dams During Gestation vs. Lactation

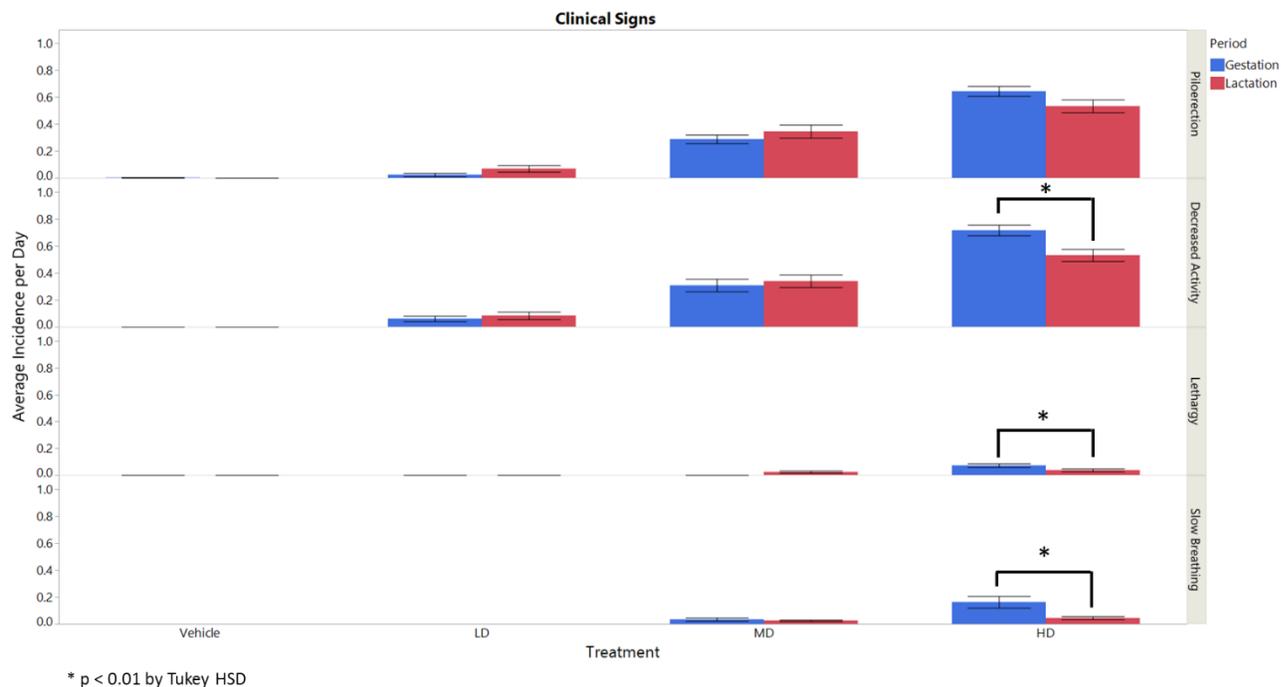
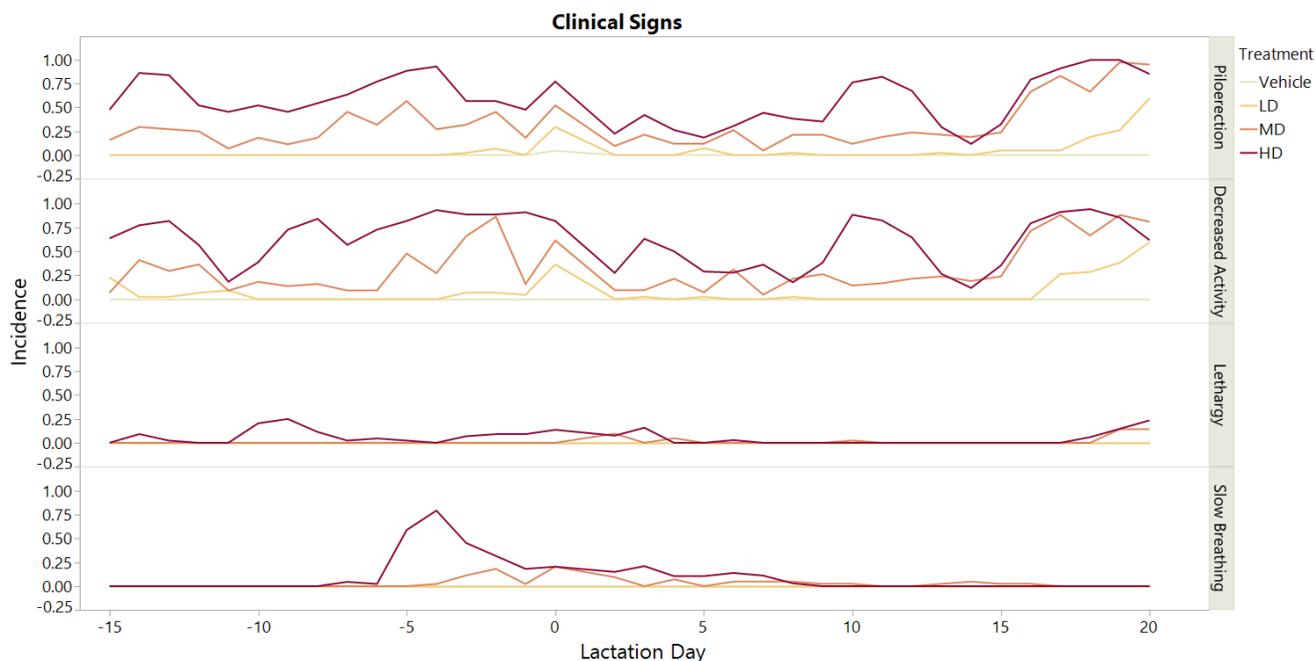


Figure 64: Daily Incidence of Clinical Signs Associated with Lofexidine Treatment in Dams Throughout Gestation and Lactation



Body Weight

Individual body weights were recorded on GD 4, 6, 9, 12, 15, 18, 20, 21 (first half of each group only), and after parturition on LAC 1, 4, 7, 10, 14, 18, and 21.

Body weights of dams were dose-dependently decreased by 13% at the HD and 10% at the MD by the end of gestation (Figure 65). Similarly, body weight gains were also dose-dependently decreased by approximately 40% at the HD and 20% at the LD across the entire gestation period, with the greatest impact at the initiation of dosing and during the last week of gestation (Figure 66). No effect on body weights or body weight gains was observed at the LD. During the lactation period, the changes in body weights observed during gestation persisted but did not continue to decrease as no significant changes in body weight gains were observed lofexidine-treated dams (Figure 67; Figure 68).

Figure 65: Impact of Lofexidine Treatment on Body Weights in Dams During Gestation

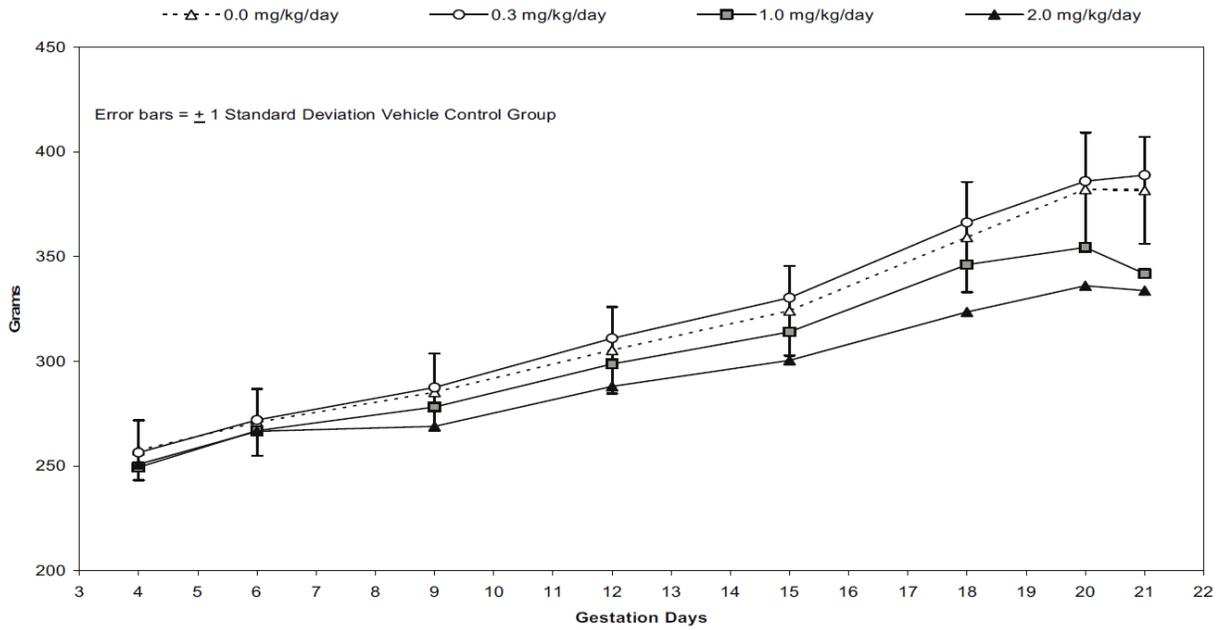


Figure 66: Impact of Lofexidine Treatment on Body Weight Gains in Dams During Gestation

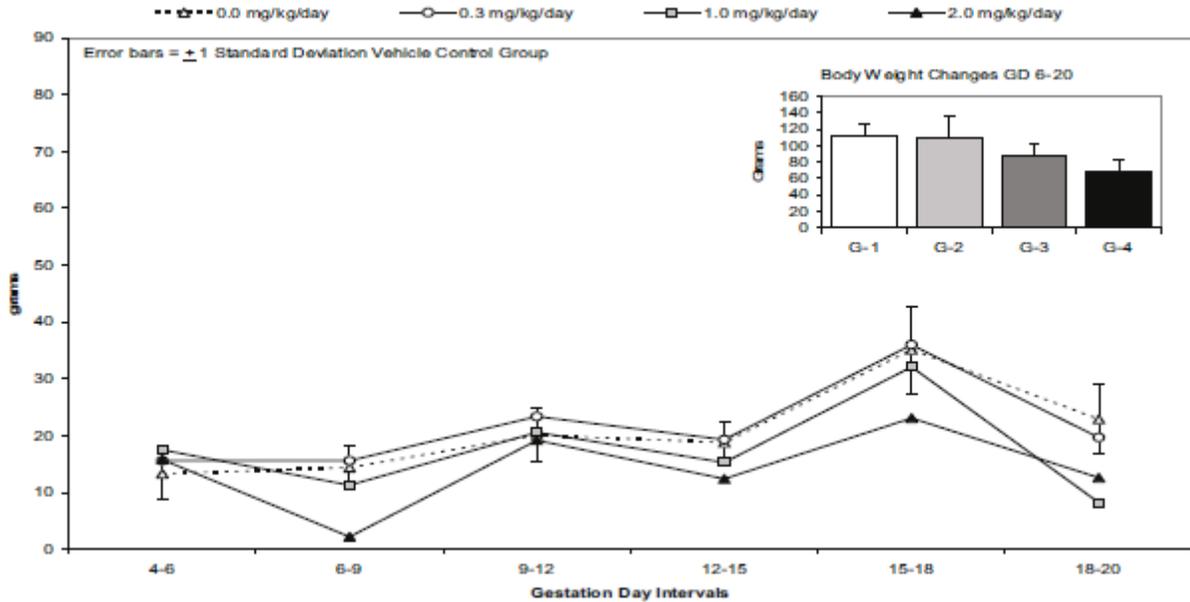


Figure 67: Impact of Lofexidine Treatment on Body Weights in Dams During Lactation

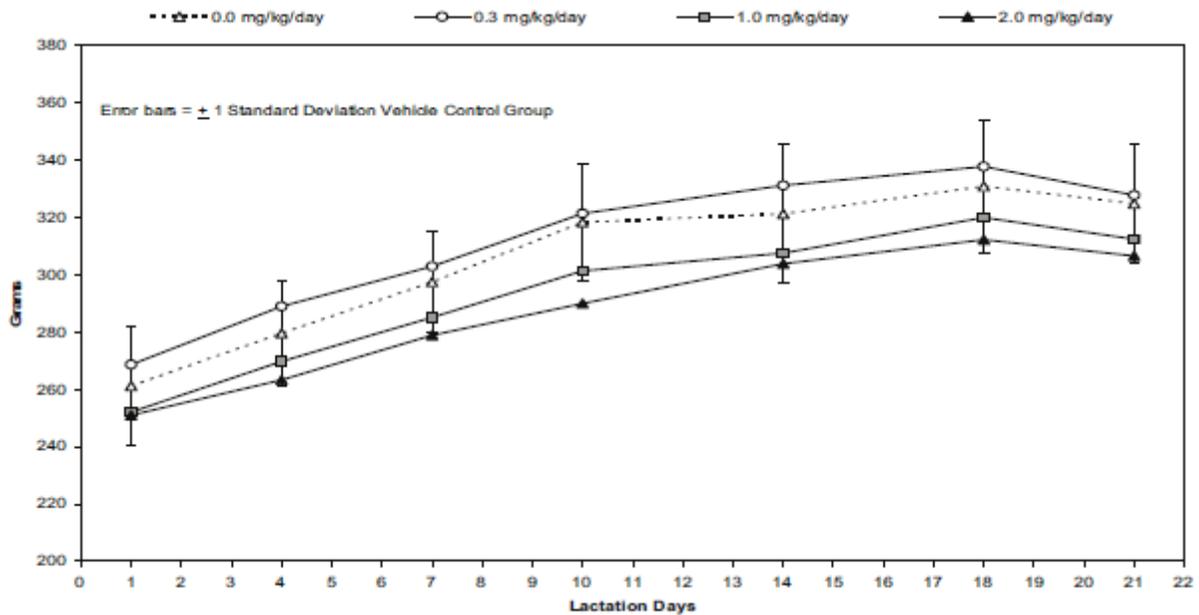
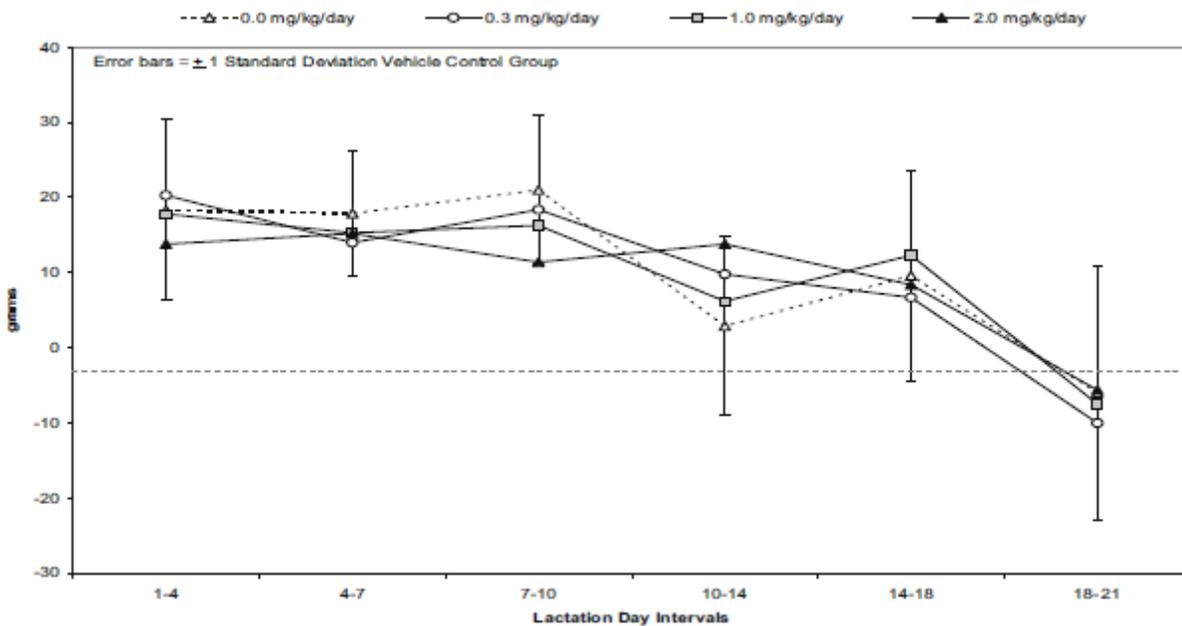


Figure 68: Impact of Lofexidine Treatment on Body Weight Gains in Dams During Lactation



Food Consumption

On the same days as body weights were recorded, feeders were reweighed and the resulting weight was subtracted from the full feeder weight to obtain the grams consumed per animal over the period.

Food consumption was dose-dependently decreased by approximately 20% at the HD and 10% at the MD relatively consistently throughout gestation (Figure 69). Similar dose-dependently decreased food consumption was observed at the MD and HD with slightly increasing magnitude throughout lactation. No effects on food consumption were observed during gestation or lactation at the LD.

Figure 69: Impact of Lofexidine Treatment on Food Consumption in Dams During Gestation

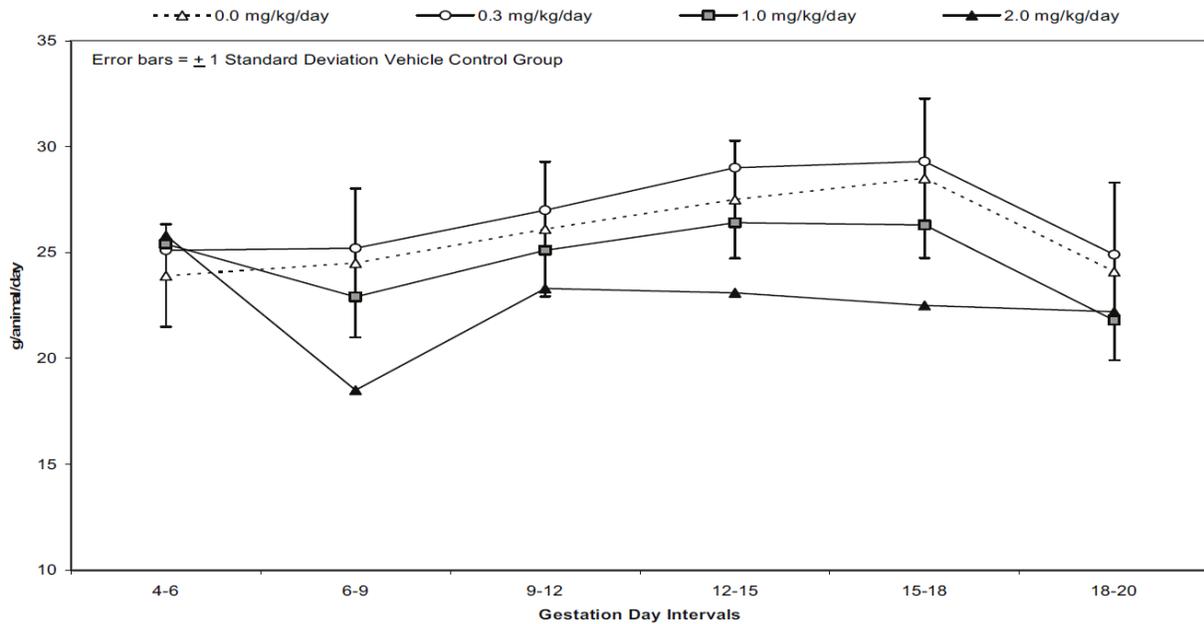
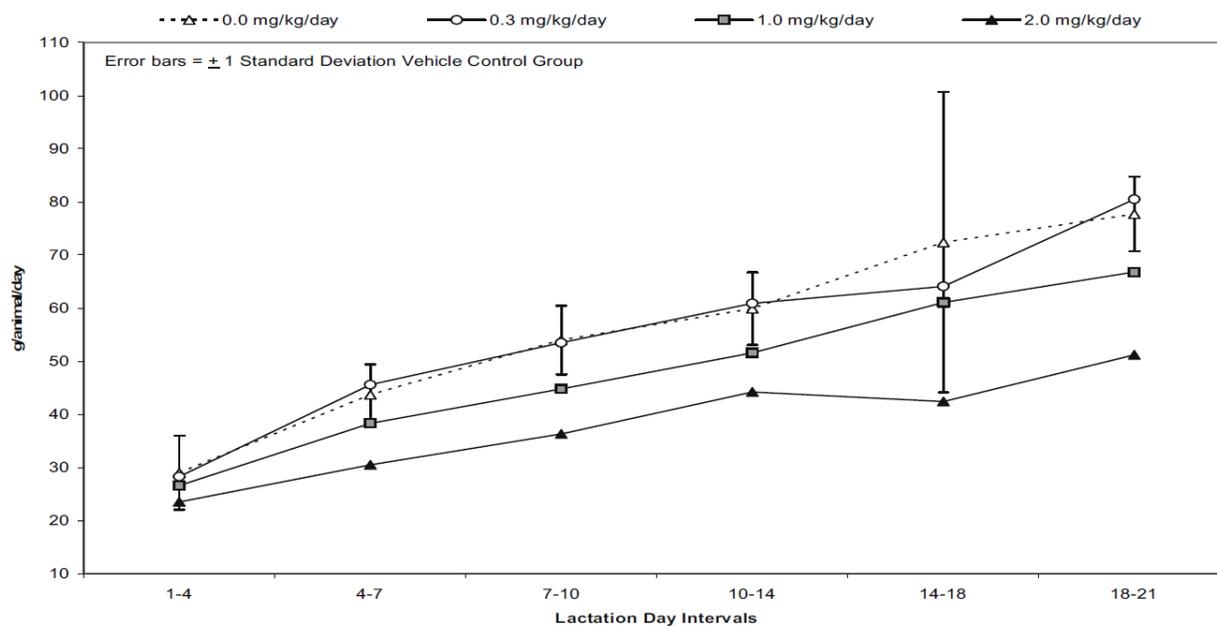


Figure 70: Impact of Lofexidine Treatment on Food Consumption in Dams During Lactation



Natural Delivery and Litter Observations

Litters were observed as soon as possible after parturition was complete and the number of live and dead pups, pup abnormalities, and the sex of each pup was recorded.

One rat in the LD treatment group was not pregnant, but the rest of the F₀ dams in all treatment groups were pregnant. Length of gestation was not impacted by lofexidine treatment. The number of implantation sites was also not impacted by lofexidine treatment; however, a significant increase in the percent of unaccounted-for implantation sites as well as a significant reduction in the Delivery Index was observed at the HD (Table 57). A statistically insignificant dose-dependent trend towards an increase in the number and percentage of stillbirths was also observed at the MD and HD (Table 58).

Table 57: Percent Unaccounted Implantation Sites and Delivery Index

	Dose levels (mg/kg/day)			
	0	0.3	1.0	2.0
Unaccounted implantation sites (%) ^a	5.1%	7.0%	6.7%	18.2%**
Delivery Index ^b	92.8%	90.5%	89.6%	78.1%**

^aUnaccounted implantation sites % = (100x(#implantation sites - #pups delivered) / #implantation sites.

^bDelivery Index % =(100 x # live pups delivered/# implantations)

**= p<0.01

Table 58: Number and Percentage of Litters with Stillbirths

	Dose levels (mg/kg/day)			
	0	0.3	1.0	2.0
No. Stillborn (SB)	6	7	11	11
% Stillborn	2.2	2.6	3.9	4.5
Litters with SB	3	4	6	8
Litters	22	21	22	22
% Litters with SB	13.6%	19.0%	27.3%	36.4%

Necropsy

Dams were euthanized on LAC 21. Macroscopic postmortem examinations were performed, and any gross lesions identified during the gross macroscopic examination (other than common incidental findings, such as minor patchy hair loss) were preserved in 10% neutral buffered formalin (NBF). The number of visible implant sites (scars) was recorded, and the uterus with cervix of any non-pregnant dam was weighed and then stained with ammonium sulphide to confirm the non-pregnant status. The ovaries, oviducts, uterus, cervix, and vagina from all dams were preserved in 10% NBF for optional further examination.

Lofexidine treatment was not associated with an increase in the frequency of findings at necropsy.

Toxicokinetics

Blood was collected from each F₀ dam on LAC 14. All animals in each group were bled once. Samples were collected at one of the following time points: predose, 0.5, 1, 2, 4,

8, and 24 hours postdose, thus providing nominally 2-4 samples per time point per group.

Toxicokinetics analysis revealed that C_{max} and AUC increased approximately dose-proportionally between the LD and MD but increased greater than dose-proportionally between the MD and HD (Table 59). T_{max} ranged between 0.5 and 1 hour for all dose groups, and the half-life was similar for the LD and MD (1.07 and 1.51 hours, respectively) but was significantly longer at the HD (5.26 hours). The increased half-life at the HD may explain the greater than dose-proportional increase in C_{max} and AUC observed at this dose level due to increased accumulation of the test article.

Table 59: Toxicokinetics Parameters from Pre-Postnatal Development Study

Dose (mg/kg/day)	AUC _{0-tlast} (hr•ng/mL)	AUC _{0-tlast} /Dose ((hr•ng/mL)/mg/kg)	C _{max} (ng/mL)	C _{max} /Dose ((ng/mL)/mg/kg)	t _{1/2} (hr)	T _{max} (hr)
0.3	3.67	12.2	1.76	5.87	1.07	1.00
1.0	16.5	16.5	3.63	3.63	1.51	0.50
2.0	55.0	27.5	21.1	10.6	5.26	1.00

Dosing Solution Analysis

Homogeneity of the test article formulation was evaluated by analyzing two sets of samples drawn from the top, middle, and bottom of the formulation. Stability was evaluated by analyzing two sets of samples drawn from the middle of the formulation one week later and comparing the results to the samples drawn from the middle of the formulation during homogeneity assessment. In addition, samples from the test article formulations used for each dosing group on Weeks 1, 3, and 5 were evaluated.

Testing for homogeneity and stability revealed that the dosing formulations were prepared satisfactorily (i.e. with concentrations within $\pm 10\%$ of nominal), were homogeneous, and stable for at least 1 week. Analysis of the dosing formulations used on Weeks 1, 3, and 5 were within the acceptable range, with the exception of the HD formulation on Week 5, which was only 83% of the nominal value (Table 60). There was no explanation for this finding.

Table 60: Dose Confirmation Analysis for Pre-Postnatal Development Study

Formulations used for dosing on	0 mg/kg/day (0 mg/mL)	0.3 mg/kg/day (0.030 mg/mL)	1.0 mg/kg/day (0.100 mg/mL)	2.0 mg/kg/day (0.200 mg/mL)
Week 1	0.00	103.3%	99.0%	98.0%
Week 3	0.00	92.5%	95.0%	95.0%
Week 5	0.00		96.0%	83.0%

F₁ Pups (pre-weaning)

Mortality

F₁ pups were observed for viability twice daily.

Pup mortality was dose-dependently increased throughout the entire pre-weaning period (Table 61). This resulted in significantly decreased viability and lactation indices at the HD (Table 62). Pup necropsies from PND 0-2 revealed an increase in the number of pups without milk bands at the HD as well as a dose-dependent increase in the number of partially cannibalized pups at the MD and HD (Table 63).

Table 61: F₁ Mortality

Postnatal Day	No. of dead pups			
	0 mg/kg/day	0.3 mg/kg/day	1.0 mg/kg/day	2.0 mg/kg/day
PND 0-1	3	7	16	57 ^a **
1-4 pre-cull	6	11	19	38*
4 post cull-21	2	4	11	23**

a: including four pups that were missing/cannibalized

*= p<0.05, **=p<0.01

Table 62: F₁ Viability and Lactation Indices

	Dose Level (mg/kg/day)			
	0	0.3	1.0	2.0
Viability Index ^a	96.7%	93%	86.9%	59.7%**
Lactation Index ^b	99.0%	98.0%	94.3%	83.1%**

^aViability Index (%) =(100 x #pups alive on PND 4 precull/#pups delivered live)

^bLactation Index (%) = (100 x #pups alive on PND 21/#pups alive on PND 4 post cull)

**=p<0.01

Table 63: Pup Necropsy Observations from PND 0-2

	Maternal Dose Level (mg/kg/day)							
	0		0.3		1		2	
	n	%	n	%	n	%	n	%
Completing parturition	22	-	21	-	22	-	22	-
PND 0-1								
Found Dead	3	-	7	-	16	-	57 ^a	-
in Litters	2	9.1	5	23.8	8	36.4	15	68.2
Pup with no milk bands	0	-	4	-	3	-	28	-
in Litters	0	0.0	4	19.0	2	9.1	10	45.5
Partially cannibalized^b	3	-	2	-	12	-	36 ^a	-
in Litters	2	9.1	2	9.5	7	31.8	8	36.4
PND 2								
Littered	22	-	21	-	22	-	22	-
Found Dead	3	-	0	-	2	-	11	-
in Litters	3	13.6	0	0.0	1	4.5	5	22.7
Pup with no milk bands	1	-	0	-	0	-	3	-
in Litters	1	4.5	0	0.0	0	0.0	2	9.1
Partially Cannibalized^b	1	-	0	-	0	-	2	-
in Litters	1	4.5	0	0.0	0	0.0	1	4.5

^a including 4 pups cannibalized or missing; ^b or missing

Clinical Signs

Each F₁ pup was given a gross physical examination of general condition, skin and fur, eyes, nose, oral cavity, abdomen and external genitalia, as well as, evaluation of respiration on the day of completion of parturition, then again on PND 4, and 21.

Except for the milk band observations discussed above (no evidence of milk in the belly based on external observation), no treatment-related clinical signs of toxicity were observed among the F₁ generation during the pre-weaning period.

Body Weight

Individual F₁ pup body weights were recorded on PND 1, 4, 7, 10, 14, 18, and 21.

Significant reductions in pup body weight on PND 1 of 15% and 20% were observed in both sexes at the MD and HD, respectively (Figure 71; Figure 72). These reductions in

body weights persisted and were even slightly exacerbated throughout the pre-weaning period. Correspondingly, body weight gains were dose-dependently decreased in consistently in both sexes throughout the pre-weaning period by up to 27% at the MD and 53% at the HD (Figure 73; Figure 74). There were no differences in body weights or body weight gains observed between control and LD pups throughout the entire lactation period.

Figure 71: Pre-Weaning Body Weights of Male F₁ Pups

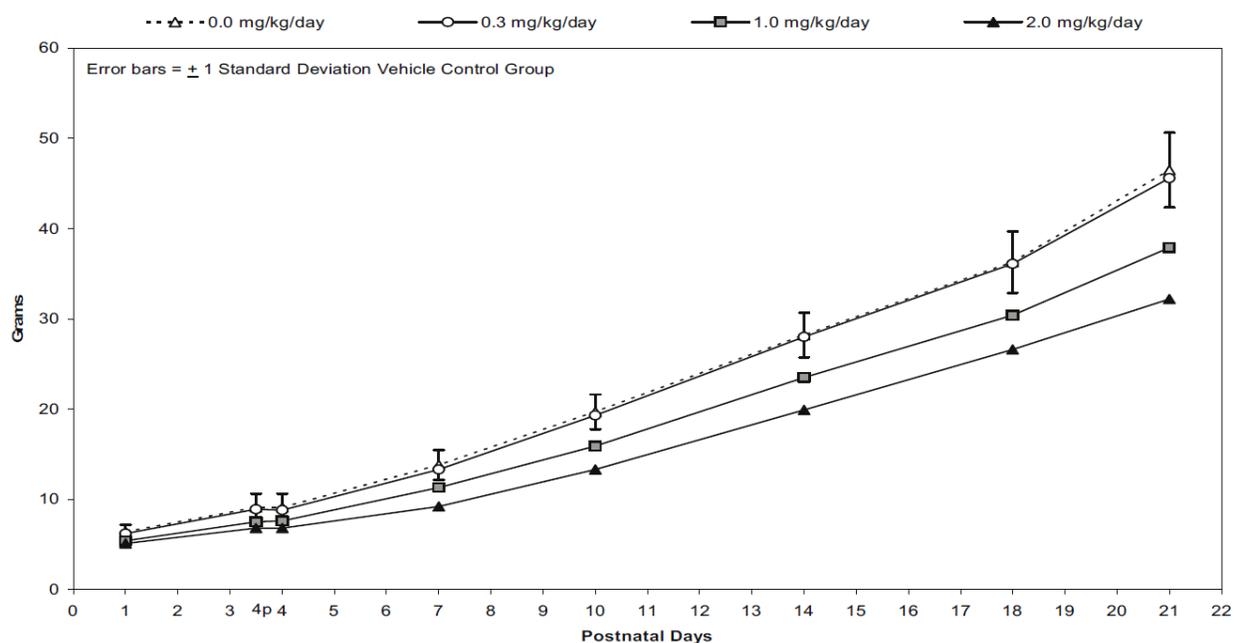


Figure 72: Pre-Weaning Body Weights of Female F₁ Pups

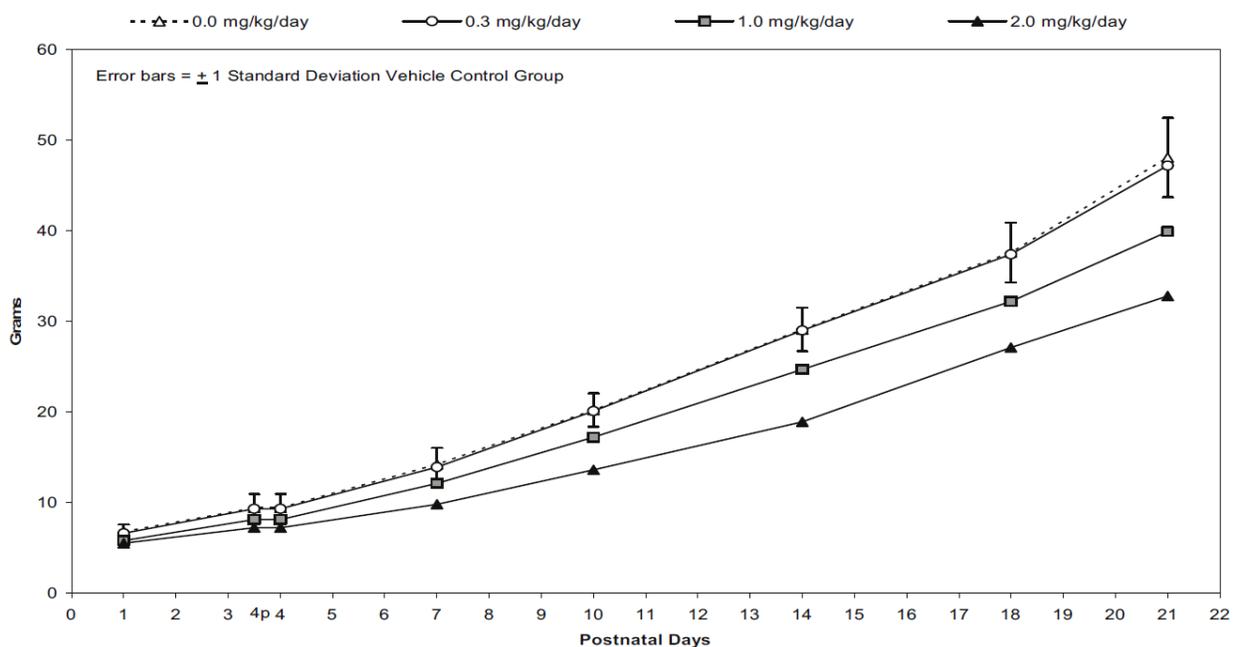


Figure 73: Pre-Weaning Body Weight Gains of Male F₁ Pups

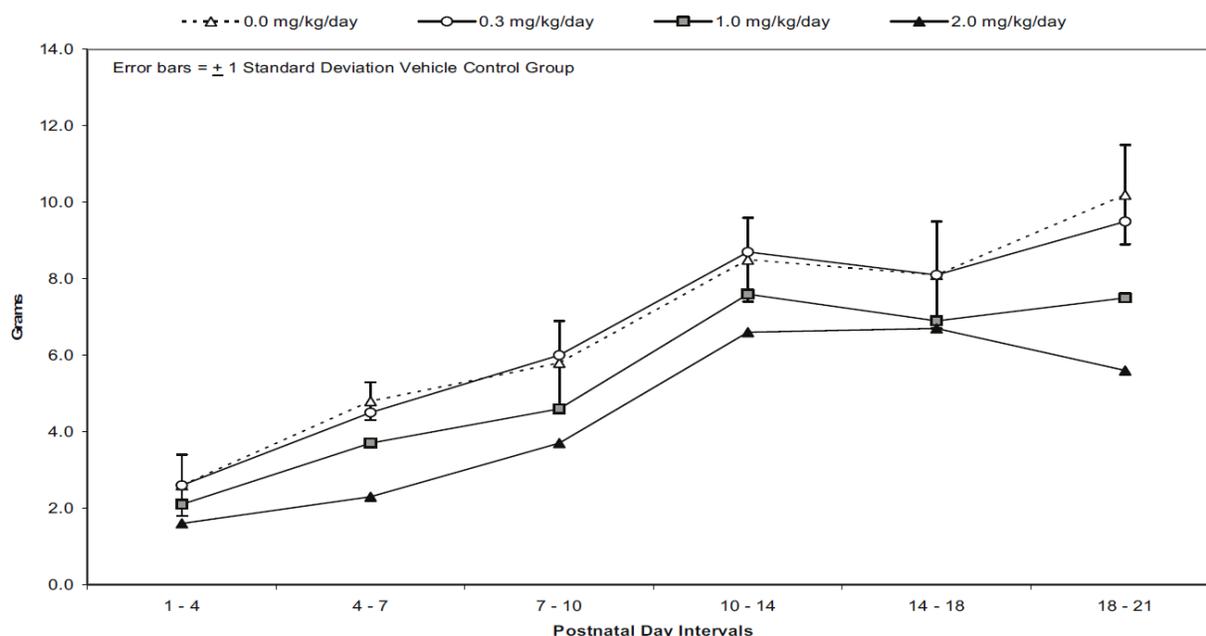
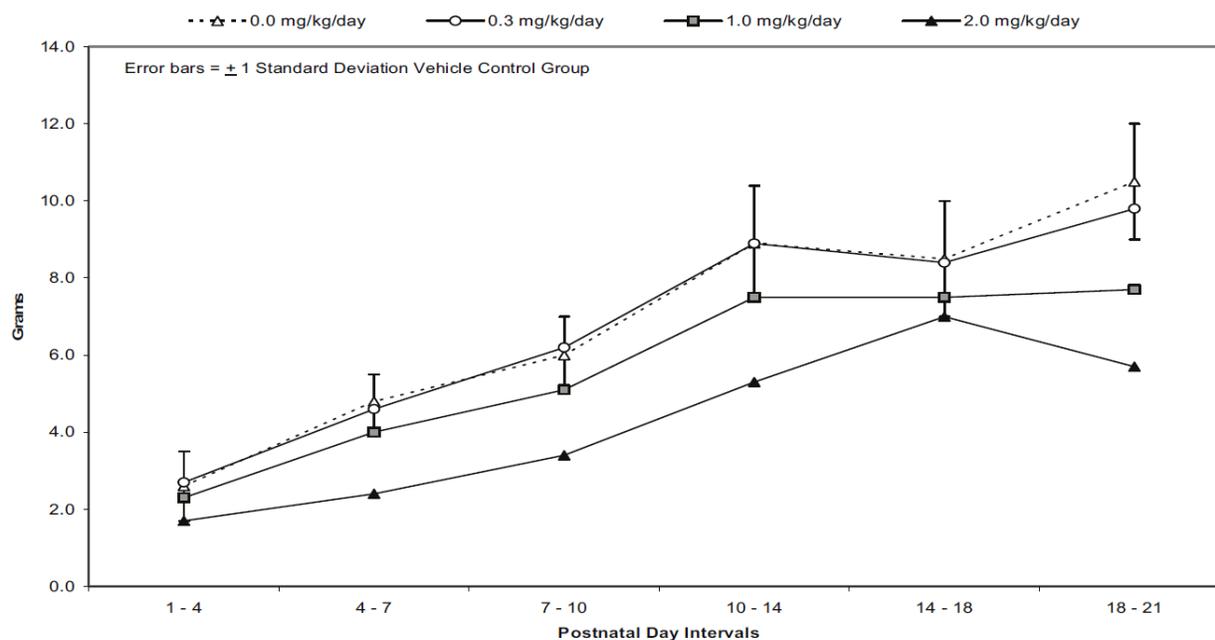


Figure 74: Pre-Weaning Body Weight Gains of Female F₁ Pups

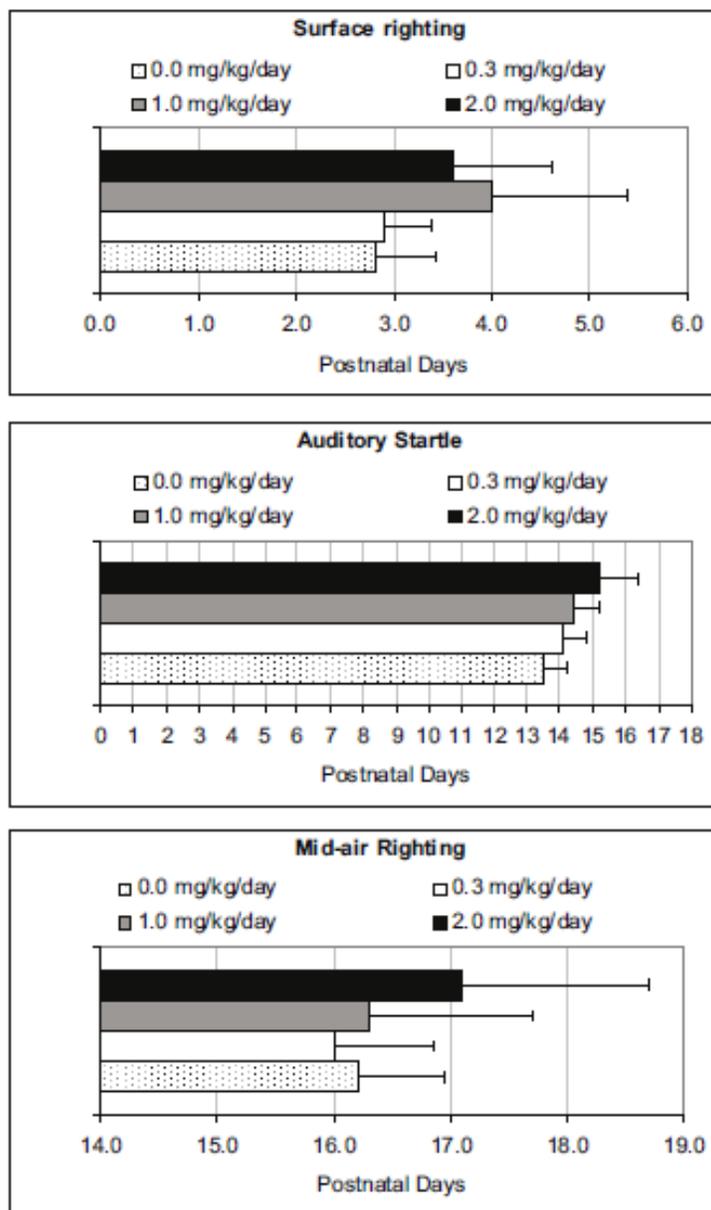


Pre-Weaning Functional Observations

Surface righting was assessed from PND 1 until achieved. Mid-air righting was assessed from PND 14 until achieved. Auditory function (startle response to a sudden sound) was assessed from PND 10 until achieved. Visual function (pupil closure response of dark-adapted eyes) was assessed on PND 20.

Surface righting was statistically significantly delayed by approximately 1 day at the MD and HD (Figure 75). Auditory startle was dose-dependently delayed by approximately 0.5, 1, and 1.5 days at the LD, MD, and HD, respectively (Figure 75). There was no significant effect of lofexidine treatment on the development of mid-air righting (Figure 75). Additionally, approximately 5% of HD pups failed the visual function assessment whereas 100% of pups in all other groups passed.

Figure 75: Pre-Weaning Functional Assessments in F₁ Pups



F₁ Rats (post-weaning)

Mortality

F₁ rats were observed cage-side twice daily for viability and obvious abnormalities (mortality, moribundity, and signs of severe toxicity).

There were no treatment-related deaths in the F₁ generation during the post-weaning period. One LD male rat was sacrificed on Cohabitation Day 10 due to broken/fractured upper incisors.

Clinical Signs

Each rat was examined in more detail on one day in each week (with body weights), including observations of general condition, skin and fur, eyes, nose, oral cavity, abdomen and external genitalia, as well as evaluation of respiration.

There were no overt signs of toxicity related to F₀ maternal exposure among the selected F₁ rats during the post-weaning period.

Body Weight

Rats were weighted on PND 24, 28, 31, 35, 38, 42, 45, 49, 52, 56, and 59, and on a weekly basis until mating/termination. Mated females were weighed on GD 0, 7, and 14.

Body weights were significantly decreased in MD and HD rats of both sexes at the beginning of the post-weaning period, and although this effect persisted throughout the post-weaning period, it was somewhat attenuated by end of the post-weaning period (Figure 76; Figure 77; Table 64). There was no difference between the body weights of control and LD rats.

Figure 76: Body Weights of Male F₁ Rats During Post-Weaning Period

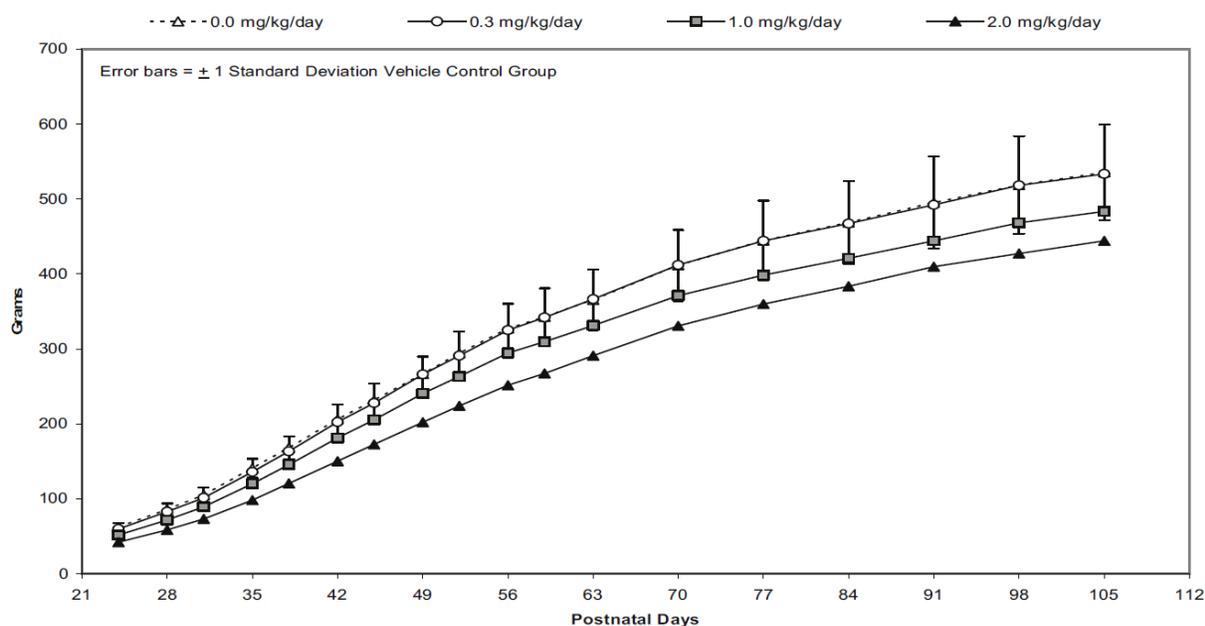
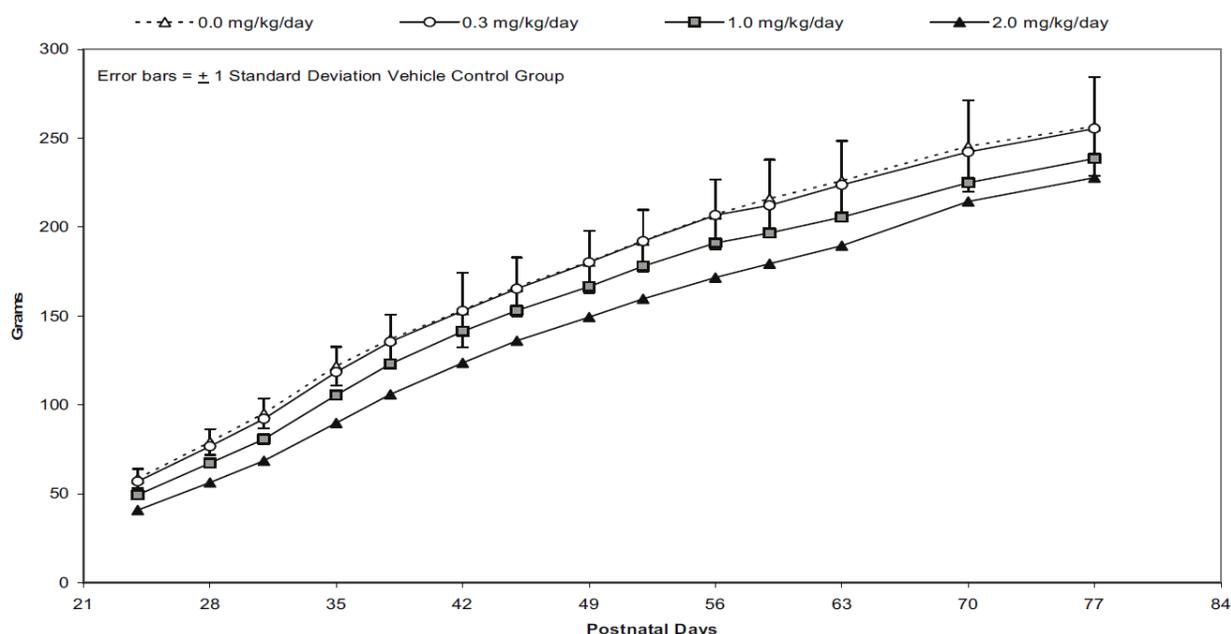


Figure 77: Body Weights of Female F₁ Rats During Post-Weaning Period**Table 64: Comparison of Body Weights at MD and HD to Control at Beginning and End of Post-Weaning Period**

Dose Level	Sex	Percent Decrease in Body Weight Compared to Controls	
		PND 24	PND 77
MD	Male	17%	10%
	Female	16%	7%
HD	Male	32%	19%
	Female	30%	11%

Food Consumption

Food consumption was measured weekly after weaning.

Food consumption was significantly decreased at the beginning of the post-weaning period in the MD and HD groups across both sexes but this effect was attenuated over time. At the MD food consumption was decreased by approximately 10% and persisted through the first two weeks of the post-weaning period in males and only the first week in females. At the HD food consumption was decreased by approximately 20% and persisted through the first 4.5 weeks of the post-weaning period in males and only the first 1.5 weeks in females. Maternal dosing at the LD had no effect on food consumption in either sex.

Figure 78: Food Consumption of Male F₁ Rats During Post-Weaning Period

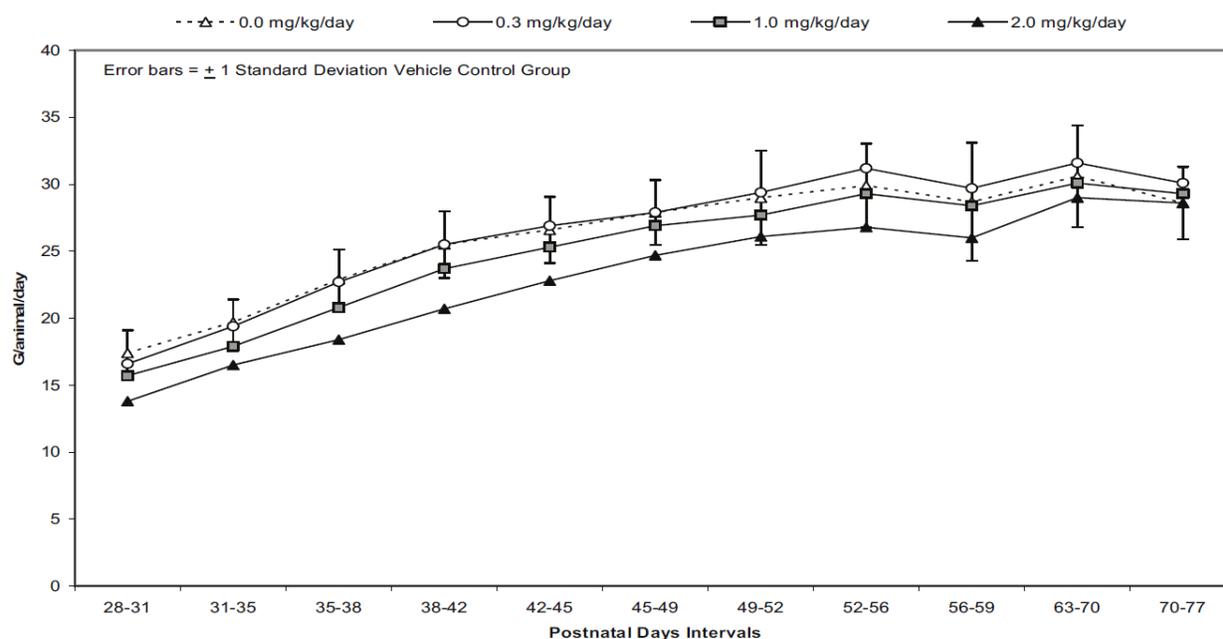
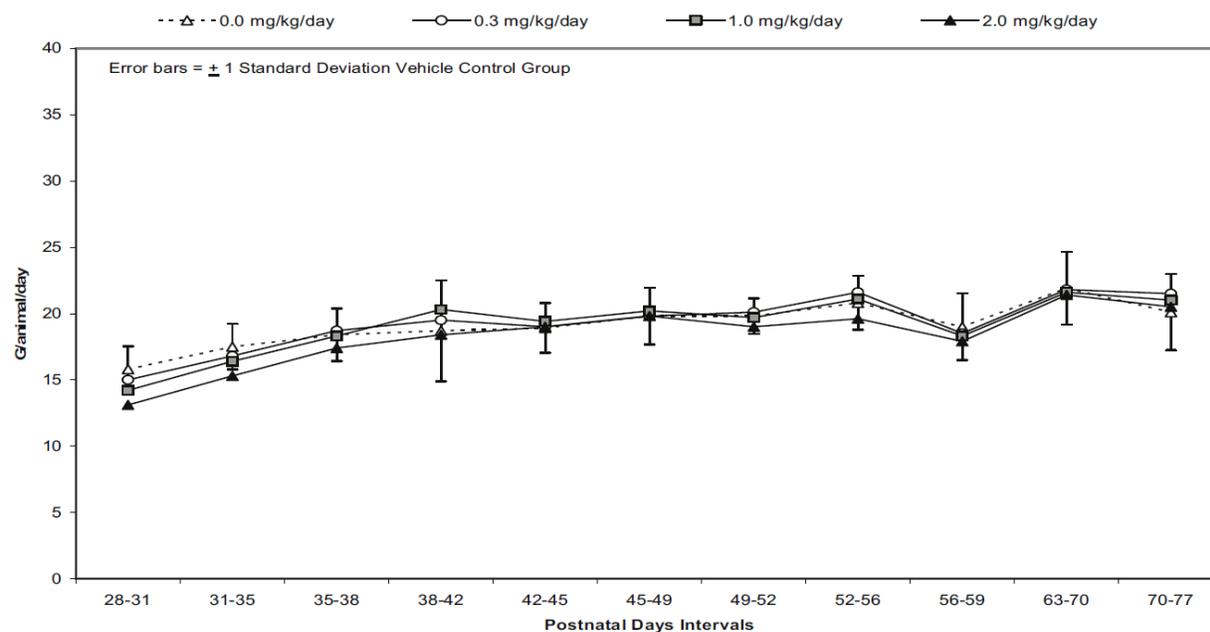


Figure 79: Food Consumption of Female F₁ Rats During Post-Weaning Period



Sexual Maturation

Males were observed daily for preputial separation, beginning on PND 37, until separation occurred, at which time body weight was also recorded. Females were observed daily for vaginal opening, beginning on PND 28, until opening occurred, at which time body weight was also recorded.

A statistically significant delay in preputial separation of approximately 6 days was observed in in male F₁ rats at the HD (Table 65). Vaginal opening was dose-dependently delayed by up to 4 days at the HD in female F₁ rats (Table 66).

Table 65: Mean Age at Preputial Separation of F₁ Rats and Differences vs. Control

Dose group (mg/kg/day)	Age (PND)		Difference vs Control (days)
	Mean	s.d.	
0.0	46.91	2.54	-
0.3	46.55	1.90	-0.36
1.0	47.05	2.68	+0.14
2.0	53.14***	6.43	+6.23

Note: *** = p<0.001

Table 66: Mean Age at Vaginal Opening of F₁ Rats and Differences vs. Control

Dose group (mg/kg/day)	Age (PND)		Difference vs Control (days)
	Mean	s.d.	
0.0	32.43	1.65	-
0.3	32.70	1.15	+0.27
1.0	33.73*	1.86	+1.23
2.0	36.68***	4.05	+4.18

=p<0.01; * = p<0.001

Behavioral Evaluation

For open field evaluation, rats were observed for 1 minute on PND 22 for abnormalities of posture, gait, and for any abnormal behavior or vocalization. For locomotor activity evaluation, spontaneous exploratory activity during a 60-minute session was measured on PND 28 by counting the number of photobeam breaks that occurred during each 5-minute interval using an automated Photobeam Activity System. Learning and memory were evaluated at approximately 8 weeks of age, using a water-filled Biel maze (multiple T-maze). On Day 1 of the test, each rat was required to swim in a straight line to the exit ramp. Learning was evaluated on Days 2 through 5 by requiring rats to swim the entire maze. Memory was evaluated by requiring each rat to swim the maze after a 2-day rest period (on Day 8).

Maternal treatment with lofexidine yielded no adverse effects in F₁ rats with respect to open field, motor activity, or learning and memory assessments. The only potentially adverse effect noted in the behavioral evaluations was a statistically significant, approximately 2 second increase in the average trial time during swimming ability

evaluations on Day 1 of the Biel maze at the MD and HD in female F₁ rats; however, no increases in trials times were observed during learning or memory evaluation trials in these rats.

Mating/Fertility

Daily vaginal smears were taken from each female for two weeks prior to initiation of mating. At an approximate age of 10-11 weeks, females were cohabitated with males from the same treatment group. Cohabitation continued until positive evidence of mating was detected or 20 nights had elapsed. Vaginal smears were taken each morning, and a female was considered to have mated if sperm was observed microscopically in the vaginal smear and/or a vaginal plug was observed *in situ*. The day on which positive evidence of mating was observed was defined as GD 0. Where a female had shown no positive evidence of mating after 14 nights, the female was mated with another male (which had previously mated successfully).

Maternal treatment with lofexidine yielded no adverse effects with respect to mating and fertility indices in F₁ rats of either sex (Table 67) and did not impact estrous cycling in F₁ female rats. A slight decrease in fertility index was observed at the MD and HD, but these results were of small magnitude and did exceed the range of historical control values.

Table 67: Mating and Fertility Indices in F₁ Rats

	Maternal Dose Level (mg/kg/day)			
	0	0.3	1.0	2.0
Male Mating Index (%)	100	100	100	95.5
Female Mating Index (%)	100	100	100	100
Male Fertility Index (%)	95.5	100	86.4	90.5
Female Fertility Index (%)	95.5	100	86.4	90.9

Cesarean Section and Necropsy Results

Females were euthanized on GD 14 or if appeared pregnant on GD 18. Males were sacrificed after it had been determined that they were no longer required for mating (nominally shortly after females were sacrificed). Macroscopic postmortem examinations were performed, and any gross lesions identified during the gross macroscopic examination (other than common incidental findings, such as minor patchy hair loss) were preserved in 10% NBF. For females, corpora lutea were counted and the number per ovary recorded, then the numbers of total, right, and left implantations were recorded for each uterine horn. The ovaries, oviducts, uterus, cervix, and vagina from all dams were preserved in 10% NBF for optional further examination. For males, the testes, epididymides, prostate, and the seminal vesicles with coagulating gland were weighed, and then fixed and preserved (testes and epididymides weighed individually, with the testes initially fixed in modified Davidson's solution and then transferred to NBF).

Dose-dependent decreases in the number of corpora lutea and implantations was observed in the MD and HD, but there was no effect on the rate of pre-implantation loss (Table 68). Per the Applicant, the mean values were within the concurrent control range and therefore, the effect was deemed incidental. Maternal treatment with lofexidine was not associated with any gross pathology findings in male or female F₁ rats. Decreased absolute organ weights were observed for the epididymides, testes, and seminal vesicles in male F₁ rats at the HD. Except for seminal vesicles, these organ weight changes appeared to be correlated to the decreased terminal body weights in these rats and no effects were observed with respect to organ to body weight ratio in organs. Seminal vesicle weights were not proportionally decreased at the MD in comparison to terminal body weights, which manifested as a statistically significant increase in organ-to-body weight ratio (Table 69). One possible interpretation of this result, is that the decrease in absolute seminal vesicle weights at the HD was a primary effect of the test article rather than a secondary effect due to decreased body weights. The Applicant attributed these changes to the overall pattern of growth retardation at the dose level. Per the Applicant, the changes were not considered adverse as they did not impact male reproductive capacity; however, rats are extremely fertile and changes in organs weights or histopathology in rats is likely more indicative of a potential impact in humans, which are less fertile than rats.

Table 68: Cesarean Section Results in F₁ Female Rats

	Corpora Lutea	Implant- ations	Pre-Implantation Loss (%)
Group 1 – 0.0 mg/kg/day			
Mean	16.1	14.5	9.9
S.D.	2.45	2.68	10.65
N	21	21	21
Group 2 - 0.3 mg/kg/day			
Mean	15.0	14.2	5.1
S.D.	2.40	2.25	7.05
N	22	22	22
Group 3 - 1.0 mg/kg/day			
	*		
Mean	14.2	13.3	5.9
S.D.	1.68	1.19	6.30
N	19	19	19
Group 4 - 2.0 mg/kg/day			
	**	**	
Mean	14.0	12.8	7.6
S.D.	2.55	1.68	10.76
N	20	20	20

*Significantly different from control mean; $p \leq 0.05$.

**Significantly different from control mean; $p \leq 0.01$.

Table 69: Effect of F₀ Maternal Lofexidine Treatment on F₁ Seminal Vesicle Weights

Animal Number	Term Bwt (g)	Seminal Vesicles	
		(g)	%Body
Group 1 – 0 mg/kg/day			
Mean	553.5	1.9790	0.3593
SD	64.13	0.29459	0.04846
N	22	22	22
Group 2 – 0.3 mg/kg/day			
Mean	551.2	1.9935	0.3644
SD	52.62	0.28795	0.06023
N	21	21	21
Group 3 – 1.0 mg/kg/day			
	**		**
Mean	499.4	2.0518	0.4132
SD	47.05	0.26853	0.05984
N	22	22	22
Group 4 – 2.0 mg/kg/day			
	**	*	
Mean	458.7	1.7833	0.3932
SD	51.93	0.21707	0.06095
N	22	22	22

*Significantly different from control mean; p≤0.05.

**Significantly different from control mean; p≤0.01.

10 Special Toxicology Studies

No special toxicology studies were submitted in this Application. A preliminary dose range-finding juvenile animal study has been completed (USWM-LX0-TOX-0012) but will not be reviewed here as the current NDA does not include pediatric use.

10.1 Juvenile Animal Studies

The Applicant is seeking an indication of both the mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation therapy.

(b) (4)

Because lofexidine is a centrally acting drug, the Division recommended juvenile animals studies to support the future pediatric development program with the focus on neuronal development. However, PeRC also recommended that the studies evaluate the potential impact on reproductive performance and bone growth, in part, based on data from juvenile animal studies with clonidine that suggested the potential for delayed sexual development and data to suggest that clonidine can impact bone resorption (Limonard et al., 2016).

The Division and PeRC have agreed to a pediatric study plan (PSP) which includes several dose range-finding studies and definitive studies in juvenile animals to support the complex clinical studies in this diverse patient population (b) (4). In all cases the effects of the drug in appropriately aged juvenile animals will be studied prior to studies in pediatric patients.

The clinical studies are intended focus on adolescent opioid withdrawal (b) (4) (PK, safety (b) (4) in children 12 to 17 years of age). Second, PK, safety (b) (4) will be studied in children with IOWS in children 6 to 17 years of age followed by studies in children with IOWS >7 days to 6 years of age. Safety and efficacy of lofexidine in children diagnosed with NOWS will be studied in neonates (postnatal age <7 days). Preliminary dose range finding studies will be completed to determine PK and inform the definitive safety and efficacy studies. The (b) (4) formulation will be used in children aged 12 to 17. Formulation development for children under 12 has yet to be completed (potentially (b) (4)).

The nonclinical program will consist of 5 different studies, two of which are dose range-finding studies, which need not be specifically listed as PMRs. The first definitive study, intended to support dosing in pediatric patients aged (b) (4) to 17, will study the drug in rats from PND 36 to PND 90 (b) (4). This study will include assessments on growth and development, bone development, and neurological development.

The second definitive nonclinical juvenile animal study will test lofexidine in rats from PND 7 to 90 and evaluate post-natal growth and development, reproductive (b) (4), bone development and CNS development. The Agency has provided comments to the Applicant about this protocol under the IND. The study is intended to support clinical studies in neonates to (b) (4).

(b) (4)
A protocol for this study has yet to be submitted to the Agency.

11 Integrated Summary and Safety Evaluation

US WorldMeds, LLC submitted NDA 209229 seeking approval of LUCEMYRA (lofexidine HCl), a central alpha-2 adrenergic agonist, for the mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment. To support the NDA for lofexidine, the Applicant submitted ADME, pharmacology, repeat-dose toxicology, genetic toxicology, carcinogenicity, and reproductive and developmental toxicology studies that were a mixture of older studies conducted for a different development program supplemented by nonclinical studies conducted by the current Applicant that were required by the Agency (see 2.7

Regulatory Background). It is noted that many of these original studies were conducted prior to the implementation of Good Laboratory Practices (GLP) regulations and International Council of Harmonization (ICH) testing guidelines. In many cases, the older study reports did not contain Quality Assurance Unit (QAU) inspection, dose and/or stability analyses, and toxicokinetic analyses to confirm systemic exposure. However, in agreement with the Applicant, the reports contained sufficient details related to methodology and data that supporting key findings to provide confidence that studies were well executed. Further, there was enough concordance between the toxicities observed in non-GLP and GLP studies to conclude that the older non-GLP studies provided valid evidence to support the safety of lofexidine in the current NDA.

LUCEMYRA is formulated as a 0.18 mg strength tablet containing the following excipients: lactose (b) (4), citric acid (b) (4), microcrystalline cellulose, calcium stearate, povidone (b) (4), sodium lauryl sulfate, and Opadry (b) (4) OY-S-9480 (Table 2). The proposed dosing regimen is for patients to take three or four 0.18 mg tablets orally four times daily for seven days, yielding a maximum daily dose of 2.88 mg/day (expressed as the base). As there are no novel excipients and the maximum daily intake levels for any of the listed excipients do not exceed levels in approved products, there are no concerns regarding the safety of the excipients in the formulation. Likewise, there were no safety concerns regarding the drug substance (Table 3) and drug product (Table 4) specifications for LUCEMYRA.

The primary pharmacology of lofexidine and the functionally similar structural analog, clonidine, was evaluated via receptor binding and functional activity screens (Table 5). Lofexidine demonstrated high affinity and functional activity at alpha-2A, alpha-2B, and alpha-2C adrenergic receptors, supporting the proposed mechanism of action as an adrenergic-2 receptor agonist. Although lofexidine in many cases was evaluated to be similar to clonidine, there were differences, including moderate binding and functional activity at 5-HT_{1A} and 5-HT_{1D} receptors observed for lofexidine but not clonidine. Interestingly, both lofexidine and clonidine also demonstrated potent functional activity yet only low-to-moderate binding at alpha-1A adrenergic receptors. Although both clonidine and lofexidine have classically been understood to be selective alpha-2 adrenergic receptor agonists (Papanicolaou et al., 1982; Summers et al., 1980), more recent studies show evidence of a lack of selectivity for alpha-2 over alpha-1 receptors (Gil et al., 2009). Additional secondary pharmacology binding screens were conducted on lofexidine and its major human metabolites, LADP, LDPA, and 2,6-DCP. Lofexidine displayed moderate binding at the following additional receptors: 5-HT_{2A}, 5-HT_{2B}, D_{2S},

kappa-opioid, monoamine oxidase-A, and the serotonin transporter (Table 6). In contrast, the metabolites did not show any significant binding to secondary targets.

Pharmacokinetics studies employed radiolabeling to evaluate the absorption, distribution, metabolism, and excretion of lofexidine in rats, rabbits, dogs, and monkeys. Absorption studies demonstrated that lofexidine was rapidly absorbed with T_{max} ranging from 0.5 to 4 hours across rats, dogs, and monkeys (Table 9). Lofexidine was shown to distribute widely throughout the body in a similar manner for both rats and dogs, with highest concentrations in the liver, kidneys, and throughout GI tract and low concentrations detected in the heart and eyes (Figure 9). Lofexidine was extensively metabolized in rats, rabbits and dogs, and all three major human metabolites were detected in the urine of these species (Figure 10) suggesting no human specific or disproportionate metabolites. Confirmatory studies testing plasma are being conducted and preliminary reports support this conclusion. Lofexidine was excreted via urine and feces in rats and only via urine in dogs and monkeys (Figure 11; Figure 12; Figure 13).

The toxicological profile of lofexidine was characterized by on-target exaggerated pharmacological effects in the CNS and cardiovascular system and by what appear to be indirect toxicities in the hepatic, renal, and ocular systems. Although no dedicated CNS safety pharmacology studies were submitted by the Applicant, dose-dependent clinical signs related to sedation such as decreased activity, ataxia, and hypothermia were observed in all repeat-dose toxicology studies across rats and dogs. At higher doses, clinical signs of CNS excitation were also observed such as hypersensitivity, hyperactivity, aggressive behavior, self-mutilation, tremors/convulsions, and hyperthermia. The sedative effects observed at lower doses can be attributed to the high potency of lofexidine at alpha-2 adrenergic receptors whereas the excitatory effects are likely due to the activation of alpha-1 adrenergic receptors as the selectivity of lofexidine for alpha-2 over alpha-1 adrenergic receptors may be lost at higher doses (Giovannitti et al., 2015; Puumala et al., 1997; Sinclair, 2003). It is also possible that these paradoxical excitatory effects observed at higher doses are mediated by alpha-2 adrenergic receptors as alpha-2 adrenergic receptor-mediated hypersensitivity has been observed in rats following clonidine and dexmedetomidine administration (Quartilho et al., 2004).

The cardiovascular toxicities observed primarily in dog safety pharmacology and repeat-dose toxicology studies can also be explained by the primary pharmacological effects of lofexidine. Bradycardia was observed in all three studies in dogs that included ECG evaluations, and conduction disturbances were observed in two of these studies. QT prolongation was also observed in the in vivo dog safety pharmacology study. The in vitro hERG assay did reveal mild tail current inhibition, although a statistically significant effect was only observed at the highest lofexidine concentration evaluated (Figure 1). Additional cardiovascular toxicities observed in rats and dogs included increased heart weights, myocarditis, myocardial degeneration/necrosis, and cardiac hemorrhage. Severe cardiac pathologies, i.e., myocardial degeneration/necrosis and cardiac hemorrhage were only apparent in the 1-year rat and dog studies. Some of these

adverse effects may be the result of prolonged hypotension and potentially hypoxia due to decreased tissue perfusion.

Hepatic and renal toxicities were also observed at high doses in repeat-dose toxicology studies conducted in rats and dogs, with greater incidence and severity in studies of longer duration. The liver and kidney are likely target organs as distribution studies in both rats and dogs found high concentrations of lofexidine in these organs at T_{max} . Additionally, lofexidine was shown to undergo extensive metabolism in the liver and was excreted primarily via urine. Hepatic toxicity was characterized in rats and dogs by modest, less than 2-fold, dose-dependent increases in the liver enzymes with increased liver-to-body weight ratios and cytoplasmic swelling/vacuolation of hepatocytes at the highest doses evaluated. Elevations in ALT were observed in both rats and dogs whereas AST was also elevated in rats and ALP was elevated in dogs. More severe histopathological signs of liver pathology were also observed in dogs, including centrilobular scarring and hepatocellular degeneration, necrosis, and hemorrhage. Notably, liver histopathology findings increased in severity as study duration increased, and there were no adverse findings observed in the 28-day rat study.

Renal toxicity was present but manifested differently in rats and dogs. Renal toxicity in dogs was observed at doses greater than 0.88 mg (base)/kg/day and was characterized by isolated incidences of chronic interstitial nephritis in the 3-month study with additional signs of tubular abnormalities/degeneration and cortical calcinosis in the 1-year study. In rats, renal toxicity was primarily characterized by treatment-related increases in the incidence of chronic progressive nephropathy and hydronephrosis at doses greater than 2.5 mg/kg/day in the 28-day and 3-month studies. The occurrence of these toxicities may be related to the known inhibitory effects of alpha-2 agonists on the renin-angiotensin system (Sinclair, 2003).

Additional treatment-related findings consistent with dehydration that may or may not be related to renal toxicity, included increased urea nitrogen, electrolyte imbalances (Na^+ , Cl^- , and Ca^{2+}), increased urine specific gravity with decreased urine volume, and salivary gland atrophy. Apart from increased urea nitrogen, which was also observed in the 3-month and 1-year rat studies, the rest of these findings were only observed in the 28-day rat study. Although the severity of urine volume decreases was correlated with the presence of chronic progressive nephropathy at the MD and HD in this study (Figure 24), the presence of these signs of dehydration, including decreased urine volume, at the LD suggests that renal dysfunction may exacerbate these findings but is not their root cause. These findings were also generally correlated with treatment-related decreases in body weight gain and may have been related to malnutrition. It is also possible that the sedative effects of lofexidine also played a role by decreasing water consumption, which was not directly quantified in any of the toxicology studies. Additionally, similar side effects, e.g. dry mouth, have been associated with clinical use of other alpha-2 adrenergic agonists, such as clonidine (Wilson et al., 1986).

Potentially dehydration-related, severe ocular toxicity, characterized by keratitis and corneal erosion/ulceration, was also observed in the 28-day rat study at the MD and HD

in males and without a NOAEL in females. The presence of this finding was noted to the Applicant in the 74-day letter, and the Applicant submitted additional clinical data and literature to support the safety of lofexidine with respect to ocular toxicity. The Applicant noted that although dry eye was noted during the clinical development of lofexidine, corneal lesions were not observed. Additionally, the Applicant cited a literature study in rats that had demonstrated that the incidence of corneal lesions in rats associated with reduced lacrimal secretions and blinking after administration of the alpha-2 adrenergic agonist, clonidine, could be reduced by repeated moistening of the cornea (Weisse et al., 1978). Weisse et al. noted that, based on unpublished data, corneal lesions have not been noted following clonidine administration to the rabbit, dog, or monkey. Collectively, these data suggest that the level of human risk associated with the corneal lesions observed in rats is low.

Additional toxicities associated with lofexidine treatment in both rats and dogs were limited to gastrointestinal pathology that were only observed the highest doses evaluated in studies of one-year duration. In rats stomach erosion, ulceration, and/or necrosis was observed in several HD rats, only after scheduled terminal sacrifice, suggesting that this may be a withdrawal-related effect. In dogs, gastric mucosal congestion was observed only in the two female HD dogs that were found dead and exhibited hemorrhage in several other organs, including the heart, adrenals, and thymus. There were not additional toxicities noted only in dogs; however, increased neutrophil:lymphocyte ratio and chronic/necrotizing tracheitis were observed in rats. Increased neutrophil:lymphocyte ratio was observed in all three rat studies, but may have been a compensatory response to the stress associated with the decreased food consumption and body weight gains observed in these animals. A dose-dependent increase in the incidence of chronic tracheitis was observed in the 3-month rat study with necrotizing tracheitis in one HD female. Although this finding was likely related to the gavage method of lofexidine administration, its treatment-related incidence suggests that lofexidine may have enhanced the sensitivity of the trachea to traumatic injury.

The genetic toxicology of lofexidine was evaluated via two in vitro assays, an Ames bacterial reverse mutation assay and a L5178Y/TK[±] mouse lymphoma assay, and one in vivo rat bone marrow erythrocyte micronucleus test. The Ames assay was negative for all concentrations evaluated, up to 5000 mcg/plate, with and without metabolic activation, and the micronucleus test was also negative for doses up to 65 mg/kg; however, a positive result was observed in the mouse lymphoma assay after 4 hours of exposure to 40 mcg/mL with metabolic activation. This was the highest concentration that could be assessed under these conditions as higher concentrations tested, 60 and 75 mcg/mL, were too cytotoxic to yield a valid test result. The positive results were characterized by an increase in the number of small colonies, suggesting a clastogenic mode of action rather than a mutagenic mode of action. The Applicant has committed to conducting an additional in vivo Comet Assay to provide additional weight of evidence to support the safety of lofexidine with respect to genetic toxicology. Based on a risk:benefit for this drug, the study may be completed as a postmarketing requirement.

Two carcinogenicity studies, a 2-year study in rats and an 18-month study in mice, were submitted in the Application; however, upon review these studies and consultation with the Executive Carcinogenicity Assessment Committee, these studies were deemed inadequate to characterize the carcinogenic potential of lofexidine. Neither study demonstrated a statistically significant increase in treatment-related neoplasms, but several issues related to the design and execution of these studies severely limited their utility in the carcinogenicity assessment of lofexidine. Both studies were conducted prior to the implementation of GLPs and did not assess the concentration of the drug administered via diet. Additionally, the highest dose evaluated in the rat study, 0.88 mg/kg/day, was not an adequate maximum tolerable dose as both the 3-month and 1-year rat repeat-dose toxicology studies demonstrated that the 3-fold higher dose, 2.6 mg/kg/day, would have been tolerable and appropriate for the carcinogenicity assessment. The mouse study was also inadequate with respect to the doses employed as there were no mouse repeat-dose toxicology studies cited to provide the basis of dose selection. Additionally, the planned 18-month duration of the mouse study was not adequate. Furthermore, several unscheduled deaths occurred 15 months into the study due to an erroneous 4-day, 100-fold increase in the concentration of lofexidine for all dose levels, necessitating the early sacrifice of the entire male HD treatment group. Finally, the full battery of tissues was not evaluated. As such, the labeling should reflect that adequate long-term studies in animals have not been completed to characterize the carcinogenic effect of lofexidine.

The reproductive toxicology of lofexidine was assessed via one GLP and four non-GLP studies in rabbits and rats. A GLP toxicokinetics study was also conducted in rabbits dosed from GD 6 through GD 19 to inform labeling. In two non-GLP studies, one in rabbits and one in rats, no adverse effects of oral lofexidine administration were observed with respect to fertility parameters at doses up to 5.6 mg (base)/kg/day in female rabbits and 0.88 mg (base) /kg/day in both male and female rats. However, no evaluations of sperm or male reproductive organs were performed, and maternal toxicity was not clearly demonstrated in the rat study suggesting that it was not dosed adequate to support the safety of lofexidine with respect to fertility. Given the risk:benefit, this study may be completed as a PMR. In two non-GLP embryofetal studies, one in rabbits and one in rats, no evidence of teratogenicity was observed in either study, but embryofetal toxicities along with maternal toxicities were observed. In rabbits, embryofetal toxicity characterized by increased post-implantation losses was observed at doses greater than or equal to 4.4 mg (base)/kg/day, with maternal toxicity characterized by decreased body weight gain and increased mortality observed at the HD of 13.2 mg (base)/kg/day. In rats, embryofetal toxicity characterized by decreased fetal weights was observed at the HD of 2.6 mg/kg/day, with maternal toxicity characterized by decreased body weight gain, clinical signs of distress, and death observed in the same dose group. In the GLP pre- and post-natal development study, developmental toxicities characterized by decreased pup body weights and body weight gains, increased incidence of total litter loss, increased pup mortality, developmental delays, and fertility impairments in F₁ offspring were observed at doses greater than or equal to 1.0 mg/kg/day, with maternal toxicity characterized by sedation, and decreased body weight gains in the same dose groups. Notably, maternal toxicity was also

observed in all dose groups exhibiting embryofetal and developmental toxicities in the rat studies. In the rabbit embryofetal study maternal toxicity was observed, but post-implantation losses were increased in the absence of maternal toxicity.

As shown in Table 70, the human equivalent dose (HED) using body surface area-based allometry at the NOAEL for every toxicology study exceeded maximum recommended human dose (MRHD) of 2.88 mg (base)/day. Although toxicokinetics evaluations were not performed in any of the non-GLP toxicology studies, toxicokinetics data was available from at least one study for rabbits (dams only), rats, and dogs (Table 10). This allowed for safety margins to be calculated comparing the exposure at the NOAEL's of toxicology studies to the human exposure at the MRHD. For the calculation of safety margins, the exposure associated with the NOAEL of each non-GLP rat and rabbit study was estimated to be equivalent to the exposure recorded at the closest dose in the corresponding GLP study conducted in the same species. For dogs, as the only toxicokinetics data available was from males following a 3.0 mg/kg single dose in safety pharmacology study, USWM-LX0-PHA-0002, the exposure associated with the NOAEL of each non-GLP dog study was calculated by linear extrapolation of this single data point through the origin. Linear extrapolation of the nearest data point through the origin was also used to calculate the exposure of doses outside of the measured range. As the dosing QD dosing regimen employed in the toxicology studies differs from the QID dosing regimen employed in clinical studies, the human exposure at the MRHD was estimated to be 89.24 ng/mL*h by quadrupling the $AUC_{0-\infty}$ recorded in USWM-LX1-1002 after a single dose 0.72 mg lofexidine was administered to healthy subjects. These safety margins based on exposure are approximately 10-to-20-fold more conservative than the HED-based margins for rats and dogs and approximately 500-fold more conservative for rabbits. These low exposure margins may be at least partially attributable to the QD dosing regimen employed in the nonclinical toxicology studies which exposed the animals to much higher C_{max} than an equivalent daily dose administered QID in the clinical studies. In fact, the margins were calculated with respect to C_{max} were 10-to-100 times larger than those calculated based on AUC.

Based on these exposure margins, the rat was the most sensitive species with respect to general toxicology, with an approximate exposure margin of 0.5x at the MRHD. In the pivotal GLP 28-day rat repeat-dose toxicology study, no NOAEL was established in females due to the presence of keratitis with corneal erosion/ulceration in one of ten LD rats; however, as discussed above, severe ocular toxicity was not observed in clinical studies to date (Dry eyes have been reported in clinical studies and should the product be dosed for longer periods, monitoring of ocular tissues in longer clinical studies should be considered). Additionally, this finding has also been observed after administration of the FDA approved alpha-2 adrenergic agonist, clonidine, in rats and was shown to be related to reduced blinking and was reversed by application of repeated moistening of the cornea (Weisse et al., 1978). Ocular toxicity was present in 6 males and 5 females at the MD; however, additional toxicities at this dose were limited to minimal chronic progressive nephropathy, increased heart-to-body-weight ratio, and non-adverse dehydration-related findings discussed above, such as increased urea nitrogen, electrolyte imbalances, increased urine specific gravity with decreased urine volume,

and salivary gland atrophy. Given that chronic progressive nephropathy is a common kidney pathology in rats that is not analogous to any type of human nephropathy (Hard et al., 2009), the increased heart weight was not correlated with additional cardiac toxicity, and the dehydration-related findings were not severe and likely secondary to decreased food and water intake, the MD can be considered an acceptable LOAEL for both sexes, providing a 17-fold HED-based safety margin and a 3-fold exposure based safety margin. Both the HED-based and exposure-based safety margins for the dog repeat-dose toxicology studies were greater than one. The exposure-based safety margin with respect to QT prolongation in the dog EEG cardiovascular safety pharmacology study was also less than one; however, a clinical thorough QT study has been conducted to assess the risk associated with this finding in humans directly. The HED-based safety margins with respect to reproductive toxicology are all greater than one; however, the exposure-based safety margins are all significantly less than one, suggesting that there may be serious risks associated with lofexidine treatment during pregnancy. These risks have been incorporated into the drug label in accordance with PLLR.

Overall, the toxicological profile of lofexidine was well characterized by the studies submitted in this Application, and the risks associated with the toxicities observed in these studies are acceptable for the proposed indications.

Table 70: NOAEL and Safety Margins for Lofexidine Toxicology Studies

Study Category	Species	Type of Study	Study Number	NOAEL (mg/kg/day)		Exposure Margin		
				Male	Female	Based on HED*	Based on AUC**	Based on C _{max} ***
Safety Pharmacology	Dog	Cardiovascular EEG (GLP)	USWM-LX0-PHA-0002	0.3	-	3x	0.6x	7.7x
Repeat-Dose Toxicology	Rat	28-Day (GLP)	USWM-LX0-TOX-0005	5/2.5	None	< 8x	Males: 0.5x Females: < 1.2x	Males: 5.7x Females: < 8.2x
		3-Month (non-GLP)	USWM-LX0-TOX-0006	0.88	0.88	3x	0.2x	2.0x
		1-Year (non-GLP)	USWM-LX0-TOX-0014	None	None	<9x	<0.5x	<5.7x
	Dog	3-Month (non-GLP)	USWM-LX0-TOX-0019	0.88	0.88	30x	1.8x	64x
		1-Year (non-GLP)	USWM-LX0-TOX-0020	0.88	0.88	30x	1.8x	64x
	Reproductive Toxicology	Rabbit	Fertility (non-GLP)	USWM-LX0-TOX-0017	-	5.6	38x	0.1x
Embryofetal (non-GLP)			USWM-LX0-TOX-0010	-	1.3	9x	0.02x	0.7x
Rat		Fertility (non-GLP)	USWM-LX0-TOX-0016	0.88	0.88	3x	0.2x	1.4x
		Embryofetal (non-GLP)	USWM-LX0-TOX-0018	-	0.88	3x	0.2x	1.4x
		Pre- and Postnatal Development (GLP)	USWM-LX0-TOX-0003	-	<0.3	<1x	<0.04x	<0.7x

* HED based on body surface area-based allometric dose conversion. For treatment groups that received multiple dose levels throughout the study due to dose-adjustments, the lowest dose level was used for safety margin calculation.

** AUC at MRHD: 89.24 ng/mL*h at 2.88 mg/day

*** C_{max} at MRHD: 2.51 ng/mL at 2.88 mg/day

12 Appendix/Attachments

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(b) (4)

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/s/

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04/25/2018

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04/25/2018
I concur.

Office of Clinical Pharmacology Integrated Review

NDA or BLA Number	209229
<u>Link to EDR</u>	\\Cdsub1\evsprod\NDA209229
Submission Date	September 26, 2017
Submission Type	Priority
Brand Name	Lucemyra™
Generic Name	Lofexidine
Dosage Form and Strength	0.2 mg lofexidine HCl per tablet
Route of Administration	Oral
Proposed Indication	<ul style="list-style-type: none"> • mitigation of symptoms associated with opioid withdrawal and • facilitation of completion of opioid discontinuation treatment
Applicant	US World Meds
Associated IND	47857
OCP Review Team	Wei Qiu, PhD., Kevin Krudys, PhD., Yun Xu, MD, PhD.
OCP Final Signatory	Chandra Sahajwalla, PhD Division Director Division of Clinical Pharmacology II

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1. EXECUTIVE SUMMARY

US World Meds submitted an original NME NDA 209229 on July 28, 2017 for Lucemyra (lofexidine hydrochloride) oral tablet. The Applicant is seeking approval of lofexidine, a selective adrenergic α_2 receptor agonist, for the mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment. The Division of Anesthesia, Analgesia, and Addiction Products has granted lofexidine fast track designation for the facilitation of opioid discontinuation treatment (12/15/16).

The clinical development program included 16 Phase 1 clinical pharmacology trials (i.e., absolute bioavailability and mass balance, single- and multiple-ascending dose, food effect, drug interaction, hepatic impairment, renal impairment, and QT studies), 2 Phase 2/3 supportive efficacy/safety, and 2 pivotal Phase 3 efficacy/safety trials. Throughout the review, the lofexidine hydrochloride dose was used rather than the free base dose.

DAAAP held an AC meeting on 3/27/18 to discuss mainly the results of the two pivotal Phase 3 clinical trials (3002 and 3003) and the similarity in efficacy results and differences in toxicity between the two dose levels, 2.4 mg/day and 3.2 mg/day. Most preferred the 2.4 mg/day dose to limit to mitigation of symptoms with some members advocating for flexibility in the label to increase to 3.2 mg/day if clinically appropriate.

OCP briefing was held on 4/3/18, and it was generally agreed to keep simple dosage adjustment plans in patients with renal or hepatic impairment to address the increased systemic exposures in these patients.

Key review issues include (1) the appropriateness of the dosing instruction in general patients and (2) recommendations in specific patient populations (i.e., hepatic impairment, renal impairment).

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 209229. This NDA is considered approvable from a clinical pharmacology perspective. As of 4/18/18, labeling negotiation is still ongoing with the Applicant. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	Substantial evidence of effectiveness was demonstrated by the registration trials. Clinical pharmacology studies supported the dosing regimen used in the clinical trials.

General dosing instructions	<p>The sponsor proposed that the usual dosage is four tablets taken orally four times daily for seven days. There should be 5 to 6 hours between each dose. The total daily dosage should not exceed 3.2 mg lofexidine HCL (16 tablets daily) and no single dose should exceed 0.8 mg (4 tablets). (b) (4)</p> <p>(b) (4)</p> <p>The lofexidine dose should be reduced, held, or discontinued for individuals who demonstrate a greater sensitivity to lofexidine side effects.</p> <p>Lofexidine can be administered in the presence or absence of food.</p> <p>As there is no significant improvement in effectiveness from 3 tablets QID (2.4 mg/day) to 4 tablets QID (3.2 mg/day), but the incidence of side effect such as bradycardia and hypotension is higher for 4 tablets QID, OCP recommends that the usual starting dosage is 3 tablets QID. There should be 5 to 6 hours between each dose. The total daily dosage of should not exceed 16 tablets daily and no single dose should exceed 4 tablets with dosing guided by symptoms and side effects.</p>
Dosing in patient subgroups (intrinsic and extrinsic factors)	<p>The sponsor proposed dosage adjustment in patients with hepatic or renal impairment based on relevant PK studies (the dose presented in the following tablets as lofexidine base):</p> <p>(b) (4)</p>

	<p>Overall, the proposed dosing in the patient population with renal or hepatic impairment is reasonable from PK perspective. (b) (4)</p> <p>dosage to 2 tablets QID in mild and moderate renal impairment, and 1 tablet QID in severe renal/ESRD on dialysis or hepatic impairment (b) (4)</p>
<p>Bridge between the “to-be-marketed” and clinical trial formulations</p>	<p>The to-be-marketed formulation was used in the clinical trials</p>

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Lofexidine is a selective adrenergic α_2 receptor agonist that binds to α_2 receptors on adrenergic neurons. This reduces the release of norepinephrine and moderates the symptoms of noradrenergic hyperactivity occurring when the inhibitory effect of opioids is removed. The following is a summary of the clinical pharmacokinetic features of lofexidine:

Absorption: Following oral administration, peak lofexidine plasma concentration (Cmax) was attained at approximately 3 to 5 hours. Plasma lofexidine concentrations increased approximately proportionally with increasing doses following single dose administration of 0.2 to 0.8 mg and four times daily administration of 0.2 to 0.8 mg lofexidine (i.e. total daily dose of 0.8 to 3.2 mg). The absolute bioavailability of a single oral lofexidine dose (0.4 mg in solution) compared with an intravenous infusion was 72% (90% CI: 58% to 85%). Ingestion of a high-calorie, high-fat meal slightly delayed the median (min, max) Tmax from 5 (3, 7) to 6 (2, 10) hours but did not alter the Cmax and AUC values of lofexidine so lofexidine may be administered with or without food. Results from in vitro study in Caco-2 cells suggested that lofexidine was not a substrate of P-gp.

Distribution: Mean volume of distribution values following the administration of an intravenous dose was 297.9 L, suggesting extensive distribution into body tissue. The protein binding of lofexidine in human plasma was approximately 55%. Lofexidine is not preferentially taken up by

blood cells. In a study comparing the total radioactivity attributed to lofexidine and its metabolites in plasma and whole blood around Tmax in healthy volunteers, it was determined that red blood cells contain approximately 27% of radioactivity in the plasma. The data from the incubation of whole blood samples mixed with various concentrations of lofexidine HCL suggested that lofexidine is not preferentially bound to blood cells, as evidenced by whole blood-to-plasma concentration ratios of less than 1.

Metabolism: Lofexidine is metabolized by CYP2D6, with CYP1A2 and CYP2C19 also capable of metabolizing lofexidine. Lofexidine and its major circulating metabolites (LADP, LDPA, 2,6-DCP) did not inhibit or induce major CYPs in vitro, with the exception of a slight inhibition of CYP2D6 by lofexidine, with an IC₅₀ of 4551 nM (approximately 225 times the steady state Cmax of lofexidine with 0.8 mg four times daily dosing). Interaction with CYP2D6 substrates is not expected to be clinically significant.

Elimination: Following an intravenous infusion of 0.2 mg lofexidine for 200 minutes, clearance of lofexidine is 17.63 L/h and the elimination half-life is 12 hours. A mass balance study of lofexidine (0.4 mg in solution) given orally showed nearly complete recovery of radioactivity in urine (93.5%) over 144 hours post-dose, with an additional 0.92% recovered in the feces over 216 hours post-dose, for a total recovery in the urine and feces of 94.4% of the administered dose. Thus, it appears that nearly all the administered dose was absorbed, and that the primary route of elimination of lofexidine and its metabolites was via the kidney. Renal elimination of unchanged drug accounts for approximately 15% to 20% of the administered dose.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The sponsor's proposed usual lofexidine dosage is four 0.18 mg tablets (0.72 mg lofexidine base) taken orally four times daily for seven days. There should be 5 to 6 hours between each dose. The total daily dosage of lofexidine should not exceed 2.88 mg (16 tablets daily) and no single dose should exceed 0.72 mg (4 tablets).

(b) (4)

(b) (4)

The lofexidine dose should be reduced, held, or discontinued for individuals who demonstrate a greater sensitivity to lofexidine side effects

Lofexidine can be administered in the presence or absence of food.

As there is no significant improvement in effectiveness from 3 tablets QID to 4 tablets QID, but the incidence of side effects such as bradycardia and hypotension is higher for 4 tablets QID, the

usual starting dosage should be 3 tablets QID. There should be 5 to 6 hours between each dose. The total daily dosage of should not exceed 16 tablets daily and no single dose should exceed 4 tablets with dosing guided by symptoms and side effects.

2.2.2 Therapeutic individualization

Hepatic Impairment: Lofexidine is extensively metabolized. Based on the results from a dedicated hepatic impairment study, mean C_{max} values were similar for subjects with normal, mild, and moderate hepatic impairment. Mean C_{max} values for subjects with severe hepatic impairment was approximately 67% higher than that for subjects with normal hepatic function. Mean AUC_{last} values in subjects with mild, moderate, and severe hepatic impairment were approximately 27%, 90%, and 200% higher, respectively, compared with subjects with normal hepatic function. A similar trend was observed for mean AUC_{inf} values. Mean t_{1/2} values increased as the severity of hepatic impairment increased. They were 14.91, 16.78, 37.01, 48.21 hours in subjects with normal, mild, moderate, and severe hepatic impairment, respectively. The sponsor proposed dosage adjustments based on the degree of hepatic impairment (**Table 1**). The sponsor's proposed maximum dosing regimen for mild, moderate, and severe hepatic impairment were 3 tablets QID, (b) (4) respectively. Although they are reasonable from PK perspective, we suggested the (b) (4) dosing frequency for moderate and severe hepatic impairment with 2 tablets QID and 1 tablet QID (b) (4)

Table 1 Sponsor's Proposed Dosage Recommendation in Patients with Hepatic Impairment



(b) (4)

Renal Impairment: Based on the results from a renal impairment study with a reduced study design, mean C_{max} values were similar for ESRD and normal renal function subjects. An approximately 80% greater AUC_{last} values was observed for ESRD subjects compared with normal renal function subjects. Mean t_{1/2} increased from 19.34 h in subjects with normal renal function to 26.41 h in subjects with ESRD. The impact of dialysis on the overall PK of lofexidine during a typical 4-hour dialysis was minimal.

Results from another renal impairment study with full study design, mean C_{max}, AUC_{last}, and t_{1/2} increased with severity of renal impairment. Mean C_{max} increased by 24.2%, 17.2%, and 54.3% for subjects with mild, moderate and severe renal impairment, compared to subjects with normal renal function, respectively. Mean AUC_{last} increased by approximately 57.4%, 87.0%, and 172% for subjects with mild, moderate, and severe renal impairment, compared to subjects with normal renal function, respectively. Similar trends are found for AUC_{inf}. Mean t_{1/2} was 14.24, 15.74, 20.63, and 22.29 hours in subjects with normal, mild, moderate, and severe renal impairment, respectively. The sponsor proposed dosage adjustment for different degrees of renal impairment based on the data obtained from 2 renal impairment studies (**Table 2**). The sponsor's proposed maximum dosing regimen for mild, moderate, and severe renal impairment/ESRD on dialysis is [REDACTED] (b) (4) respectively. Although they are reasonable from PK perspective, we suggested the [REDACTED] (b) (4) dosing frequency for moderate and severe renal impairment/ESRD on dialysis with 2 tablets QID and 1 tablet QID, respectively, [REDACTED] (b) (4). Because of the increases in lofexidine AUC_{last} in subjects with mild (57%) and moderate impairment (87%) are similar, the same maximum dose is recommended for mild and moderate renal impairment, 2 tablets QID.

Table 2 Sponsor's Proposed Dosage Recommendations in Patients with Renal Impairment



2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert:

- The initial dose is 2.4 mg/day given as 3 tablets QID. The dose may be increased to the recommended dose of 3.2 mg/day as 4 tablets QID. Dose should be reduced, held, or discontinued for individuals who demonstrate a greater sensitivity to lofexidine side effect.
- Patients with moderate hepatic, mild and moderate renal impairment should be [REDACTED] (b) (4) 2 tablets QID.

- Patients with severe hepatic or renal impairment/ESRD on dialysis should be (b) (4) 1 tablet QID.
- Lofexidine can be taken with or without food.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Lucemyra contains lofexidine, a selective adrenergic α_2 receptor agonist. Lucemyra tablet is intended for oral administration only. Each (b) (4) contains 0.2 mg of lofexidine hydrochloride, which is equivalent to 0.175 mg of lofexidine free base and rounded to 0.18 mg.

Lucemyra is indicated for mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment. Lofexidine has received fast-track designation for the facilitation of opioid discontinuation treatment in December 2016.

Lofexidine was submitted to the agency for hypertension in 1983 but received a non-approval action, in part for lack of efficacy. Hypertension indication was not approved in several European countries.

Lofexidine has been marketed in the UK since 1992 by Britannia Pharmaceuticals to relieve withdrawal symptoms in patients undergoing opioid detoxification. In the UK Summary of Product Characteristics, the initial dosage of lofexidine HCl is 0.8 mg/day in divided doses, and the dosage may be increased by increments of 0.4 to 0.8 mg/ day up to a maximum of 2.4 mg daily, with a maximum single dose not to exceed 4 × 0.2 mg tablets (0.8mg).

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Lofexidine is a selective adrenergic α_2 receptor agonist that binds to α_2 receptors on adrenergic neurons. This reduces the release of norepinephrine and moderates the symptoms of noradrenergic hyperactivity occurring when the inhibitory effect of opioids is removed.
QT Prolongation	QT prolongation and decrease in heart rate have been observed for lofexidine, however, no dose or exposure-response relationship could be identified in the submitted studies for QTc prolongation. Overall, the concern for QT prolongation with lofexidine appears to be mainly

	limited to settings in which it would be co-administered with other medicinal products that lead to QTc prolongation (e.g., methadone)	
General Information		
Bioanalysis	Lofexidine and its major metabolites were measured using validated LC/MS/MS methods. A summary of the method validation reports is included as appendix 4.1.	
Drug exposure at steady state following the therapeutic dosing regimen	<p>(1) Mean concentrations around Tmax (3 and 4 hour post-dose) in patients at the 2.4 mg/day (0.6 mg QID) and 3.2 mg/day (0.8 mg QID) were 3.62 – 4.29 and 4.94 – 5.20 ng/mL. The corresponding trough levels were 3.05 ng/mL and 3.98 - 4.14 ng/mL, respectively (Phase 3 Study 3003-1).</p> <p>(2) Cmax and AUC0-5h (mean ± SD) in methadone maintained subjects at the 2.4 mg/day dose (0.6 mg QID) (n = 3) were 6.29 ± 1.94 ng/mL and 25.80 ± 6.70 ng.h/mL; Cmax and AUC0-5h (mean ± SD) in methadone maintained subjects at the 3.2 mg/day dose (0.8 mg QID) (n = 5) were 6.69 ± 0.70 ng/mL and 29.00 ± 3.90 ng.h/mL (Study LX1-1005-1)</p> <p>(3) Cmax and AUC0-5h in methadone maintained subjects at the 2.4 mg/day dose (0.6 mg QID) (n = 1) were 6.33 ng/mL and 28.60 ng.h/mL; Cmax and AUC0-5h (mean ± SD) in methadone maintained subjects at the 3.2 mg/day dose (0.8 mg QID) (n = 16) were 8.18 ± 2.68 ng/mL and 34.8 ± 12.1 ng.h/mL (Study LX1-1005-2)</p> <p>(4) Cmax (mean ± SD) in buprenorphine maintained subjects at the 3.2 mg/day (0.8 mg QID) (n = 7) was 4.67 ± 1.26 ng/mL (Study LX1-1013)</p> <p>(5) Cmax and AUC0-5h (mean ± SD) in healthy subjects at the 3.2 mg/day (0.8 mg QID) (N=4) were 2.511 ± 1.754 ng/mL and 10.88 ± 7.61 ng·h/mL, respectively (Study LX1-1002)</p>	
Maximum tested dose and exposure	Single Dose	<p>2.0 mg in healthy subjects (n=4): (mean ± SD) Cmax (2.795 ± 0.593 ng/mL) and AUCinf (54.32 ± 11.59 ng.h/mL)</p> <p>2.0 mg in healthy subjects (n = 12): (mean ± SD) Cmax (2.97 ± 0.48 ng/mL) and AUCinf (71.5 ± 24.9 ng.h/mL)</p>

	<p>Multiple Dose 3.2 mg (0.8 mg QID)</p> <p>Healthy subjects: C_{max} and AUC_{0-5h} (mean ± SD) values were 2.511 ± 1.754 ng/mL and 10.88 ± 7.61 ng·h/mL, respectively. [n = 4 remained after a 67% discontinuation rate during dose escalation] (Study LX1-1002)</p> <p>Opioid-dependent subjects undergoing withdrawal: C_{max} of 4.94 – 5.20 ng/mL (Pivotal Phase 3 trial 3003-1)</p> <p>Methadone maintained subjects: C_{max} and AUC_{0-5h} (mean ± SD) (n = 5) were 6.69 ± 0.70 ng/mL and 29.00 ± 3.90 ng.h/mL (Study LX1-1005-1)</p> <p>Methadone maintained subjects: C_{max} and AUC_{0-5h} (mean ± SD) (n = 16) were 8.18 ± 2.68 ng/mL and 34.8 ± 12.1 ng.h/mL (Study LX1-1005-2)</p> <p>Buprenorphine maintained subjects: C_{max} and AUC_{0-5h} (mean ± SD) (n = 20) were 5.21 ± 0.95 ng/mL and 23.7 ± 4.5 ng.h/mL (Study LX1-1006)</p> <p>Buprenorphine maintained subjects (n = 7): C_{max} was 4.67 ± 1.26 ng/mL (Study LX1-1013)</p>
<p>Dose Proportionality</p>	<p>Overall, AUC and C_{max} of lofexidine increased approximately proportionally when the dose was increased from 0.2 to 0.8 mg and 1.2 to 2.0 mg as single dose and from 0.8 to 3.2 mg/day as QID.</p> <p>SD (n = 4): mean C_{max}, AUCl_{ast}, and AUC_{inf} were 1.59-fold, 1.67-fold, and 1.72-fold for a 1.67-fold dose increase from 1.2 mg to 2.0 mg dose in healthy subjects (study LX1-1001)</p> <p>SD (n = 12): mean C_{max}, AUCl_{ast}, and AUC_{inf} were 1.20-fold, 1.24-fold, and 1.31-fold for a 1.25-fold dose increase from 1.6 mg to 2.0 mg dose in healthy subjects (study LX1-1011)</p> <p>SD (n=4): mean C_{max}, AUC₀₋₅, and AUC_{0-inf} were 2.93- to 3.06-fold for a 4-fold dose increase from 0.2 mg to 0.8 mg in healthy subjects (Study LX1-1002)</p>

	<p>MD (n=4): mean C_{max}, AUC₀₋₅, and AUC_{0-inf} were 3.45- to 3.82-fold for a 4-fold dose increase from 0.2 mg to 0.8 mg QID (0.8 mg/day to 3.2 mg/day) in healthy subjects (Study LX1-1002)</p> <p>MD: mean trough concentrations were 1.30- to 1.35-fold, and concentrations around T_{max} (e.g., 3 and 4 h post-dose) were 1.16- to 1.37-fold for a 1.33-fold dose increase from 2.4 mg/day and 3.2 mg/day in opioid-dependent subjects undergoing withdrawal (Study LX1-3003-1)</p>
Accumulation	The accumulation factor is approximate 3-fold with QID dosing and steady state is reached by Day 4.
Absorption	Absolute bioavailability (oral solution): 72% (90% CI: 58% to 85%)
	T _{max} : 3 – 5 h
	Food effect (high-fat high-calorie): Ingestion of a high-fat high-calorie meal delayed median (min, max) T _{max} from 5 (3, 7) to 6 (2, 10) hours but did not alter the C _{max} and AUC values of lofexidine.
Distribution	Volume of Distribution: 297.9 L for an IV dose
	Plasma Protein Binding: 55%
	Blood to Plasma Ratio: < 1
Elimination	Clearance: 17.63 L/h for an IV dose
	Mean Elimination half-life: 12 hours.
	Mass balance study showed that approximately 93.5% and 0.92% radioactivity was recovered in urine and feces, respectively. Approximately 15 - 20% was excreted as unchanged lofexidine in the urine.
	Metabolism: primarily by CYP2D6, CYP1A2 and CYP2C19 also capable of metabolizing lofexidine. Plasma concentrations of inactive metabolites including LADP, LDPA, and 2,6 DCP are approximately 10-25% of that of lofexidine.
	Transporter: not a substrate of P-gp; unlikely to inhibit the transporters (e.g., P-gp, BCRP, OAT1, OAT3, OCT1, OCT2,

	OATP1B1, OATP1B3, MATE1, MATE2-K, or BSEP) at clinically relevant concentrations.
	CYP enzymes: unlikely to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 or induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP3A4/5 at clinically relevant concentrations.

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

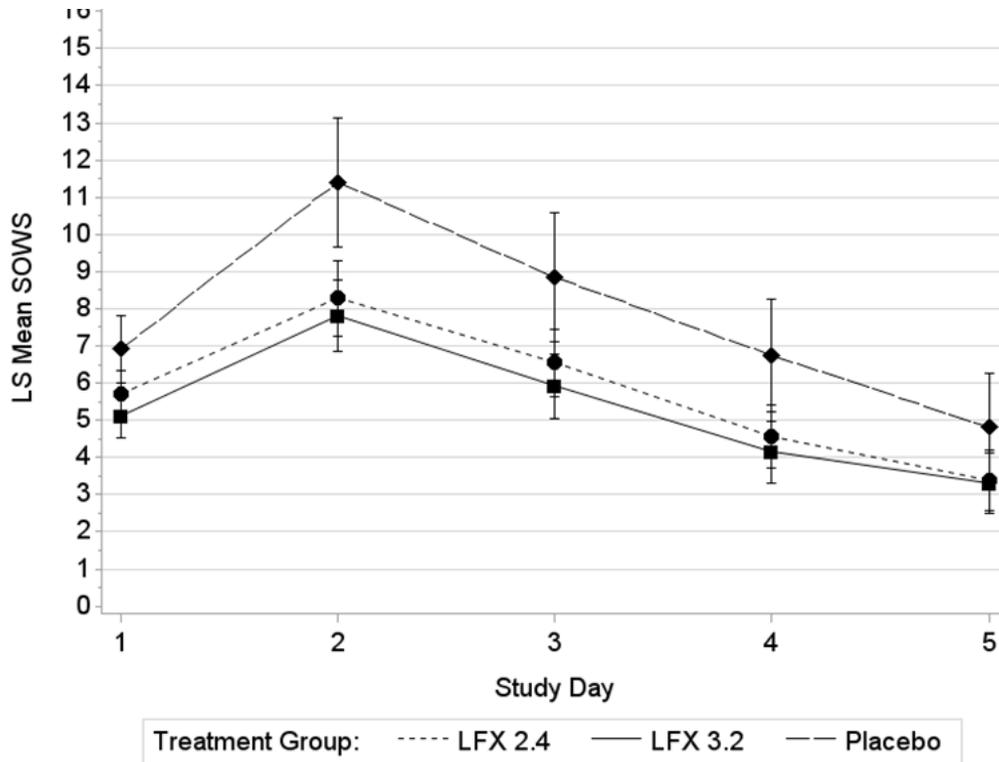
The efficacy data derive primarily from two inpatient studies of patients with opioid use disorder (OUD) abruptly discontinuing illicit use of short-acting opioids (e.g., heroin, morphine). The efficacy endpoints including Short Opiate Withdrawal Scale – Gossop (SOWS-Gossop) score and completion status were compared to the placebo group in two Phase 3 trials (LX1-3002 and LX1-3003). The SOWS-Gossop was scored by summing the 10 individual item scores ranging from 0 to 3 (None = 0, Mild = 1, Moderate = 2, and Severe = 3) with a total possible score range from 0 to 30. A higher score indicates a greater withdrawal symptom severity.

Study 3002 was designed as an inpatient, randomized, multi-center, double blind, placebo-controlled, parallel-group study. After screening, subjects were to be admitted to an inpatient unit and randomized to receive either lofexidine (0.8 mg QID) or placebo QID for five days. All subjects were then to receive placebo for two days and then be discharged on Day 8 following the post-treatment assessments. There is evidence of efficacy on symptoms and completion for the 3.2 mg/day dose.

Study 3003 is a multicenter study which consists of two parts. Part 1 of the study used an inpatient, randomized, double-blind, and placebo-controlled design from Days 1 to 7. Part 2 of the study used an open-label, variable-dose design for up to an additional 7 days in either an inpatient or outpatient setting depending on the wishes of the site investigator and the subject. The treatment period of Study 3003-1 was very similar in design to Study 3002, with the main difference being a 2.4 mg/day lofexidine arm in addition to a 3.2 mg lofexidine and placebo arm and a longer treatment period of 7 days compared to 5 days in Study 3002. There is evidence of efficacy on symptoms and completion for both doses (**Figure 1**). No statistically significant difference in mean SOWS-Gossop scores between doses was demonstrated, although SOWS-Gossop scores trended

lower for the 3.2 mg/day group compared with the 2.4 mg/day group. Completer rate was 46% and 47% for 2.4 mg/day and 3.2 mg/day in comparison to placebo (32%) on Day 5.

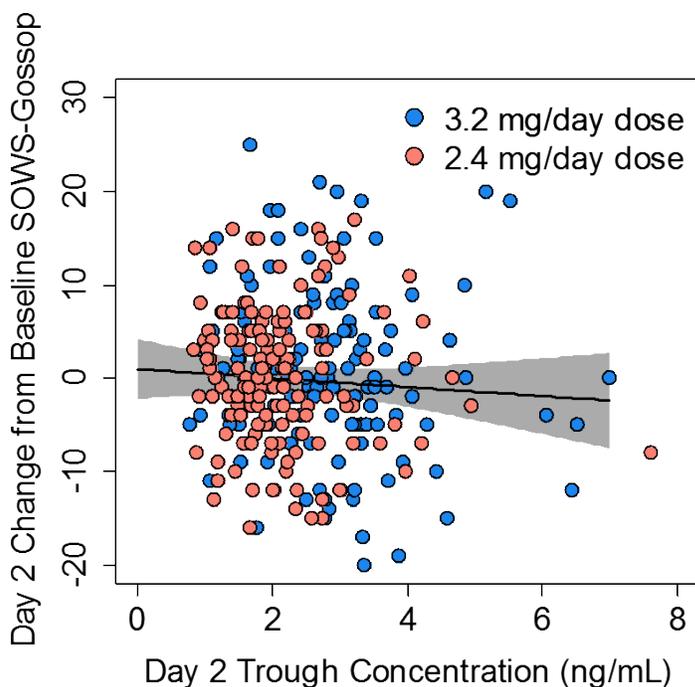
Figure 1 Mean SOWS over Time (Study 3003-1)



(Please refer to the clinical/statistical review by Dr. Pam Horn and Dr. Yi Ren for further details about the pivotal efficacy data)

An internal exposure-response analysis (**Figure 2**) using the exposures, namely, the observed trough concentrations of lofexidine on Day 2 and the reduction in SOWS-Gossop score relative to the baseline was conducted using data from Study 3003-1. The resulted shallow relationship between lofexidine levels and SOWS-Gossop scores were consistent with the observed dose-response relationship thus provided additional supportive evidence. There was also substantial overlap in lofexidine concentrations between the 2.4 mg/day and 3.2 mg/day doses. This observation combined with the shallow concentration-response relationship suggests that the 3.2 mg/day dose provides additional supportive evidence of the efficacy of the 2.4 mg/day dose.

Figure 2 FDA's Exposure-Response Analysis using the Observed Concentrations at Day 2 and Change in SOWS-Gossop Score from Baseline Results from Study 3003-1



3.3.2 Is the proposed general dosing regimen appropriate?

As there is no significant improvement in effectiveness from 2.4 mg/day as 3 tablets QID to 3.2 mg/day as 4 tablets QID, but the incidence of side effect such as bradycardia and hypotension is higher for 3.2 mg/day as 4 tablets QID, the usual dosage should start from 2.4 mg/day as 3 tablets QID. There should be 5 to 6 hours between each dose. The total daily dosage of lofexidine should not exceed 3.2 mg/day as 4 tablets QID (16 tablets daily) and no single dose should exceed 4 tablets with dosing guided by symptoms and side effects. The proposed dosing regimen of 3.2 mg QID has been demonstrated to be effective and safe so it is appropriate to be used in patients who require more than 2.4 mg/day for effectiveness and can tolerate the 3.2 mg/day dose. In addition, the results from Study 3003-1, and the internal exposure-response analyses for efficacy suggest that 2.4 mg/day is also effective. Therefore, patients should be given 2.4 mg/day initially and may be increased to the recommended dose of 3.2 mg/day as needed. The safety data submitted for lofexidine suggest that it causes clinically significant hypotension, bradycardia, and orthostatic hypotension in a dose-dependent fashion. A small number of subjects experienced syncope and there were frequent dose holds for meeting vital sign or symptomatic hypotension or bradycardia criteria in both dose groups, with the incidence being higher in the 3.2 mg group compared to the

2.4 mg group. Upon cessation of treatment with lofexidine, subjects were observed to experience rebound blood pressure elevations. These observed risks are consistent with the known effects of alpha-2 adrenergic agonists. They are monitorable and reversible upon discontinuation (Please refer to the clinical/statistical review by Dr. Pam Horn and Dr. Yi Ren for further details about the pivotal efficacy/safety data).

Additional internal exposure-response analysis of QTc interval concluded that QT prolongation and decrease in heart rate have been observed for lofexidine, however, no dose or exposure-response relationship could be identified in the submitted studies for QTc prolongation. Overall, the concern for QT prolongation with lofexidine appears to be mainly limited to settings in which it would be co-administered with other medicinal products that lead to QTc prolongation (e.g. methadone) (more details in QT review by Dr. Lars Johannesen).

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Yes, dosage adjustment is required for patients with hepatic or renal impairment.

Body Weight, Age, Gender, Race

No dosage adjustment is necessary based on body weight, age, gender, race and BMI. Cross-study comparison of the PK data from Phase 1 studies suggested no apparent relationships between PK parameters and age, body mass index (BMI), gender, race, or ethnicity. A weak trend for decreasing dose normalized PK parameters vs body weight was driven mainly by values at the lower end of the weight scale and did not seem to reflect a consistent trend across the range of body weights.

In the pivotal Phase 3 studies (3002 and 3003-1), doses were administered without adjusting for body weight, age, gender, race, or BMI. Based on the sparse PK samples collected in study 3003-1, race, ethnicity, and BMI did not appear to influence lofexidine plasma concentrations. On average, females had slightly higher plasma concentrations than males, which was accounted for by gender-related differences in body weight. This is consistent with the weak trend based on the cross-study comparison of the Phase 1 data. In addition, no statistically significant difference was found for primary efficacy in patient groups with different body weights (e.g., < 65 kg, 65-85 kg, > 85 kg) (See more details in clinical/statistical review).

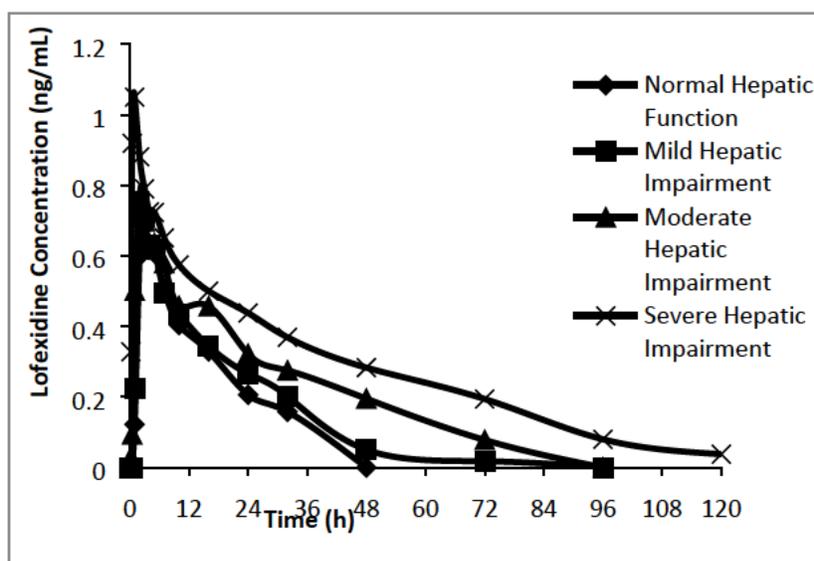
Hepatic impairment

Mean AUC values of lofexidine increased with severity of hepatic impairment so dosage adjustments are needed for various degrees of hepatic impairment.

The hepatic impairment study (Study LX1-1007) was a Phase 1, open-label, parallel-group, single-dose study of lofexidine HCl in adult subjects, including 5 subjects with normal hepatic function and 6 subjects each with mild, moderate, and severe hepatic impairment. For subjects with normal hepatic function, mean age, BMI, and gender distribution was targeted to be similar to the impaired hepatic function cohorts. Subjects received a single, oral dose of 0.4 mg lofexidine HCl. Blood samples were collected and urine samples were pooled for PK analysis at multiple time points over the 144 hours.

Lofexidine PK profiles are shown in **Figure 3**. PK parameters are summarized in **Table 3**. Mean C_{max} values were similar for subjects with normal, mild, and moderate hepatic impairment. Mean C_{max} values for subjects with severe hepatic impairment was approximately 67% higher than that for subjects with normal hepatic function. Mean AUC_{last} values in subjects with mild, moderate, and severe hepatic impairment were approximately 27%, 90%, and 200% higher, respectively, compared with subjects with normal hepatic function. A similar trend was observed for mean AUC_{inf} values. The T_{1/2} values increased as the severity of hepatic impairment increased. Mean T_{1/2} values were 14.91, 16.78, 37.01, 48.21 hours in subjects with normal, mild, moderate, and severe hepatic impairment, respectively. The sponsor proposed dosage reductions according to the severity of hepatic impairment.

Figure 3 Mean Lofexidine Plasma Concentration-time Profiles After Oral Administration of Lofexidine HCl 0.4 mg to Subjects with Normal Hepatic Function and Subjects With Mild, Moderate, or Severe Hepatic Impairment (Study LX1-1007)



Source: Study report LX1-1007 recreated Figure 2

Table 3 Mean (SD) Pharmacokinetic Parameters of Oral Lofexidine (2 tablets of 0.2 mg Lofexidine HCl) in Subjects with Various Degrees of Hepatic Impairment and the Control Group with Normal Hepatic Function (Study LX1-1007)

Pharmacokinetic Parameters	Normal Hepatic Function (N=5) ^a Mean (SD)	Hepatic Impairment		
		Mild (N=6) Mean (SD)	Moderate (N=6) Mean (SD)	Severe (N=6) Mean (SD)
T _{max} (h) – Mean (SD)	3.40 (1.14)	2.33 (0.52)	3.17 (2.04)	0.75 (0.27)
T _{max} (h) – Median (range)	3.00 (2.00, 5.00)	2.0 (2.00, 3.00)	3.00 (1.00, 7.00)	0.75 (0.50, 1.00)
C _{max} (ng/mL)	0.701 (0.123)	0.795 (0.143)	0.794 (0.208)	1.17 (0.296)
AUC _{last} (h•ng/mL)	10.46 (2.216)	13.29 (5.686)	19.83 (6.364)	31.77 (8.479)
AUC _{inf} (h•ng/mL)	14.79 (4.521)	16.71 (5.728)	28.87 (8.744)	41.01 (7.143)
AUC _{Extrap} (%)	27.25 (10.96)	21.45 (9.88)	30.98 (12.99)	23.25 (11.17)
λ _z (h ⁻¹)	0.0512 (0.0175)	0.0450 (0.0156)	0.0226 (0.0088)	0.0163 (0.0061)
T _{1/2} (h)	14.91 (5.07)	16.78 (4.97)	37.01 (21.19)	48.21 (19.37)
T _{last} (h)	30.40 (3.58)	40.33 (17.04)	57.00 (17.70)	92.00 (23.60)
C _{last} (ng/mL)	0.187 (0.0696)	0.141 (0.0377)	0.167 (0.0252)	0.136 (0.0347)
CL/F (L/h)	25.66 (8.349)	22.64 (6.007)	13.28 (4.666)	8.759 (1.440)
Total A _e (μg)	51.9695 (26.1609)	29.1765 (8.7505)	53.8064 (26.3336)	95.4028 (33.4476)
% Total A _e	14.82 (7.46)	8.32 (2.50)	15.34 (7.51)	27.20 (9.54)

Source: Study report LX1-1007 Table 6

Reviewer’s Comment: The sponsor’s proposed maximum dosing regimen for mild, moderate, and severe hepatic impairment were 2.4 mg/day as 3 tablets QID, (b) (4)

(b) (4)

perspective, we suggested the (b) (4) dosing frequency for moderate and severe hepatic impairment with 1.6 mg/day as 2 tablets QID, and 0.8 mg/day as 1 tablet QID (b) (4)

Table 4 Dosage Adjustment in Patients with Various Degrees of Hepatic Impairments

Hepatic Function	Increase in AUClast or AUCinf	Dosing Regimen	
		Sponsor’s Proposed (b) (4)	Reviewer’s Recommendation (b) (4)
Mild Impairment	27%	3 tablets QID (2.4 mg/day)	agree
Moderate Impairment	1.9-fold	2 tablets QID (1.6 mg/day)	2 tablets QID (1.6 mg/day)

Severe Impairment	3-fold	(b) (4)	1 tablet QID (0.8 mg/day)
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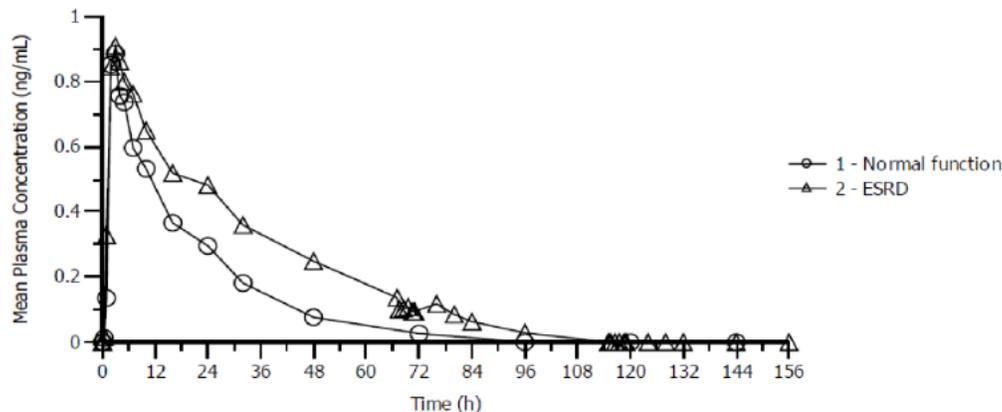
Renal impairment

Mean AUC values of lofexidine increased with severity of renal impairment so dosage adjustments are needed for various degrees of renal impairment.

Based on the results from a mass balance study, an approximately 15% to 20% of the administered dose excreted as unchanged drug in the urine. Therefore, exposure increase is anticipated in patients with renal impairment. The sponsor initially conducted a renal impairment study with a reduced design and then conducted a full design study to characterize the effect of various degrees of renal impairment on the pharmacokinetics of lofexidine per agency's recommendation. The recommendation was based on the preliminary study results from the reduced design study.

In a parallel-group single dose study (Study LX1-1008), the pharmacokinetics of lofexidine (0.4 mg) was determined in 8 end-stage renal disease (ESRD) subjects on 3 times weekly hemodialysis in comparison to 8 control subjects with normal renal function (eGFR \geq 90 mL/min/1.73 m²). For control subjects, age, BMI, and gender were matched with ESRD subjects. Lofexidine HCl was administered near the beginning of a 3-day, between-dialysis interval. Lofexidine PK profiles are shown in **Figure 4**. PK parameters are summarized in **Table 5**. Mean C_{max} values were similar for ESRD and normal renal function subjects. An approximately 80% greater AUC_{last} values was observed for ESRD subjects compared with normal renal function subjects. Mean T_{1/2} increased from 19.34 h in subjects with normal renal function to 26.41 h in subjects with ESRD. The impact of dialysis on the overall PK of lofexidine during a typical 4-hour dialysis was minimal; the drop in lofexidine plasma concentrations produced during the dialysis session was transient, with a rebound to nearly pre-dialysis concentrations after re-equilibration within a few hours following completion of the dialysis cycle. Mean lofexidine clearance during the first dialysis session was approximately 5-6 L/h, the 4-hour dialysis session removed an average of 2.86 μ g of lofexidine, less than 1% of the 351 μ g lofexidine free base administered.

Figure 4 Mean Lofexidine Plasma Concentration-Time Profiles after Administration of Lofexidine HCl 0.4 mg to Subjects with Normal Renal Function and ESRD (Study LX1-1008)



Source: Study report LX1-1008 Figure 2

Table 5 Summary of Lofexidine PK Parameters in ESRD and Control Subjects (Study LX1-1008)

Parameters	Renal Function	
	NRF N=8 Mean (SD)	ESRD N=8 Mean (SD)
T_{max} (h) ^a	3.00 (2.00, 3.00)	2.50 (2.00, 7.00)
C_{max} (ng/mL)	0.915 (0.217)	0.954 (0.160)
AUC_{0-32} (h•ng/mL)	13.25 (3.669)	17.83 (2.656)
AUC_{last} (h•ng/mL)	15.57 (5.528)	28.11 (6.761)
AUC_{inf} (h•ng/mL)	19.18 (5.864)	32.79 (7.123)
AUC_{extrap} (%)	19.66 (6.36)	14.56 (4.59)
λ_z (h ⁻¹)	0.0409 (0.0154)	0.0269 (0.0045)
$T_{1/2}$ (h)	19.34 (7.93)	26.41 (4.32)
T_{last} (h)	46.00 (17.50)	76.95 (16.27)
C_{last} (ng/mL)	0.134 (0.0193)	0.123 (0.0325)
CL/F (L/h) ^b	19.85 (5.994)	11.10 (2.156)
Total A_e (μg)	77.65 (21.20)	NC ^c
Total A_e (% of dose)	22.14 (6.05)	NC ^c
CL _R (L/h)	4.293 (1.354)	NC ^c
CL _d (L/h)	NC	5.680 (0.7234)

a T_{max} presented as median (minimum, maximum).

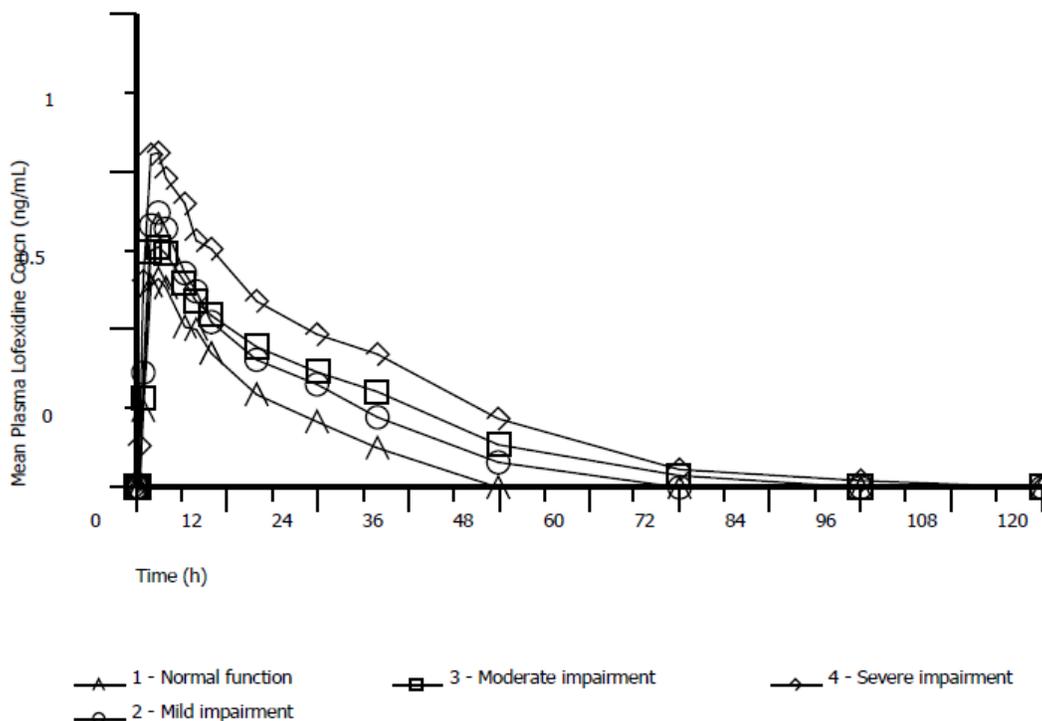
b CL/F values were calculated using lofexidine free base dose (0.3507 mg)

c Urine data were available for 1 ESRD subject only (Subject ^(b)(6)); the profile was incomplete with quantifiable lofexidine concentrations in urine for 6 hours through 144 hours post-dose.

Source: Study report LX1-1008 Table 5

In a later parallel-group single dose study (Study LX1-1012), the pharmacokinetics of lofexidine (0.4 mg) in 6 subjects with mild renal impairment, 6 subjects with moderate renal impairment, 5 subjects with severe renal impairment but not requiring dialysis were determined and compared to 6 control subjects with normal renal function. For control subjects, age, BMI and gender distribution was targeted to be similar to the impaired renal function cohorts. Lofexidine PK profiles are shown in **Figure 5**. PK parameters are summarized in **Table 6**. Mean C_{max}, AUC_{last}, AUC_{inf}, and t_{1/2} increased with severity of renal impairment. Mean C_{max} increased by 24.2%, 17.2%, and 54.3% for subjects with mild renal impairment, moderate renal impairment and severe renal impairment, compared to subjects with normal renal function, respectively. Mean AUC_{last} increased by approximately 57.4%, 87.0%, and 172% for subjects with mild renal impairment, moderate renal impairment, and severe renal impairment, compared to subjects with normal renal function, respectively. Similar trends are found for AUC_{inf}. Mean T_{1/2} was 14.24, 15.74, 20.63, and 22.29 hours in subjects with normal, mild, moderate, and severe renal impairment, respectively. Therefore, the sponsor proposed dosage reductions according to the severity of renal impairment.

Figure 5 Mean Lofexidine Plasma Concentration-time Profiles After Oral Administration of Lofexidine HCl 0.4 mg to Subjects with Normal Renal Function and Subjects With Mild, Moderate, or Severe Renal Impairment (Study LX1-1012)



Source: Study report LX1-1012 Figure 2

Table 6 Mean (SD) Pharmacokinetic Parameters of Oral Lofexidine (2 tablets of 0.2 mg Lofexidine HCl) in Subjects with Various Degrees of Renal Impairment and the Control Group with Normal Hepatic Function (Study LX1-1012)

Time (h)	Normal Renal Function (N = 6)			Renal Impairment								
				Mild (N = 6)			Moderate (N = 6)			Severe (N = 5)		
	Mean (ng/mL)	SD (ng/mL)	CV (%)	Mean (ng/mL)	SD (ng/mL)	CV (%)	Mean (ng/mL)	SD (ng/mL)	CV (%)	Mean (ng/mL)	SD (ng/mL)	CV (%)
T _{max} (h)	2.83	0.98	34.70	2.84	0.74	26.11	3.43	1.79	52.11	2.20	0.84	38.03
C _{max} (ng/mL)	0.739	0.0600	8.12	0.918	0.216	23.57	0.866	0.196	22.63	1.14	0.142	12.44
AUC _{last} (h•ng/mL)	10.28	1.855	18.04	16.18	4.412	27.27	19.22	4.003	20.83	27.98	5.781	20.66
AUC _{inf} (h•ng/mL)	13.53	3.102	22.92	19.48	3.609	18.53	23.42	3.751	16.02	32.82	5.489	16.73
AUC _{Extrop} (%)	23.36	4.75	20.34	17.98	9.82	54.59	18.37	5.67	30.87	15.13	3.54	23.38
λ _z (h ⁻¹)	0.0502	0.0092	18.27	0.0446	0.0056	12.59	0.0343	0.0054	15.64	0.0319	0.0053	16.59
t _{1/2} (h)	14.24	2.87	20.15	15.74	1.99	12.65	20.63	3.39	16.44	22.29	4.22	18.94
T _{1/2} (h)	30.67	3.27	10.65	42.67	8.26	19.36	53.33	15.73	29.50	62.40	21.47	34.40
C _{last} (ng/mL)	0.154	0.0362	23.45	0.143	0.0422	29.53	0.144	0.0432	29.92	0.156	0.0430	27.50
CL/F (L/h)	26.94	5.466	20.29	18.53	3.391	18.30	15.29	2.376	15.54	10.89	1.530	14.05
CL (L/h)	19.31	3.918	20.29	13.28	2.431	18.30	10.96	1.703	15.54	7.806	1.097	14.05
V _z /F (L)	535.5	32.54	6.08	423.7	109.1	25.74	448.8	61.13	13.62	343.3	25.09	7.31

Note: CL/F, CL, and V_z/F values were calculated using lofexidine free base dose (0.3507 mg) and represent the overall CL/F, CL, and V_z/F calculated using data from the entire pharmacokinetic profile.

Source: Study report LX1-1012 Table 10

Reviewer’s comment: The sponsor’s proposed maximum dosing regimen for mild, moderate, and severe renal impairment/ESRD on dialysis were (b) (4) respectively (Table 7). Although they are reasonable from PK perspective, we suggested the (b) (4) dosing frequency for moderate and severe renal impairment/ESRD on dialysis with 1.6 mg/day as 2 tablets QID and 0.8 mg/day as 1 tablet QID, respectively, (b) (4). Because of the increases in lofexidine AUC_{last} in subjects with mild (57%) and moderate impairment (87%) are similar, the same maximum dose is recommended for mild and moderate renal impairment, 2 tablets QID.

Table 7 Dosage Adjustment in Patients with Various Degrees of Renal Impairment

Renal Function	Increase in AUC _{last} or AUC _{inf}	Dosing Regimen	
		Sponsor’s Proposed (b) (4)	Reviewer’s Recommendation (b) (4)

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No significant food effect has been identified so lofexidine may be administered with or without food. PK results obtained from the drug-drug interaction studies with paroxetine, a strong inhibitor of CYP2D6, and with methadone, buprenorphine, or naltrexone, agents which might be co-administered with lofexidine in patients withdrawing from opioids suggested that dosage adjustment is not warranted, however, close monitoring in subjects who are co-administered with CYP2D6 inhibitor may be needed.

Lofexidine is not found to be a substrate of P-gp. Lofexidine (12 μM) did not inhibit P-gp mediated digoxin efflux in Caco-2 cells, but a 73% inhibition of P-gp mediated quinidine transport in MDCK-II transfected cells by lofexidine (1.1 μM) was observed. The difference may be due to different P-gp binding sites for the substrates tested, or the transporter specificity associated with the different cell line. Lofexidine was not found to be an inhibitor of major transporter proteins, human OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE2-K, or BCRP. Lofexidine inhibits the cellular uptake of substrates by several transporters in MDCK-II transfected cells, including OCT1 (19.5%) and MATE1 (65.1%). The tested lofexidine concentration (1.1 μM) is approximately 50 times higher than expected steady-state peak plasma lofexidine concentrations (0.02 μM) so the inhibition of these transporters is not expected to be clinically significant.

Based on *in vitro* studies, lofexidine is primarily metabolized by CYP2D6, with CYP1A2 and CYP2C19 also capable of metabolizing lofexidine. *In vitro* studies suggest that lofexidine and its 3 major metabolites (LADP, LDPA, or 2, 6-DCP) did not inhibit or induce CYP450 isoforms (i.e., CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, and CYP3A4/5) except a slight inhibition of CYP2D6 with an IC_{50} of 4551 nM (approximately 225 times the steady-state C_{max} for lofexidine with 0.72 mg 4 times daily dosing). Lofexidine interaction with CYP2D6 substrates is not expected to be clinically significant.

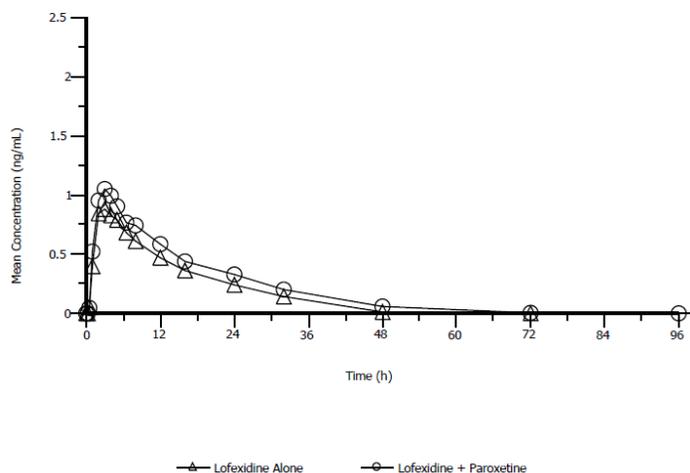
Drug-drug interactions were tested in PK studies with paroxetine, a strong inhibitor of CYP2D6, and with methadone, buprenorphine, or naltrexone, agents which might be co-administered with lofexidine in patients withdrawing from opioids. Lofexidine exposures were approximately 30% greater with co-administration of paroxetine. Naltrexone did not affect lofexidine PK, but lofexidine delayed naltrexone T_{max} , and slightly reduced the C_{max} of naltrexone (36%) and 6 β -naltrexol (19%), AUC values of naltrexone (8%), but did not affect the AUC values of 6 β -naltrexol. Buprenorphine and methadone PK were not altered by lofexidine in patients maintained on high doses of buprenorphine (16-24 mg/day Suboxone) or methadone (80-120 mg/day). Although these studies were not designed to evaluate if the PK of lofexidine were altered by long-acting opiates, in both studies, lofexidine concentrations remained within the clinical range observed in the larger Phase 3 trials with short-acting opiates.

Effect of Strong CYP2D6 Inhibitor (Paroxetine) on lofexidine

Paroxetine did not affect mean lofexidine C_{max} values and slightly increased mean AUC values by approximately 30%.

Based on the *in vitro* studies, lofexidine is a substrate for CYP2D6. Because exposure of lofexidine may be increased in subject who were co-administered with CYP2D6 inhibitors, the sponsor was recommended to conduct a drug interaction study a strong CYP2D6 inhibitor. Following the agency's recommendation, the sponsor conducted a drug-drug interaction study (Study LX1-1010) with a strong CYP2D6 inhibitor, paroxetine. Study LX1-1010 was an open-label, single sequence study in healthy subjects to compare the PK of lofexidine given alone to that during paroxetine administration. Subjects received a single oral dose of 0.4 mg lofexidine HCl on Days 1 and 13. Following a 72-hour washout period, subjects then received paroxetine 20 mg once daily (QD) on Days 4-6, 40 mg QD on Days 7-19, 20 mg QD on Day 20, and 10 mg QD on Days 21-22. On Day 13, a single 0.4 mg dose of lofexidine HCl was given 2 hours after the paroxetine dose. Blood samples for CYP2D6 genotyping were obtained from subjects prior to the first dose of lofexidine. Lofexidine PK profiles are shown in **Figure 6**. PK parameters are summarized in **Table 8**. Overall, mean lofexidine C_{max} values were similar. Mean AUClast and AUC_{inf} values were 32% and 30% greater, respectively, after co-administration of lofexidine + paroxetine (Day 13) compared to that after administration of lofexidine alone (Day 1). The mean t_{1/2} was slightly prolonged from 12.57 to 14.47 hours in the presence of paroxetine.

Figure 6 Mean Plasma Lofexidine Concentration-Time Profiles after Administration of Lofexidine HCl Alone (0.4 mg) on Day 1 and Lofexidine HCl (0.4 mg) + Paroxetine HCl (40 mg) on Day 13 (N = 24) (Study LX1-1010)



Source: Study report LX1-1010 Figure 2

Table 8 Summary of Pharmacokinetic Parameters of Lofexidine in the Absence and Presence of Paroxetine (Study LX1-1010)

Parameter	Day 1: Lofexidine HCl Alone (0.4 mg)				Day 13: Lofexidine HCl (0.4 mg) + Paroxetine HCl (40 mg)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (h)	24	2.80 (1.00, 5.00)			24	3.02 (1.00, 8.02)		
C _{max} (ng/mL)	24	1.03	0.366	35.56	24	1.12	0.257	22.99
AUC _{last} (h*ng/mL)	24	13.27	3.417	25.75	24	17.58	5.926	33.71
AUC _{inf} (h*ng/mL)	24	16.00	3.838	23.98	24	20.72	6.027	29.09
AUC _{Extrap} (%)	24	17.41	4.17	23.93	24	15.93	6.13	38.47
λ _z (h ⁻¹)	24	0.0571	0.0105	18.36	24	0.0506	0.0121	24.01
T _{1/2} (h)	24	12.57	2.52	20.05	24	14.47	3.43	23.69
T _{last} (h)	24	32.35	5.52	17.07	24	39.33	10.79	27.43
C _{last} (ng/mL)	24	0.150	0.0270	17.96	24	0.150	0.0352	23.47
CL/F (L/h)	24	23.23	5.884	25.33	24	18.19	4.857	26.69
Dependent Variable	Geometric Mean ^a Test		Ratio (%) ^b (Test/Ref)	90% CI ^c Lower		Upper	Power	ANOVA CV%
ln(C _{max})	1.0928	0.9829	111.18	103.32	119.64	0.9990	14.91	
ln(AUC _{last})	16.7383	12.8272	130.49	120.29	141.56	0.9967	16.56	
ln(AUC _{inf})	19.9622	15.5505	128.37	118.48	139.08	0.9972	16.30	

Source: Tables 12 and 13 of study report for protocol LX1-1010

Drug Interaction between Lofexidine and Naltrexone

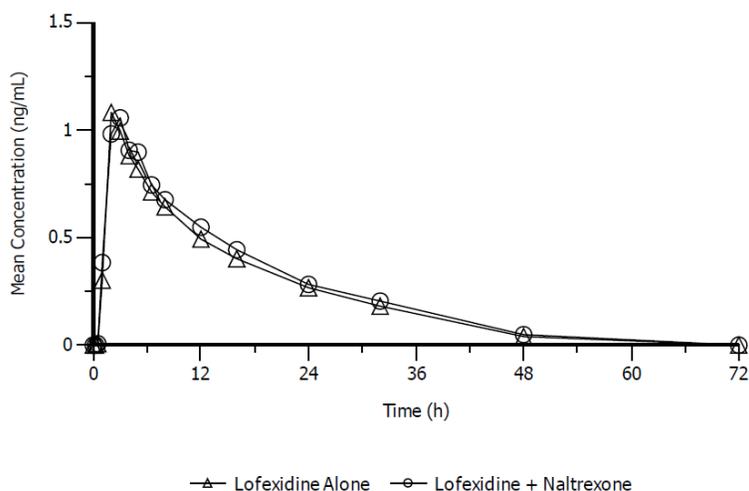
Naltrexone did not affect the C_{max} or AUC values of lofexidine. Lofexidine delayed naltrexone T_{max}, and slightly reduced the C_{max} of naltrexone (36%) and 6β-naltrexol (19%), AUC values of naltrexone (8%), but did not affect the AUC values of 6β-naltrexol.

As lofexidine is likely to be used in the transition from opiate agonist to opiate antagonist maintenance or possibly to attenuate withdrawal already precipitated by naltrexone administration, drug-drug interaction study (Study LX1-1009) was conducted. The primary objective was to determine the effect of naltrexone on the lofexidine PK. The secondary objective was to determine the effect of lofexidine on the steady-state PK of oral naltrexone. Study LX1-1009 was an open-label single-arm study in healthy subjects, two single doses of 0.4 mg lofexidine HCl (the first on Day 1 and the second on Day 11) and multiple daily doses of naltrexone (50 mg/day) (from Days 4 to 13) were administered to 24 adult healthy subjects. Single dose lofexidine PK were determined on Day 1 and 11. Naltrexone multiple dose PK were determined on Day 10 and 11.

Lofexidine, naltrexone, and 6β-naltrexol PK profiles are shown in **Figures 7, 8, and 9**, respectively. PK parameters for lofexidine, naltrexone, and 6β-naltrexol are summarized in **Table 9, 10, and 11**, respectively. Daily doses of naltrexone (50 mg/day) slightly delayed the median T_{max} of lofexidine by 1 hour but did not affect C_{max}, AUC_{last}, AUC_{inf}, or t_{1/2} values of lofexidine. Single dose of lofexidine (0.4 mg) delayed T_{max} values for both naltrexone and 6β-naltrexol (2-3 hours), decreased naltrexone C_{max} of naltrexone and 6β-naltrexol by 36% and 19%,

respectively. The steady state AUC0-24 values for naltrexone were slightly decreased (8%) but AUC0-24 values of 6 β -naltrexol were not affected. It is possible that naltrexone efficacy may be slightly reduced in some patients if used concomitantly with lofexidine. Changes in the PK of naltrexone in the presence of lofexidine are believed to be related to an interaction affecting naltrexone absorption from the gut.

Figure 7 Mean Lofexidine Concentration-Time Profiles after Administration of Lofexidine HCl Alone (2 x 0.2 mg) on Day 1 and Lofexidine HCl (2 x 0.2 mg) + Naltrexone HCl (50 mg) on Day 11 (Study LX1-1009)



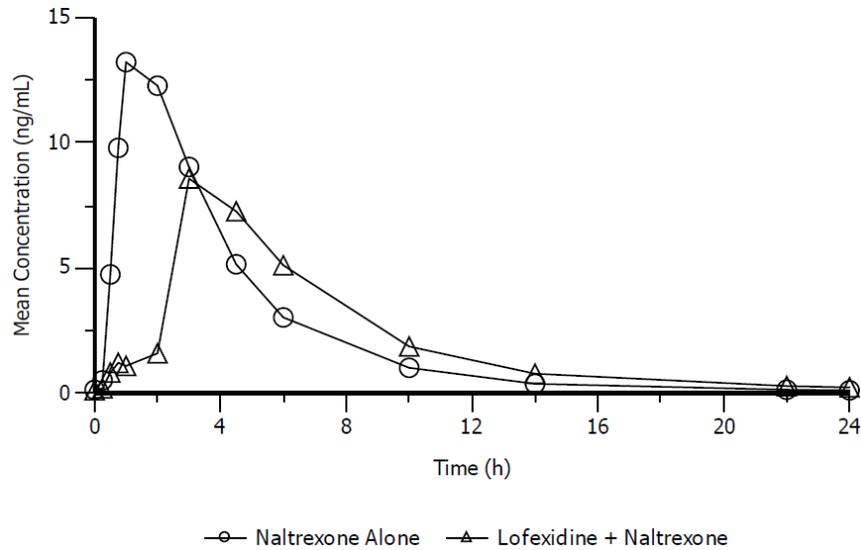
Source: Study report LX1-1009 Figure 2

Table 9 Plasma Pharmacokinetic Parameters for Lofexidine Alone (Reference) Versus Lofexidine plus Naltrexone (Test) (Study LX1-1009)

Parameter	Day 1: Lofexidine HCl Alone (2 x 0.2 mg)				Day 11: Lofexidine HCl (2 x 0.2 mg) + Naltrexone HCl (50 mg)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (h)	24	2.00	(2.00, 4.00)		24	3.00	(1.92, 5.00)	
C _{max} (ng/mL)	24	1.14	0.301	26.49	24	1.16	0.338	29.23
AUC _{last} (h•ng/mL)	24	15.17	4.901	32.31	24	16.44	4.923	29.94
AUC _{inf} (h•ng/mL)	24	18.48	5.316	28.77	24	19.94	5.218	26.16
AUC _{extrap} (%)	24	18.59	5.66	30.46	24	18.11	5.07	27.98
λ _z (h ⁻¹)	24	0.0500	0.0105	20.95	24	0.0481	0.0103	21.50
T _{1/2} (h)	24	14.50	3.23	22.27	24	15.05	3.12	20.75
T _{last} (h)	24	36.00	8.17	22.70	24	37.67	8.33	22.12
C _{last} (ng/mL)	24	0.157	0.0356	22.63	24	0.163	0.0404	24.88
CL/F (L/h)	24	20.77	7.199	34.66	24	19.06	6.599	34.62
Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI				
	Test	Ref		Lower	Upper			
ln(C _{max})	1.1138	1.0995	101.30	97.80	104.93			
ln(AUC _{last})	15.7157	14.3873	109.23	105.16	113.46			
ln(AUC _{inf})	19.2284	17.7135	108.55	104.02	113.28			

Source: Table 11 and 14 of study report for protocol LX1-1009

Figure 8 Mean Naltrexone Concentration-Time Profiles after Administration of Naltrexone HCl Alone (50 mg) on Day 10 and Lofexidine HCl (2 x 0.2 mg) + Naltrexone HCl (50 mg) on Day 11 (Study LX1-1009)



Source: Study report LX1-1009 Figure 3

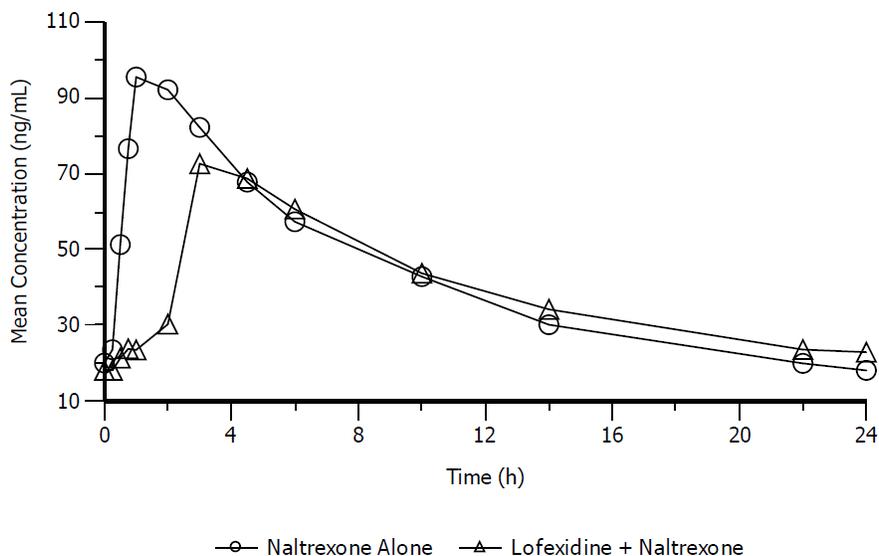
Table 10 Plasma Pharmacokinetic Parameters for Naltrexone in the Absence and Presence of Lofexidine (Study LX1-1009)

Parameter	Day 10: Naltrexone HCl Alone (50 mg)				Day 11: Lofexidine HCl (2 x 0.2 mg) + Naltrexone HCl (50 mg)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	24	1.00 (0.75, 3.00)			24	3.00 (0.73, 6.00)		
C_{max} (ng/mL)	24	17.5	7.80	44.59	24	10.5	5.27	50.44
AUC_{0-24} (h•ng/mL)	24	58.82	25.30	43.00	24	52.34	24.95	47.66
λ_z (h ⁻¹)	24	0.1680	0.0774	46.05	24	0.1498	0.0399	26.62
$T_{1/2}$ (h)	24	5.35	3.86	72.08	24	5.15	2.30	44.71
T_{last} (h)	24	22.92	2.81	12.24	24	23.93	0.05	0.22
C_{last} (ng/mL)	24	0.132	0.164	124.31	24	0.237	0.262	110.63
CL/F (L/h)	24	1305	2388	183.03	24	1029	398.5	38.73

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI	
	Test	Ref		Lower	Upper
$\ln(C_{max})$	9.2425	14.4050	64.16	46.12	89.26
$\ln(AUC_{0-24})$	47.6627	51.5749	92.41	72.00	118.62

Source: Table 12 and 15 of study report for protocol LX1-1009

Figure 9 Mean 6 β -naltrexol Concentration-Time Profiles after Administration of Naltrexone HCl Alone (50 mg) on Day 10 and Lofexidine HCl (2 x 0.2 mg) + Naltrexone HCl (50 mg) on Day 11(Study LX1-1009)



Source: Study report LX1-1009 Figure 4

Table 11 Plasma Pharmacokinetic Parameters for 6 β -naltrexol in the Absence and Presence of Lofexidine (Study LX1-1009)

Parameter	<u>Day 10:</u> Naltrexone HCl Alone (50 mg)				<u>Day 11:</u> Lofexidine HCl (2 x 0.2 mg) + Naltrexone HCl (50 mg)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	24	1.00 (0.00, 3.00)			24	3.78 (0.73, 10.00)		
C_{max} (ng/mL)	24	116	43.7	37.83	24	89.5	25.8	28.86
AUC₀₋₂₄ (h•ng/mL)	24	1025	289.5	28.25	24	945.1	207.3	21.93
λ_z (h⁻¹)	24	0.0600	0.0171	28.54	23 ^a	0.0470	0.0119	25.34
T_{1/2} (h)	24	12.34	3.01	24.38	23 ^a	15.66	3.94	25.15
T_{last} (h)	24	23.92	0.00	0.01	24	23.93	0.05	0.22
C_{last} (ng/mL)	24	18.2	7.27	40.01	24	23.0	6.98	30.36
Dependent Variable	Geometric Mean ^a		Ratio (%) ^b		90% CI			
	Test	Ref	(Test/Ref)		Lower	Upper		
ln(C_{max})	85.5354	106.1919	80.55		68.90	94.17		
ln(AUC₀₋₂₄)	922.0967	968.8171	95.18		86.43	104.81		

Source: Table 13 and 16 of study report for protocol LX1-1009

Effect of Lofexidine on Buprenorphine

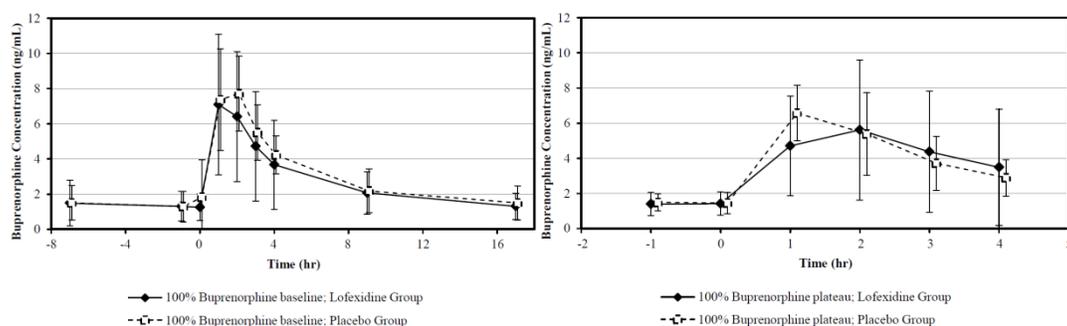
Lofexidine did not affect the buprenorphine or norbuprenorphine exposures in subjects on buprenorphine maintenance.

Study LX1-1006 is a randomized double-blind placebo-controlled multiple ascending dose study of lofexidine in subjects on buprenorphine maintenance. The primary objective of this study was to assess lofexidine related effects on QTc in subjects receiving buprenorphine (Suboxone) maintenance. The secondary objectives of the study were to evaluate the safety and tolerability of lofexidine; to describe effects on opiate withdrawal when lofexidine is introduced following a 50% buprenorphine dose reduction, as required to elicit a withdrawal response.

Subjects receiving a stable sublingual buprenorphine maintenance dose of 16 to 24 mg/day for at least 30 days were randomized in a 4:1 ratio to receive lofexidine plus buprenorphine or placebo plus buprenorphine. Inpatient treatment included buprenorphine baseline (1 day), initial lofexidine HCl titration (3 to 5 days), 1 or 2 lofexidine plateau (2 to 4 days), buprenorphine reduction (2 to 6 days), buprenorphine re-titration and discharge (2 to 4 days). Lofexidine HCl was initiated at 2 tablets (0.4 mg or placebo) QID and titrated in daily increments of a single tablet (0.2 mg or placebo) QID to a dose of 0.8 mg QID (or placebo), if tolerated by the subject. Lofexidine plateau started the day after subjects reached the maximum lofexidine HCl dose of 3.2 mg/day, or after they had reached their maximum tolerated lofexidine HCl dose. Buprenorphine doses during the treatment phase were administered 1 hour after the lofexidine or placebo doses so that the peak lofexidine and peak buprenorphine plasma concentrations would occur nearly simultaneously. Blood samples were collected on the second day of lofexidine plateau for buprenorphine and lofexidine PK analysis. Subjects had a 50% decrease in their daily buprenorphine dose during the buprenorphine reduction phase.

Buprenorphine PK profiles are shown in **Figure 10**. PK parameters for buprenorphine, norbuprenorphine, and lofexidine are summarized in **Tables 12, 13, and 14**, respectively. There was no apparent effect of lofexidine on the PK of buprenorphine and norbuprenorphine. The results for the buprenorphine pharmacokinetic parameters during the first Lofexidine Plateau were similar for the buprenorphine + lofexidine and the buprenorphine + placebo groups.

Figure 10 Mean Concentrations of Buprenorphine for Baseline Profiles (Left Panel) and Plateau (Right Panel) for the Buprenorphine plus Lofexidine and the Buprenorphine plus Placebo Groups (Study LX1-1006)



Source: Study report LX1-1006 Appendix 16.5 Synopsis Figures 8-9 and 8-10

Table 12 Summary of Pharmacokinetic Parameters of Buprenorphine (Study LX1-1006)

Variable	Study Phase	Buprenorphine + Lofexidine Group		Buprenorphine + Placebo Group	
		Mean ± SD	n	Mean ± SD	n
C_{max} (ng/mL)	Baseline	8.27 ± 4.50	24	8.74 ± 2.36	6
	Plateau	6.19 ± 4.19	24	6.81 ± 1.82	6
	2nd Plateau at 50%	3.05 ± 2.35	3	-	-
Ratio C_{max}	Plateau/baseline	0.851 ± 0.480	24	0.800 ± 0.201	6
T_{max} (hr)	Baseline	1.12 (1.10-3.32)	24	1.62 (1.12-2.13)	6
	Plateau	1.65 (1.08-4.10)	24	1.11 (1.10-2.12)	6
	2nd Plateau at 50%	1.13 (1.12-3.10)	3	-	-
AUC_{-1to4} (ng•hr/mL)	Baseline	22.0 ± 10.9	24	25.3 ± 7.9	6
	Plateau	18.9 ± 10.9	24	19.7 ± 6.6	6
	2nd Plateau at 50%	9.06 ± 5.36	3	-	-
Ratio AUC_{-1to4}	Plateau/Baseline	0.970 ± 0.524	24	0.804 ± 0.241	6
AUC_{-7to17} (ng•hr/mL)	Baseline	58.2 ± 31.3	24	64.5 ± 26.9	6
Cl/F (L/hr)	Baseline	406 ± 277	24	293 ± 132	6
λ_z (hr ⁻¹)	Baseline	0.0766 ± 0.0271	22	0.0892 ± 0.0357	5
$t_{1/2}$ (hr)	Baseline	10.1 ± 3.2	22	9.14 ± 4.49	5

^a The values for T_{max} are medians and ranges.

Source: Study report LX1-1006 Appendix 16.5 Synopsis Table 1-1

Table 13 Summary of Pharmacokinetic Parameters of Norbuprenorphine (Study LX1-1006)

Variable	Study Phase	Buprenorphine + Lofexidine Group		Buprenorphine + Placebo Group	
		Mean ± SD	n	Mean ± SD	n
C_{max} (ng/mL)	Baseline	3.38 ± 1.61	24	3.80 ± 1.34	6
	Plateau	2.94 ± 1.31	24	4.80 ± 1.62	6
	2nd Plateau at 50%	1.37 ± 1.00	3	-	-
Ratio C_{max}	Plateau/baseline	0.921 ± 0.351	24	1.28 ± 0.23	6
T_{max} (hr)	Baseline	2.12 (1.10-4.12)	24	2.12 (1.12-3.10)	6
	Plateau	2.61 (1.10-4.15)	24	2.10 (1.10-3.12)	6
	2nd Plateau at 50%	1.13 (1.12-3.10)	3	-	-
AUC_{-1to4} (ng•hr/mL)	Baseline	13.3 ± 6.4	24	15.1 ± 6.6	6
	Plateau	12.6 ± 5.4	24	21.1 ± 6.9	6
	2nd Plateau at 50%	5.65 ± 4.80	3	-	-
Ratio AUC_{-1to4}	Plateau/Baseline	1.03 ± 0.45	24	1.46 ± 0.31	6
AUC_{-7to17} (ng•hr/mL)	Baseline	58.0 ± 28.9	24	62.5 ± 28.5	6
λ_z (hr ⁻¹)	Baseline	0.0260 ± 0.0080	9	0.0449 ± 0.0203	3
$t_{1/2}$ (hr)	Baseline	29.6 ± 11.2	9	17.9 ± 8.3	3

^a The values for T_{max} are medians and ranges.

Source: Study report LX1-1006 Appendix 16.5 Synopsis Table 1-2

At 3.2 mg/day dose level, the mean (SD) C_{max} and AUC_{0-5h} were 5.21 (0.95) ng/mL and 23.7 (4.5) ng.h/mL, respectively. The mean (SD) lofexidine C_{max} and AUC_{0-5h} values for the 3 subjects receiving 3.2 mg/day during the second lofexidine plateau with 50% reduced buprenorphine dose were 5.36 (1.27) ng/mL and 23.7 (4.9) ng.h/mL, which were similar to the values for the subjects receiving 3.2 mg/day during the first lofexidine plateau.

Table 14 Summary of PK Parameters for Lofexidine (Study LX1-1006)

Parameter	Lofexidine Dose (mg/day)	1st Plateau		2nd Plateau	
		100% Maintenance Buprenorphine plus Lofexidine	n	50% Maintenance Buprenorphine plus Lofexidine	n
		Mean ± SD		Mean ± SD	
C _{max} (ng/mL)	1.6	3.08	2	-	-
	2.4	3.09	1	-	-
	3.2	5.21 ± 0.95	20	5.36 ± 1.27	3
	All	4.93 ± 1.15	23	5.36 ± 1.27	3
T _{max} (hr)	1.6	3.14 (2.13-4.15)	2	-	-
	2.4	1.05	1	-	-
	3.2	2.13 (1.03-4.13)	20	3.13 (0-3.15)	3
	All	2.13 (1.03-4.15)	23	3.13 (0-3.15)	3
AUC _{0.5} (ng•hr/mL)	1.6	13.8	2	-	-
	2.4	14.7	1	-	-
	3.2	23.7 ± 4.5	19	23.7 ± 4.9	3
	All	22.4 ± 5.4	22	23.7 ± 4.9	3
NC _{max} (ng/mL)/ (mg/day)	1.6	1.93	2	-	-
	2.4	1.29	1	-	-
	3.2	1.63 ± 0.30	20	1.68 ± 0.40	3
	All	1.64 ± 0.30	23	1.68 ± 0.40	3
NAUC _{0.5} (ng•hr/mL)/ (mg/day)	1.6	8.63	2	-	-
	2.4	6.11	1	-	-
	3.2	7.40 ± 1.39	19	7.40 ± 1.56	3
	All	7.45 ± 1.40	22	7.40 ± 1.56	3

Standard deviation values were not calculated for n < 3.

^a Values for T_{max} are medians and ranges.

Source: Study report LX1-1006 Appendix 16.5 Synopsis Table 1-3

Effect of Lofexidine on Methadone

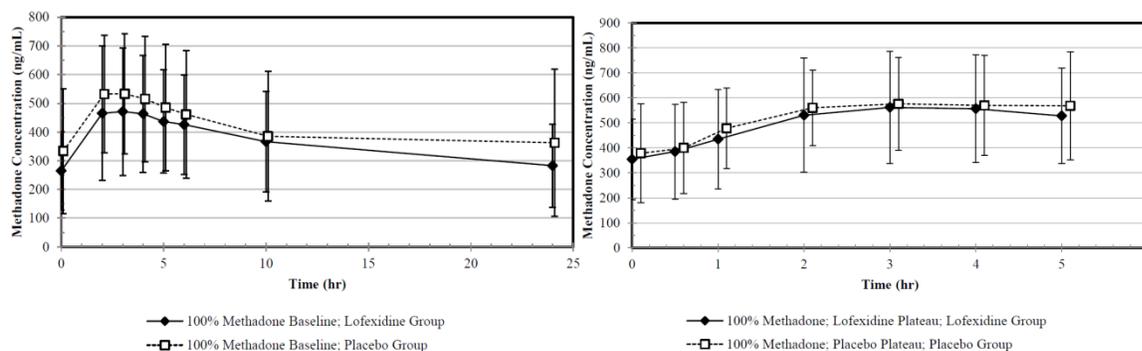
Lofexidine did not affect methadone exposure in subjects on methadone maintenance.

Study LX1-1005-2 was a randomized double-blind placebo-controlled multiple ascending dose study in subjects on methadone maintenance (80-120 mg/day). The primary objective of the study was to assess QTc interaction effects between lofexidine and methadone. The secondary objectives were to evaluate safety, tolerability; describe effects on opiate withdrawal when lofexidine was introduced following a 50% methadone dose reduction.

Subjects receiving a stable sublingual methadone maintenance dose of 80 to 120 mg/day (methadone HCl oral solution or tablet) for at least 4 weeks were randomized in a 3:1 ratio to receive lofexidine plus methadone or placebo plus methadone. Inpatient treatment included methadone baseline (1 day), 1 or 2 lofexidine HCl titration (3 to 5 days), first lofexidine plateau (2 to 4 days), methadone reduction (2 to 6 days), methadone re-titration and discharge (2 to 4 days). Lofexidine HCl was initiated at 2 tablets (0.4 mg or placebo) QID and titrated in daily increments of a single tablet (0.2 mg or placebo) QID to a dose of 0.8 mg QID (or placebo), if tolerated by the subject. Lofexidine plateau started the day after subjects reached the maximum lofexidine HCl dose of 3.2 mg/day, or after they had reached their maximum tolerated lofexidine HCl dose. Methadone doses during the treatment phase were administered at the same time as lofexidine or placebo doses. Blood samples were collected on the second day of lofexidine plateau for methadone and lofexidine PK analysis. Subjects had a 50% decrease in their daily methadone dose during the methadone reduction phase.

Methadone PK profiles are shown in **Figure 11**. PK parameters for methadone and lofexidine are summarized in **Tables 15** and **16**, respectively. Methadone PK parameters during baseline and the first lofexidine plateau were similar for the lofexidine and placebo groups. There was no apparent effect of lofexidine on the PK profiles of methadone.

Figure 11 Mean Concentrations of Methadone for Baseline Profiles (Left Panel) and Plateau (Right Panel) for the Methadone plus Lofexidine and the Methadone plus Placebo Groups (Study LX1-1005-2)



Source: Study report LX1-1005-2 Appendix 16.5 Figures 8-5 and 8-6

Table 15 Summary of Pharmacokinetic Parameters of Methadone (Study LX1-1005-2)

Variable	Study Phase	Lofexidine		Placebo	
		Mean ± SD	n	Mean ± SD	n
C _{max} (ng/mL)	Baseline	488 ± 226	18	551 ± 214	7
	Plateau	583 ± 225	18	602 ± 194	7
	2nd Plateau at 50%	407	2		
Ratio C _{max}	Plateau/baseline	1.24 ± 0.22	18	1.12 ± 0.16	7
T _{max} (hr)	Baseline	3.12 (2.12-5.23)	18	3.12 (2.10-4.12)	7
	Plateau	3.17 (2.05-5.12)	18	3.12 (1.90-5.20)	7
	2nd Plateau at 50%	4.12 (4.12-4.12)	2		
AUC ₀₋₅ (ng•hr/mL)	Baseline	2,106 ± 991	18	2,417 ± 1,054	7
	Plateau	2,528 ± 1,064	18	2,624 ± 889	7
	2nd Plateau at 50%	1,813	2		
Ratio AUC ₀₋₅	Plateau/Baseline	1.24 ± 0.21	18	1.12 ± 0.20	7
AUC ₀₋₂₄ (ng•hr/mL)	Baseline	8,682 ± 4,026	18	9,832 ± 5,367	7
Cl/F (L/hr)	Baseline	13.0 ± 4.9	17	14.3 ± 6.5	5
λ _z (hr ⁻¹)	Baseline	0.0240 ± 0.0101	16	0.0281 ± 0.0101 ^b	4 ^b
t _{1/2} (hr)	Baseline	34.6 ± 16.0	16	26.6 ± 7.4 ^b	4
NC _{max} (ng/mL)/ (mg/day)	Baseline	4.97 ± 2.31	18	4.96 ± 1.88	7
	Plateau	5.96 ± 2.35	18	5.42 ± 1.73	7
	2nd Plateau at 50%	8.20	2		
Ratio NC _{max}	Plateau/Baseline	1.24 ± 0.22	18	1.12 ± 0.16	7
NAUC ₀₋₅ (ng•hr/mL)/ (mg/day)	Baseline	21.4 ± 10.0	18	21.7 ± 9.2	7
	Plateau	25.8 ± 11.0	18	23.6 ± 8.0	7
	2nd Plateau at 50%	36.6	2		
Ratio NAUC ₀₋₅	Plateau/Baseline	1.24 ± 0.21	18	1.12 ± 0.20	7

^a The values for T_{max} are medians and ranges.

^b The apparent outlier values for Subject (b) (6) were excluded.

Source: Study report LX1-1005-2 Appendix 16.5 Synopsis Table 1-1

At 3.2 mg/day dose level, the mean (SD) C_{max} and AUC_{0-5h} were 8.18 (2.68) ng/mL and 34.8 (12.1) ng.h/mL, respectively. The lofexidine C_{max} and AUC_{0-5h} values for the 1 subject receiving 3.2 mg/day during the second lofexidine plateau with 50% reduced methadone dose were within the range for the subjects receiving 3.2 mg/day during the first lofexidine plateau. Cross-study comparison suggested that lofexidine levels in methadone maintained subjects appears to be higher than that in buprenorphine maintained subjects.

Table 16 Summary of Pharmacokinetic Parameters of Lofexidine (Study LX1-1005-2)

Parameter	Lofexidine Dose (mg/day)	Plateau at 100% Methadone Maintenance		2nd Plateau at 50% Methadone Maintenance		
		Mean ± SD	n	Mean	Range	n
C _{max} (ng/mL)	1.6	3.32	1			
	2.4	6.33	1	6.35	-	1
	3.2	8.18 ± 2.68	16	12.0	-	1
	All	7.81 ± 2.79	18	9.18	(6.35-12.0)	2
T _{max} (hr)	1.6	2.15 ^a	1			
	2.4	4.13 ^a	1	1.13 ^a	-	1
	3.2	3.11 (2.08-5.25) ^a	16	3.13 ^a	-	1
	All	3.11 (2.08-5.25) ^a	18	2.13 ^a	(1.13-3.13)	2
AUC ₀₋₅ (ng•hr/mL)	1.6	15.6	1			
	2.4	28.6	1	29.6	-	1
	3.2	34.8 ± 12.1	16	56.1	-	1
	All	33.4 ± 12.3	18	42.9	(29.6-56.1)	2
NC _{max} (ng/mL)/ (mg/day)	1.6	2.08	1			
	2.4	2.64	1	2.65	-	1
	3.2	2.56 ± 0.84	16	3.75	-	1
	All	2.54 ± 0.80	18	3.20	(2.65-3.20)	2
NAUC ₀₋₅ (ng•hr/mL)/ (mg/day)	1.6	9.77	1			
	2.4	11.9	1	12.3	-	1
	3.2	10.9 ± 3.8	16	17.5	-	1
	All	10.9 ± 3.6	18	14.9	(12.3-14.9)	2

^a Values for T_{max} are medians and ranges.

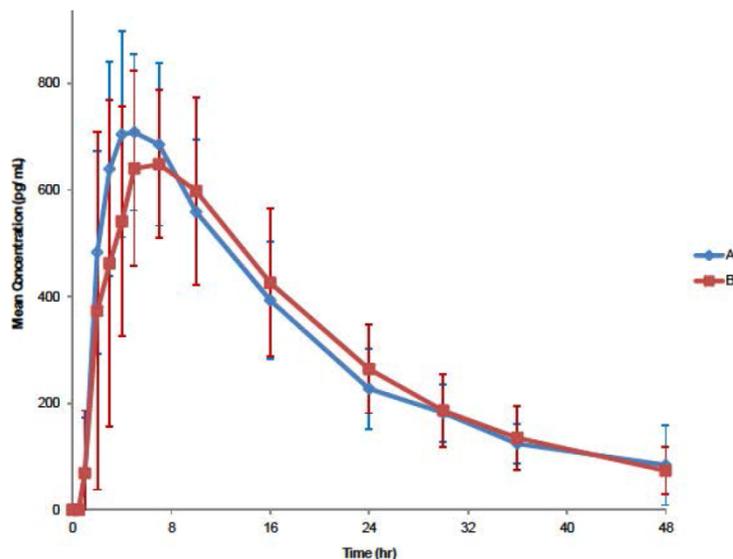
Source: Study report LX1-1005-2 Appendix 16.5 Synopsis Table 1-2

Effect of Food

High-fat high calorie meal did not affect the C_{max} and AUC values of lofexidine.

Food effect was assessed in a single dose, open-label, randomized, two-way crossover study (LX1-1004) in healthy subjects. Lofexidine PK profiles are shown in **Figure 12**. PK parameters are summarized in **Table 17**. Ingestion of a high-fat and high-calorie meal slightly delayed the median (min, max) T_{max} from 5.00 (3.00, 7.00) to 5.98 (2.00, 10.00) hours but did not alter the C_{max} and AUC values of lofexidine so lofexidine may be administered with or without food.

Figure 12 Mean (\pm SD) Lofexidine Concentration-Time Profiles after Administration of Lofexidine HCl 0.4 mg under Fasted Condition (A) and Fed Condition (B) (Study LX1-1004)



Source: Study report LX1-1004 Appendix 16.4 Figure 1

Table 17 Summary of Pharmacokinetic Parameters (Mean \pm SD) of Lofexidine in Fasted and Fed Condition (Study LX1-1004)

PK parameters	0.4 mg Lofexidine HCl (Fasted) (N=12)	0.4 mg Lofexidine HCl Fed (N=12)		
C_{max} (ng/mL)	0.744 \pm 0.181	0.732 \pm 0.180		
T_{max} (h)*	5.00 (3.00, 7.00)	5.98 (2.00, 10.00)		
AUC_{last} (h*ng/mL)	14.16 \pm 3.48	14.23 \pm 4.21		
AUC_{inf} (h*ng/mL)	15.40 \pm 3.89	16.00 \pm 4.77		
$T_{1/2}$ (h)	13.68 \pm 2.92	14.09 \pm 2.93		
Statistical Analysis				
PK parameters	Geometric Mean		Ratio (%)	90%CI
	Fed	Fasted		
C_{max}	0.712	0.724	98.34	88.66 – 109.09
AUC_{last}	13.62	13.73	99.24	91.02 – 108.20
AUC_{inf}	14.98	14.92	100.44	90.53 – 111.43
Source: Tables 11.4.3.1 and 11.4.3.2 in study report for protocol USWM-LX1-1004				

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be-marketed formulation?

The to-be-marketed formulation is the same as the clinical trial formulation. The quantitative composition of the clinical and proposed commercial (b) (4) drug products are provided in **Table 18**.

Table 18 Composition of Lofexidine Tablet

Tablet Component	Component	% w/w	Quantity (mg)	Function
(b) (4)	Lofexidine hydrochloride ¹	(b) (4)	0.20	Active ingredient
	Lactose (b) (4)		92.60	(b) (4)
	Citric acid (b) (4)		12.30	
	Microcrystalline cellulose		5.70	
	Calcium stearate		1.40	
	Povidone (b) (4)		1.10	
	Sodium lauryl sulfate		0.70	
			(b) (4)	
			(b) (4)	
	Opadry OY-S-9480		--	
			(b) (4)	
	TOTAL Tablet Weight (mg)		116.00	

¹ Provides 0.18 mg lofexidine free base per tablet

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation

Table 19 Summary of Analytical Assays for Lofexidine

	Validation report	Study (Report)	Precision (%CV)	Accuracy (% Bias)
Lofexidine in Heparinized	(b) (4) 1002919 - re-validated by	LX1-1002 (1003617) QCs: 0.15, 2, and 8 ng/mL	2.3 – 4.0%	-9.1 - -6.7%

Human Plasma	(b) (4) ATM-1423 LC/MS/MS 0.05 – 10 ng/mL 0.2 mL plasma	LX1-1003 (02749MZ) QCs: 0.15, 0.8, and 2 ng/mL	3.1 - 3.6%	-7.3 - -6.5%
		LX1-1004 (3006001) QCs: 0.15, 2, and 8 ng/mL	2.1 – 3.3%	-8.0 - -5.3%
		LX1-1011 (01496KM) QCs: 0.15, 2, and 8 ng/mL	1.1 – 2.4%	-13 - -0.4%
Lofexidine in Human Plasma Containing K2EDTA	(b) (4) 3006114 - further re- validated by (b) (4) ATM-1801 LC/MS/MS: 0.1 – 10 ng/mL 0.025 mL plasma	LX1-1005-2 (3006758) QCs: 0.3, 1.5, and 8 ng/mL	4.2 – 6.0%	-7.0 - -1.3%
		LX1-1006 (3006317) QCs: 0.3, 1.5, 8 ng/mL	3.1 – 4.6%	-1.3 – 2.7%
		LX1-1007 (4001370) QCs: 0.3, 0.75, 1.5, and 8 ng/mL	3.4 – 9.6%	-8.4 - -0.7%
		LX1-1008 (4002566) QCs: 0.3, 1.5, 8 ng/mL	2.0 – 4.0%	-0.7 – 3.8%
		LX1-1009 (4002690) QCs: 0.3, 1.5, and 8 ng/mL	4.5 – 5.2%	2.0 – 3.6%
		LX1-1010 (4004306) QCs: 0.3, 1.5, an 8 ng/mL	2.4 – 15.8%	-5.8 - -1.7%
		LX1-1012 (4004500) QCs: 0.3, 1.5, and 8 ng/mL	2.7 – 6.4%	-9.3 - -3.7%
		LX1-1013 (4004831) QCs: 0.3, 1.5, and 8 ng/mL	1.8 – 4.6%	-5.3 - -4.0%
		LX1-3003-1 (3006997) QCs: 0.3, 1.5, and 8 ng/mL	2.2 – 5.9%	-3.9 – 7.0%
		LX1-3003-2 (4002170) QCs: 0.3, 1.5, and 8 ng/mL	3.5 – 4.5%	-0.7 – 0.4%
Lofexidine in Human Urine	(b) (4) 3007081 LC/MS/MS ATM-1925 0.05 to 50 ng/mL 0.2 mL urine	LX1-1007 (4001370) QCs: 0.15, 2.5, and 40 ng/mL	3.2 – 8.6%	-2.3 – 3.3%
		LX1-1008 (4002566) QCs: 0.15, 2.5, and 40 ng/mL	3.6 – 6.7%	-5.8 – 6.0%
		LX1-1012 (4004500) QCs: 0.15, 2.5, and 40 ng/mL	4.0 – 6.2%	-6.5 - -0.7%
Lofexidine in Human Dialysate	(b) (4) 4002554 LC/MS/MS ATM-2066 0.01 to 1 ng/mL 0.3 mL dialysate	LX1-1008 (4002566) QCs: 0.03, 0.15, and 0.8 ng/mL	--	-5 - -1%
Lofexidine in Human Plasma Ultracentrifug	(b) (4) 4001411 LC/MS/MS ATM-2048 0.05 to 5 ng/mL	LX1-1007 (4001370) QCs: 0.15, 0.75, and 4 ng/mL	1.6 – 4.0%	-4.7 – 1.3%
		LX1-1008 (4002566)	--	-4.7 - -3.6%

e	0.05 mL mixed matrix	QCs: 0.15, 0.75, and 4 ng/mL		
Lofexidine Metabolites 2, 6-DCP and LDPA in human plasma	(b) (4) 4004115 LC/MS/MS ATM-2181 0.5 to 10 ng/mL for DCP and 0.25 to 5 ng/mL for LDPA 0.1 mL plasma	LX1-1013 (4004831) DCP QCs: 1.5, 4.5, and 8.5 ng/mL	3.4 – 5.4%	-3.3 – 0.7%
		LX1-1013 (4004831) LDPA QCs: 0.75, 2.25, and 4.25 ng/mL	2.2 – 2.7%	-4.7 – 0.8%
Lofexidine metabolite LADP in plasma	(b) (4) 4004116 ATM-2190 LC/MS/MS 0.05 to 5 ng/mL 0.1 mL plasma	LX1-1013 (4004831) LADP QCs: 0.15, 0.75, and 4 ng/mL	1.9 – 2.8%	-4.8 - -3.2%
Methadone in plasma	(b) (4) 1004135 LC-MS/MS ATM-1505 0.5 to 150 ng/mL 0.2 mL plasma	LX1-1005-1 (3006420) QCs: 1.5, 15, and 120 ng/mL	2.9 – 5.6%	-6.7 – 1.3%
		(b) (4) 1004372 LC-MS/MS ATM-1896 3 to 900 ng/mL 0.1 mL plasma	LX1-1005-2 (3006758) QCs: 9, 80, and 720 ng/mL	5.6 – 7.8%
Buprenorphine and norbuprenorphine in plasma	(b) (4) 1004373 LC-MS/MS ATM-1899 0.5 mL plasma 0.05 to 25 ng/mL for buprenorphine and 0.04 to 20 ng/mL for norbuprenorphine 0.500 mL plasma	LX1-1006 (3006317) QCs (buprenorphine): 0.15, 2, and 20 ng/mL	3.5 – 5.8%	-7.0 - -5.0%
		LX1-1006 (3006317) QCs(norbuprenorphine): 0.12, 1.6, and 16 ng/mL	3.1 – 4.4%	-5.0 - -4.2%
Naltrexone and 6-β-naltrexol in plasma	(b) (4) 1004240 LC-MS/MS ATM-1656 0.05 to 20 ng/mL for naltrexone and 0.5 to 200	LX1-1009 (4002690) Naltrexone QCs: 0.15, 4, and 16 ng/mL	2.6 – 3.8%	-8.0 - -1.0%
		LX1-1009 (4002690) 6-β-naltrexol QCs: 1.5, 40, and 160 ng/mL	2.1 – 4.6%	-2.0 – 3.0%

	ng/mL for 6-β-naltrexol 0.2 mL plasma			
Paroxetine in plasma	(b) (4) 11-A38-V2 L-MS/MS ATM-2189 0.1 to 60 ng/mL 0.2 mL plasma	LX1-1010 (4004306) QCs: 0.3, 10, and 45 ng/mL	1.2 – 10.7%	1.1 – 11.7%

4.2 Detailed Labeling Recommendation

Additions are highlighted and deletions are ~~double-strikethrough~~ in Red.

Section 2.2 Dosage Recommendations for Patients with Hepatic Impairment

Recommended dosage adjustments based on the degree of hepatic impairment are shown in Table 1. (b) (4)
[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

Table 1: Dosage Recommendations in Patients with Hepatic Impairment

Table 1: Dosage Recommendations in Patients with Hepatic Impairment

	(b) (4)	Mild Impairment	Moderate Impairment	Severe Impairment
Child-Pugh score	(b) (4)	5-6	7-9	> 9
	(b) (4)	2.16 mg/day (3 tablets 4x/day)	1.44 mg/day (2 tablets 4x/day)	(b) (4) 0.72 mg/day (b) (4) 1 tablet (b) (4) 4x/day

Section 2.3 Dosage Recommendations for Patients with Renal Impairment

Recommended dosage adjustments based on the degree of renal impairment are shown in Table 2. LOFEXIDINE may be administered without regard to the timing of dialysis [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

Table 2: Dosage Recommendations in Patients with Renal Impairment

(b) (4)

Section 7.4 CYP2D6 Inhibitor - Paroxetine

Coadministration of LOFEXIDINE and paroxetine resulted in 28% increase in the extent of absorption of lofexidine. Monitoring the adverse events such as orthostatic hypotension and bradycardia when an inhibitor of CYP2D6 is used concomitantly with LOFEXIDINE.

Section 8.6 Hepatic Impairment

Hepatic impairment slows the elimination of LOFEXIDINE but (b) (4) exhibits less effect on the peak plasma concentration following a single dose. Dosage adjustments are recommended based on the degree of hepatic impairment (b) (4)

(b) (4) [see Dosage and Administration (2.2), Clinical Pharmacology (12.2)].

Section 8.7 Renal Impairment

Renal impairment slows the elimination of LOFEXIDINE but (b) (4) exhibits less effect on the peak plasma concentration following a single dose. Dosage adjustments are recommended based on the degree of renal impairment [see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].

Section 8.9 CYP2D6 Poor Metabolizers

Although the pharmacokinetics of LOFEXIDINE have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to LOFEXIDINE would be increased similarly to taking strong CYP2D6 inhibitors (approximately 28%). Monitoring the adverse events such as orthostatic hypotension and bradycardia in known CYP2D6 poor metabolizers. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) [see Clinical Pharmacology (12.3)].

Section 12.3 Pharmacokinetics

LOFEXIDINE shows approximately dose-proportional pharmacokinetics. Administration of LOFEXIDINE with food does not alter its pharmacokinetics. (b) (4)

Absorption

LOFEXIDINE is (b) (4) well absorbed and achieves peak plasma concentration 3 to 5 hours after administration of a single dose.

The absolute bioavailability of a single oral LOFEXIDINE dose (b) (4) 0.36 mg in solution) compared with an intravenous infusion (0.2 mg infused for 200 minutes) was 72% (b) (4). Mean LOFEXIDINE C_{max} after the oral dose and intravenous infusion was 0.82 ng/mL (at median T_{max} of 3 hours) and 0.64 ng/mL (at median T_{max} of 4 hours), respectively. Mean estimates of overall systemic exposure (AUC_{inf}) were 14.9 ng•h/mL and 12.0 ng•h/mL, respectively.

Distribution

Mean LOFEXIDINE apparent volume of distribution and volume of distribution values following the administration of an oral dose and an intravenous dose were 480.0 L and 297.9 L, respectively, which are appreciably greater than total body volume, suggesting extensive LOFEXIDINE distribution into body tissue.

LOFEXIDINE protein binding is (b) (4) approximately (b) (4) 55% (b) (4).

LOFEXIDINE is not preferentially taken up by blood cells. In a study comparing LOFEXIDINE concentrations in plasma and whole blood at the time of peak LOFEXIDINE concentrations in human volunteers, it was determined that red blood cells contain approximately 27% the LOFEXIDINE concentration of the plasma.

Metabolism

From absolute bioavailability results, approximately 30% of the administered LOFEXIDINE dose is converted to inactive metabolites during the first pass effect associated with drug absorption from the gut.

LOFEXIDINE and its major metabolites did not induce or inhibit any CYP450 isoforms, with the exception of a slight inhibition of CYP2D6 by LOFEXIDINE, with an IC₅₀ of 4551 nM (approximately 225 times the steady-state C_{max} for LOFEXIDINE with 0.72 mg 4 times daily dosing). Any LOFEXIDINE interaction with CYP2D6 substrates is not expected to be clinically significant.

LOFEXIDINE is (b) (4) metabolized when incubated *in vitro* with human liver microsomes (b) (4), the major contributor to the hepatic metabolism of LOFEXIDINE is CYP2D6, with CYP1A2 and CYP2C19 also capable of metabolizing LOFEXIDINE.

(b) (4)
The elimination half-life is approximately 12 (b) (4) hours and mean clearance is 17.6 L/h following an IV infusion. (b) (4)

A mass balance study of LOFEXIDINE showed nearly complete recovery of radiolabel in urine (93.5%) over 144 hours postdose, with an additional 0.92% recovered in the feces over 216 hours postdose. Thus, it appears that all, or nearly all, of the dose was absorbed, and that the primary route of elimination of the parent drug and its metabolites is via the kidney. Renal elimination of unchanged drug accounts for approximately 15% to 20% of the administered dose.

LOFEXIDINE has (b) (4) a terminal half-life of approximately 11 to 13 hours following the first dose. At steady-state, the terminal half-life is approximately (b) (4) 17 to 22 hours. Accumulation occurs up to 4 days with repeat dosing, following the recommended dosing regimen. (b) (4)

Specific Populations

(b) (4) *Hepatic Impairment*

Hepatic impairment slows the elimination of LOFEXIDINE but (b) (4) exhibits less effect on the peak plasma concentration following a single dose. In a study comparing the pharmacokinetics of LOFEXIDINE (0.36 mg) in mild, moderate, and severe hepatically impaired subjects to subjects with normal hepatic function (6 subjects in each hepatic function group), mean C_{max} values were similar for subjects with normal, mild, and moderate hepatic impairment. (b) (4)

(b) (4)

(b) (4) *Renal Impairment*

Renal impairment slows the elimination of LOFEXIDINE but (b) (4) exhibits less effect on the peak plasma concentration following a single dose. In a study comparing the pharmacokinetics of LOFEXIDINE (0.36 mg) in 8 end-stage renal disease subjects on 3 times weekly hemodialysis to 8 subjects with normal renal function matched for sex, age, and body mass index, mean C_{max} values were similar for end-stage renal disease and normal renal function subjects, indicating no change in maximum LOFEXIDINE exposure with renal impairment. (b) (4)

The impact of dialysis on the overall PK of LOFEXIDINE during a typical 4-hour dialysis was minimal; the drop in LOFEXIDINE plasma concentrations produced during the dialysis session was transient, with a rebound to nearly predialysis concentrations after re-equilibration within a few hours following completion of the dialysis cycle [see *Dosage and Administration (2.3)*, *Use in Specific Populations (8.6)*].

In a study comparing the pharmacokinetics of LOFEXIDINE (0.36 mg) in 6 subjects each with normal renal function, mild renal impairment, and moderate renal impairment as well as 5 subjects with severe renal impairment but not requiring dialysis, mean (b) (4) AUC_{last} , AUC_{∞} , and $t_{1/2}$ increased with severity of renal impairment. Mean C_{max} increased by 24.2%, 17.2%, and 54.3% for subjects with mild, moderate and severe renal impairment, compared to subjects with normal renal function, respectively. Mean AUC_{last} increased by approximately 57.4%, 87.0%, and 172% for subjects with mild, moderate, and severe renal impairment, compared to subjects with normal renal function, respectively. Similar trends are found for AUC_{inf} . (b) (4)

Dosage adjustments are recommended based on the degree of renal impairment

Drug Interaction Studies

LOFEXIDINE coadministered with methadone

In a double-blind placebo-controlled study of 23 patients maintained on a methadone dose of 80-120 mg/day and concomitantly administered LOFEXIDINE up to 2.88 mg/day, LOFEXIDINE did not alter the pharmacokinetics of methadone. LOFEXIDINE

concentrations may be slightly increased when coadministered with methadone; however, the increase at concentrations expected with recommended dosing is not clinically meaningful.

LOFEXIDINE coadministered with buprenorphine

In a double-blind placebo-controlled study of 30 subjects maintained on buprenorphine (16-24 mg/day) concomitantly administered LOFEXIDINE up to 2.88 mg/day, no pharmacokinetic or pharmacodynamic interactions between LOFEXIDINE and buprenorphine were seen.

LOFEXIDINE coadministered with naltrexone

In an open-label, single-arm study of 24 healthy subjects, naltrexone (50 mg/day) did not significantly alter the single-dose pharmacokinetics of LOFEXIDINE (0.36 mg). The alteration in steady-state pharmacokinetics of oral naltrexone was statistically significant in the presence of LOFEXIDINE. The t_{max} was delayed for both naltrexone and 6 β -naltrexol (2-3 hours), and overall exposure was slightly reduced when naltrexone was administered with LOFEXIDINE. (b) (4)

LOFEXIDINE coadministered with paroxetine

In an open-label, single-sequence study of 24 healthy subjects, the strong CYP2D6 inhibitor paroxetine (b) (4) 40 mg/day increased LOFEXIDINE (0.36 mg) C_{max} and AUC_{∞} by approximately 11% and 28%, respectively. (b) (4)

Monitoring the adverse events such as orthostatic hypotension and bradycardia when (b) (4) are used concomitantly (b) (4)

4.3 PK/PD Analyses

An independent PK/PD analysis was performed to further inform the efficacy of the 2.4 mg/day dose, which was only studied in one trial (Study 3003-1). Study 3003-1 was the only trial to include sparse PK sampling and thus was the only study available for analysis. The sparse sampling schedule was designed to collect data on initial exposure, the accumulation phase and at steady-state (Table 2) and was generally planned to coincide with ECG measurements. The overall PK population included 479 subjects, 243 in the 2.4 mg/day treatment group and 236 in the 3.2 mg/day treatment group. The SOWS-Gossop was completed by each subject at baseline (before assignment to treatment) and once daily at 3.5 hours after the study medication on Days 1 to 7. Subjects were instructed to consider their symptoms over the last 24 hour period or since the last time the subject took the test.

Table 2: Schedule for Collection of PK Samples in Study 3003-1.

Day and Time Sequence^a	Stage^b	Study Day	Time Point	Hours From First Dose (8 AM on Day 1)
D1T1	NA	1	Pre 8 AM	0
D1T2	Stage 1	1	Pre 1 PM	5
D1T3	Stage 2	1	4 PM	8
D1T4	Stage 2	1	5 PM	9
D2T1	Stage 3	2	Pre 8 AM	24
D3T5	Stage 4	3	9 PM	61
D3T6	Stage 4	3	10 PM	62
D4T1	Stage 4	4	Pre 8 AM	72
D6T5	Stage 4	6	9 PM	133
D6T6	Stage 4	6	10 PM	134
D7T1	Stage 4	7	Pre 8 AM	144
D7T2	Stage 4	7	Pre 1 PM	149
D7T3	Stage 4	7	4 PM	152
D7T4	Stage 4	7	5 PM	153

^a D = day of Treatment, T1 = predose 8 AM, T2 = predose 1 PM, T3 = 3 hr post 1 PM dose, T4 = 4 hr post 1 PM dose, T5 = 3 hr post 6 PM dose, T6 = 4 hr post 6 PM dose.

^b Stage 1 = first dose trough; Stage 2 = early accumulation phase; Stage 3 = transition to steady state; Stage 4 = steady-state phase. NA = not applicable.

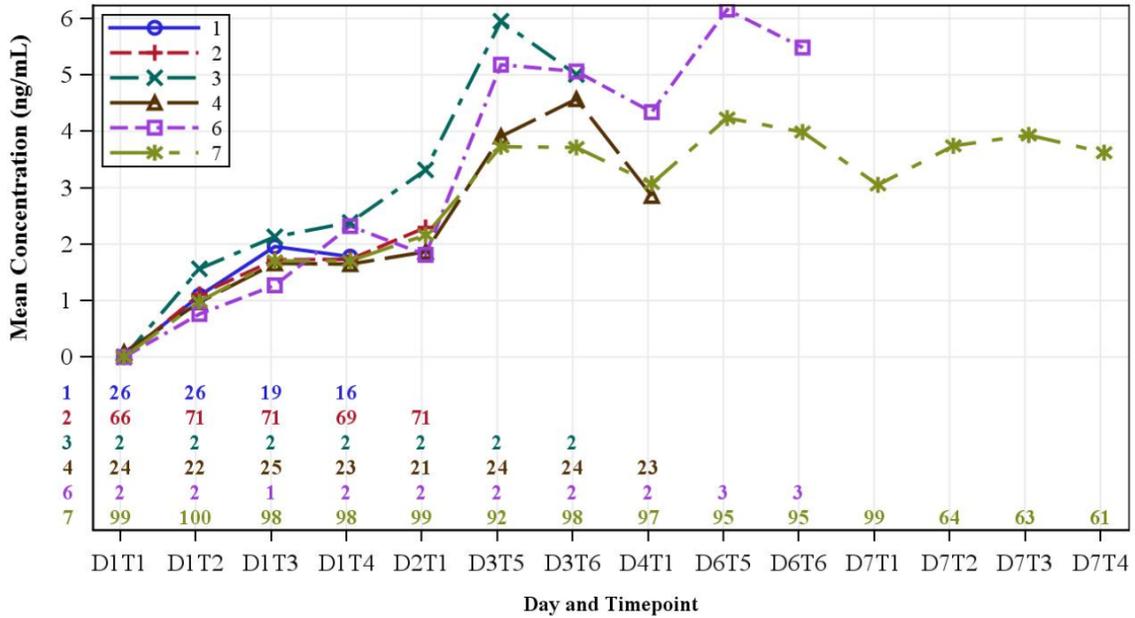
Source: uswm-lx1-3003-1 pharmacokinetic report, Table 1 on page 11 of 611

4.3.1 Applicant's Analysis

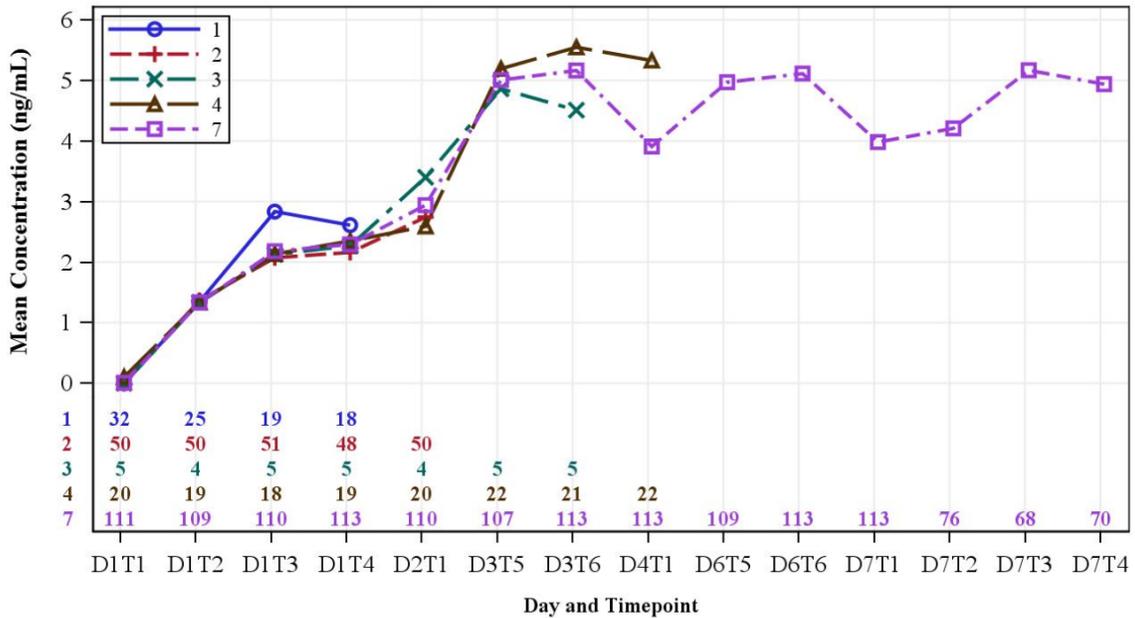
The Applicant plotted the mean plasma concentration over time based on how long subjects stayed in the study, as evidenced by their last PK value (Figure 1). Plasma concentrations were also plotted by reason for discontinuation in the study. Results suggested that subjects with higher maximum lofexidine concentrations were more likely to complete, which the Applicant notes is inconsistent with the expectation that increasing concentrations should increase the likelihood of significant adverse events.

Figure 1: Mean Lofexidine Concentration by Time Point of Last PK Sample

Lofexidine HCl 2.4 mg/day Treatment Group



Lofexidine HCl 3.2 mg/day Treatment Group

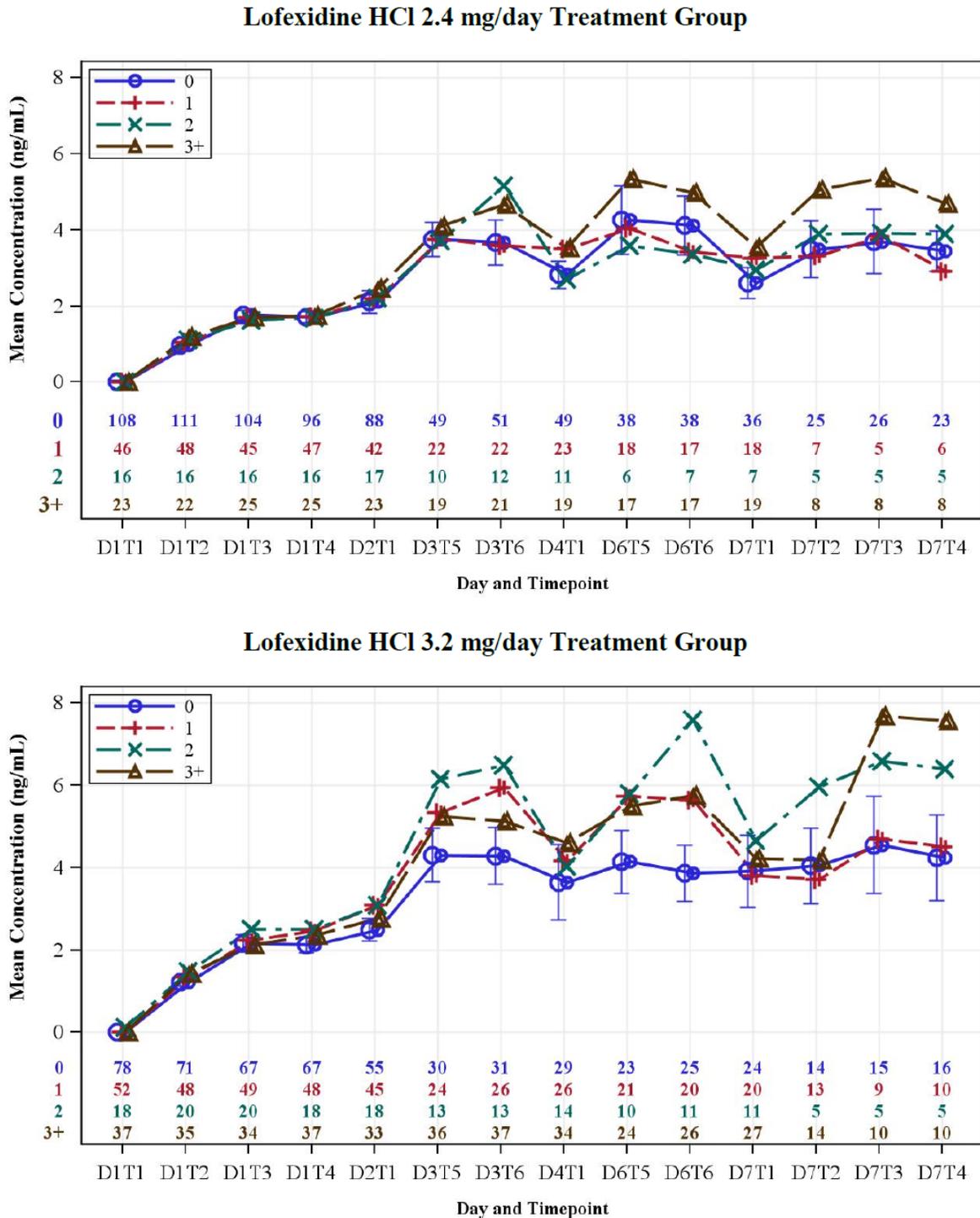


Source: uswm-lx1-3003-1 pharmacokinetic report, Figure 23 on page 45 of 611

The Applicant also plotted the mean lofexidine concentration for groups of subjects according to the number of days a subject had an adverse event of hypotension (Figure 2) or bradycardia. With the

exception of hypotension in the 2.4 mg/day group, there was a trend for the group of subjects with 0 days with an adverse event to show the lowest mean concentrations.

Figure 2: Lofexidine Plasma Concentration by Number of Days Subject had an Adverse Event of Hypotension



Source: uswm-lx1-3003-1 pharmacokinetic report, Figure 30 on page 55 of 611

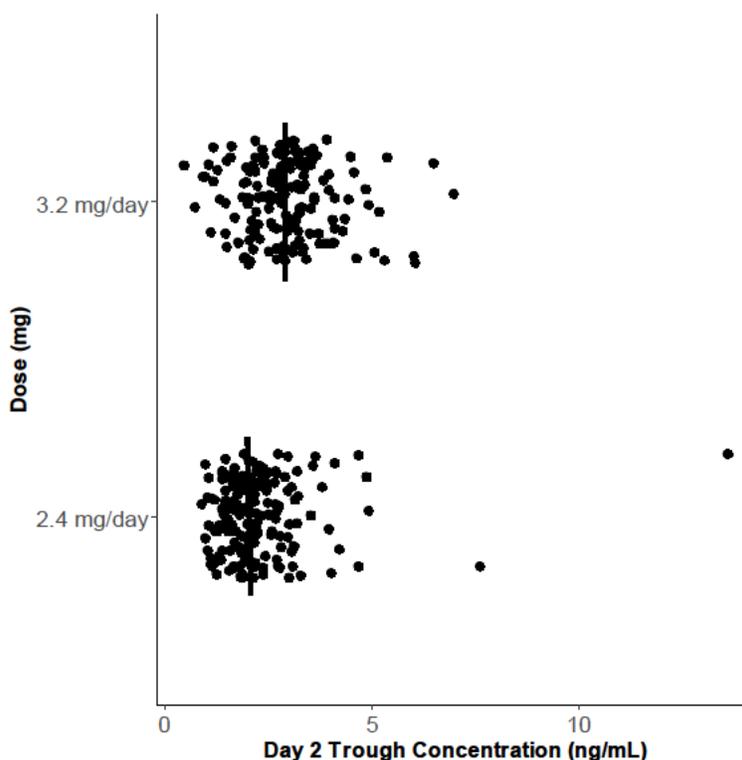
The Applicant concludes that their analyses were unable to identify any strong trends to support a useful quantitative exposure-response relationship due to limitations in the design of the study. For example, concentrations values may not accurately represent an individual's concentration at the time of events of interest. Furthermore, some events are influenced by the cumulative impact of earlier events that occurred during the treatment program.

Reviewer's Comments: The reviewer agrees that the study execution, including the timing of sampling, number of dropouts and the extent of dose holds and dose reductions, makes it difficult to identify exposure-response relationships. To address some of these limitations, the reviewer conducted independent analysis focusing only on early time points in which most patients had PK collected at their nominal dose and were still in the study.

4.3.2 Reviewer's Analysis

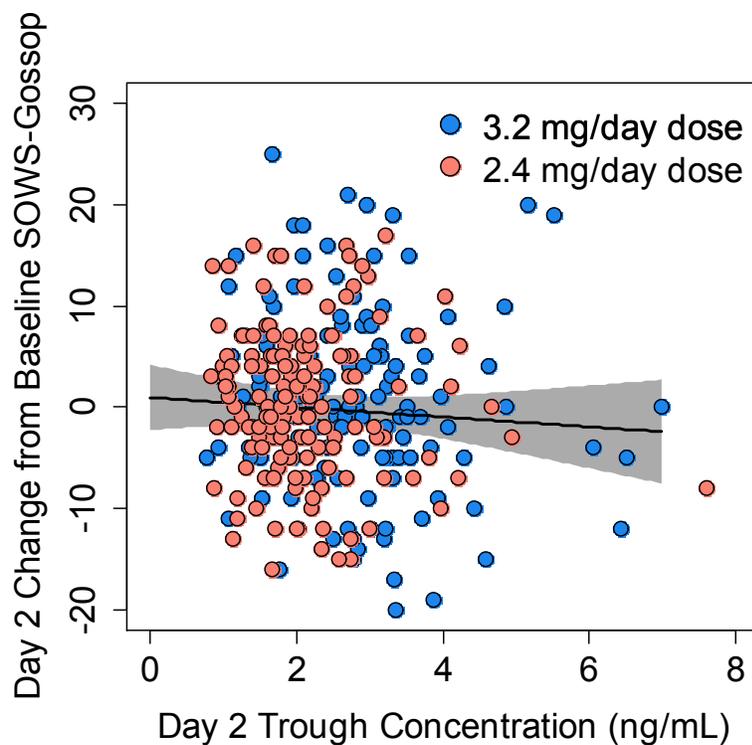
First, to illustrate the difference in lofexidine exposure between the two treatment arms due solely to PK variability (and not dose reductions), the reviewer plotted trough lofexidine concentrations on the morning of Day 2 vs. treatment group for patients who received all assigned doses on Day 1 (Figure 3). The dataset included 180 subjects receiving the 2.4 mg/day dose and 164 subjects receiving the 3.2 mg/day dose. The results show that there is considerable overlap in lofexidine exposures from the two doses due solely to PK variability. This suggests that the 3.2 mg/day treatment group can serve as an independent source of information to help inform and support the efficacy results observed in the 2.4 mg/day treatment group.

Figure 3: Day 2 Lofexidine Concentrations vs. Dose



The next step in the analysis was to examine the relationship between lofexidine concentrations and SOWS-Gossop at Day 2. Day 2 was used because the maximum drug effect in the study was observed on this day and most subjects were still in the study (and therefore had concentration measurements) and did not have their dose withheld or reduced. A total of 152 subjects in the 2.4 mg/day treatment group and 143 subjects in the 3.2 mg/day treatment group had both Day 2 concentration measurements and Day 2 Sows-Gossop scores and were included in the analysis. The results are presented in Figure 4. The relationship is relatively flat and consistent between the two dose groups and suggests that the data from the 3.2 mg/day treatment group predicts an effective response for the 2.4 mg/day treatment group.

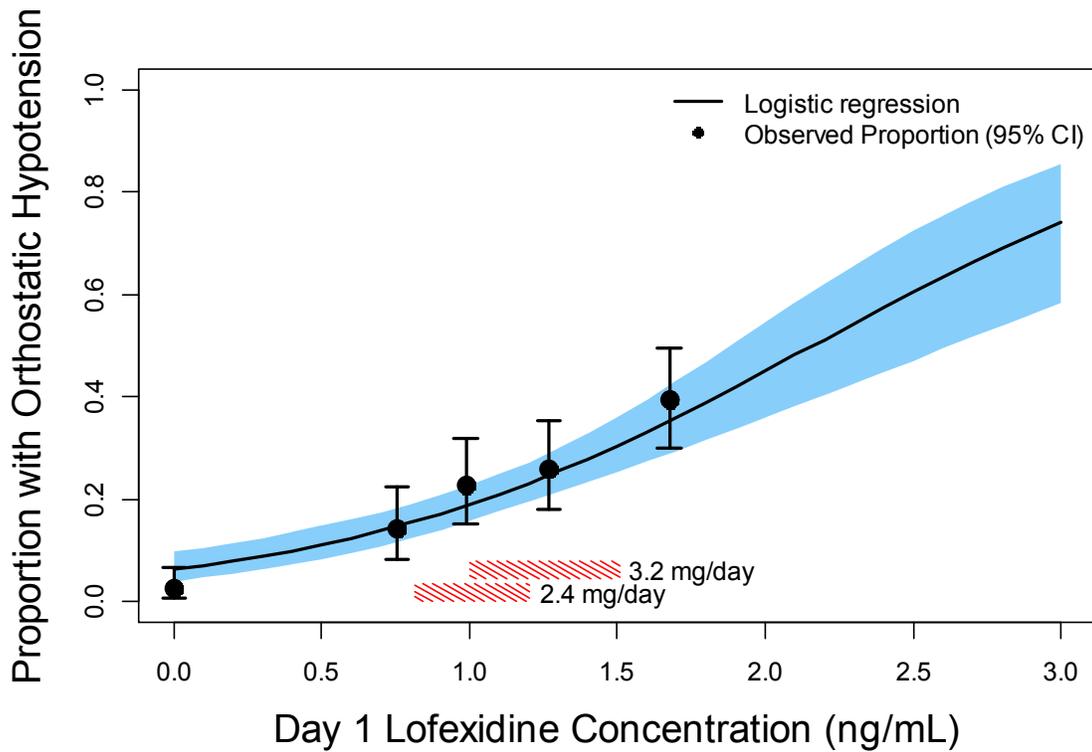
Figure 4: Relationship between Day 2 Change from Baseline SOWS-Gossop and Day 2 Lofexidine Concentration



To further inform risk-benefit considerations for the two dose levels, the reviewer also investigated the relationship between lofexidine concentrations and the incidence of orthostatic hypotension. For this analysis, lofexidine concentration on Day 1 after the first dose was used as the measure of exposure. This measurement was used because many occurrences of orthostatic hypotension occurred on Day 1 and doses were subsequently reduced on Day 1. The occurrence of orthostatic hypotension on Day 1 or Day 2 was chosen as the response variable because most instances occurred early in treatment. Also, orthostatic hypotension which occurred later in the study was likely to be more confounded by dropout and dose modifications throughout the course of treatment. Logistic regression was performed to describe the relationship between exposure and response. A total of 112 occurrences of orthostatic

hypotension were included in the analysis. The results are illustrated in Figure 5 and suggest that the relationship is relatively steep at the concentration range observed in the study.

Figure 5: Relationship between Orthostatic Hypotension (Day 1 or Day 2) and Day 1 Lofexidine Concentration. The red boxes correspond to the 25th percentile to 75th percentile of concentrations from each treatment arm.



It is worth noting that there are still significant limitations to the reviewer's analysis due to trial design and execution. Even though the reviewer focused on early measurements, a significant proportion of subjects (approximately 20%) dropped out of the study even within the first two days and were thus not included in the analysis. Also, the analysis does not take into account useful information at later time point in the study.

4.4 Individual Study Synopsis

4.4.1 Study LX1-1002: SAD and MAD

USWM-LX1-1002 Clinical Study Report Synopsis ⁴⁰⁷⁴⁴⁷

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: Pharmacokinetics of Ascending Single and Multiple Lofexidine Doses.		
Principal Investigator: Wayne E. Spencer, MD, HARI		
Investigators:		
Study center(s): Heart of America Research Institute (now Lee Research Institute), Shawnee, KS		
Publications (reference): None		
Studied period (years): Date first patient enrolled: 20 October 2008 Date last patient completed: 17 December 2008	Phase of development: 1	
<p>Objectives: The primary objective of this phase I clinical trial was to determine the single dose and multiple dose pharmacokinetics of lofexidine. The secondary objective was to determine the safety and tolerability of lofexidine in healthy normal male and female volunteers.</p>		
<p>Methodology: This was a single center, open-label, multiple-dose, three-period, single-sequence study with at least a 7-day washout period between each dosing period. A screening visit was held within 14 days prior to entering the clinical research center (CRC) on Day -1. During the screening visit the investigator performed a physical examination, medical history and medication history. In addition, the following was obtained: height (cm) and weight (Kg); vital signs (blood pressure and 30 second pulse rate); 12-lead ECG; clinical laboratories (hematology, clinical chemistry, urinalysis, Hepatitis A, B, and C, and HIV testing); pregnancy testing in the females (urine); and urine drug screening for all major drugs of abuse. For each treatment period, the subjects entered the CRC prior to dosing (Day -1). At that time, the following tests were performed: vital signs (blood pressure and 30 second pulse rate); on admission (in the afternoon) to the CRC and again in the evening of Day-1; 12-lead ECG; clinical laboratories (hematology, clinical chemistry, urinalysis); pregnancy testing in the females (urine); and urine drug screening for all major drugs of abuse. Prior to dosing on Day 0 of each treatment period, all vital signs, ECG, and clinical laboratories were reviewed by the investigator and found to be within the normal ranges. Values outside of normal</p>		

ranges were acceptable if they were deemed to be not clinically significant by the investigator. Urine drug screening results were all negative. For females, the pregnancy tests were negative.

The subjects fasted for at least 10 hours (water permitted) prior to dosing on Day 0 and for 3 hours following the Day 0 dose for Treatment Period 1. On Day 0 of Treatment Period 1, the subjects took a single 200 µg lofexidine dose with 240 mL of water (no ice). Blood samples for lofexidine concentrations were obtained at time 0 (just prior to the dose) and at 0.5, 1, 2, 3, 4, 5, 7, 10, 16, 24, 30 and 48 hr postdose. Subjects were discharged from the CRC following the 30 hour blood sample and returned to the CRC on Day 2 for 48 hr blood sample. After the 48 hr (Day 2) blood sample was obtained, the subjects were given the first dose of the four times daily (200 µg QID) doses of lofexidine, administered at 0800, 1300, 1800, and 2300 (+/- 15 min) with 240 mL of water (no ice). Subjects took the QID doses for five (5) days. Subjects remained as outpatients but returned to the CRC in the morning of Days 4, 5, and 6 prior to taking their AM lofexidine dose. At these times, a blood sample for lofexidine concentration was obtained. The subjects returned to the CRC in the evening of day 6. The subjects fasted for at least 10 hours (water permitted) prior to receiving the final dose on Day 7 and for 3 hours following the Day 7 dose. On the morning of Day 7, a blood sample for lofexidine concentration was obtained prior to the last dose of lofexidine. Following this dosing, blood samples were obtained at 0.5, 1, 2, 3, 4, 5, 7, 10, 16, 24, 30, 48, and 72 hours postdose. Subjects were discharged after the 30 hour blood sample was obtained on Day 8 and returned to the clinic on Days 9 and 10 for the 48 and 72 hour blood samples, respectively.

After at least a one week (7-10 days) washout from the final dose of the multiple dose phase, subjects returned to the clinic for a similar sequence of events with a 400 µg dose (single dose phase followed by a 5-day QID treatment phase) and the associated pharmacokinetic sampling periods. Subjects fasted for at least 10 hours before and 3 hours after the single (first) 400 µg dose but did not fast before or following the last dose on Day 7. In the cases where the subjects took the drug while not fasting, the doses of study medication were given immediately prior to the meals/snacks to improve the tolerability of the higher lofexidine doses.

In the multiple-dose phase, subjects returned to the clinic on the morning of Day 2 after having been discharged after the 30 hr blood sample on Day 1 and remained as inpatients until discharged after the 30 hour blood sample was obtained on Day 8. Subjects had blood samples taken on Days 4, 5, 6 and 7 prior to taking their AM lofexidine dose and at 0.5, 1, 2, 3, 4, 5, 7, 10, 16, 24, and 30 hours after the Day 7 dose. The subjects returned to the clinic on Days 9 and 10 for the 48 and 72 hour blood samples, respectively.

After at least a one week washout from the final dose of the 400 µg treatment, one half of the subjects returned to the clinic for a similar sequence of events with the 800 µg dose (single dose phase followed by a 5-day QID treatment phase) and the associated pharmacokinetic sampling periods. As this lofexidine dose level was reasonably tolerated after 48 hours of QID dosing, the remaining half of the subjects began the single and chronic dosing of lofexidine 800 µg. All subjects were kept in-house following the 48 hour postdose blood sample on Day 2 and throughout the five days of QID dosing until after collection of the 30 hour postdose blood sample on Day 8. Subjects had blood samples taken on Days 4, 5, 6 and 7 prior to taking their AM lofexidine dose and at 0.5, 1, 2, 3, 4, 5, 7, 10, 16, 24, and 30 hours after the Day 7 dose. Subjects returned in the mornings of Days 9 and 10 for the 48 and 72 hour postdose blood samples. Subjects were not fasted prior to the first lofexidine dose (Day 0) nor the last lofexidine dose (Day 7). In the cases where the subjects took the drug while not fasting, the doses of study medication were given immediately prior to the meals/snacks to improve the tolerability of the higher lofexidine doses. Adverse events were collected throughout each treatment period. At study completion or early discontinuation, each subject underwent a physical examination,

<p>routine clinical laboratory testing, vital signs, 12-lead ECG, urine testing for drugs of abuse and urine for pregnancy testing in females.</p> <p>Vital signs were obtained within 15 minutes prior to every dose of study medication administered in the CRC. Vital signs were obtained 3.5 hours ± 10 min after the single dose of study medication administered on Day 0 of each treatment period. ECGs were obtained 4 hours ± 10 min after the single dose of study medication administered on Day 0 of each treatment period. For the 800 µg dose, additional ECGs were obtained 4 hours ± 10 minutes after the first dose administered on each day of the inpatient QID dosing phase.</p>
<p>Number of patients (planned and analyzed): Twelve healthy male and female volunteers were planned and enrolled. It was planned that eight would complete all 3 treatment periods. Twelve volunteers completed the first treatment period, eight completed the first and second treatment periods, and four completed all three treatment periods.</p>
<p>Diagnosis and main criteria for inclusion: Subjects were healthy male and female volunteers between 18 and 45 years with a BMI of 19 to 29 kg/m², inclusive and were willing and able to provide written informed consent. Females were non-pregnant, non-lactating and had a negative pregnancy test before entering each of the 3 treatment periods and at study completion.</p>
<p>Test product, dose and mode of administration, batch number: Lofexidine 200 µg tablets, using a sufficient multiple of tablets for the 400 µg dose (2 tablets) and the 800 µg dose (4 tablets). All doses were given orally. The manufacturer was (b) (4) for US WorldMeds. The expiration date of the tablets was 16 May 2011. The lot number was 2271V.</p>
<p>Duration of treatment: Lofexidine was administered for 6 days (single dose followed 48 hours later with QID dosing x 5 days for a total of 22 doses) in each treatment period.</p>
<p>Reference therapy, dose and mode of administration, batch number: None.</p>
<p>Criteria for evaluation:</p> <p>Pharmacokinetics:</p> <p>The pharmacokinetic profiles following the single and multiple dosing of three treatment regimens—200 µg, 400 µg, and 800 µg.</p> <p>Safety: Adverse events (AEs), clinical laboratories, vital signs and 12-lead electrocardiogram (ECG).</p>
<p>Statistical methods:</p> <p>Pharmacokinetics: The primary statistical comparisons were based on the AUC₍₀₋₅₎, AUC_(0-inf), and C_{max} derived from the pharmacokinetic profiles of each subject's dose period. Single and multiple dose profiles were described separately. Regression lines for the dose-normalized parameters were tested for a value of the slope statistically significantly different from 0.0. Pharmacokinetics consistent with dose proportionality were concluded if the slope through all three doses was not statistically different from 0.00. Pairwise comparisons were done if part of the dose range appeared to be dose proportional, and part not dose proportional.</p> <p>Safety:</p> <p>All subjects that received one dose of the study medication (ITT population) were included in all listings, summaries, and analyses. Descriptive statistics of the data included counts, means, standard</p>

deviations, medians, coefficient of variation, minimums, and maximums for continuous data, and frequencies and percentages for categorical data.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS RESULTS:

Plasma Lofexidine Concentrations:

In the single dose segments, the time of observed mean maximal concentrations were 5, 4 and 3 hours postdose for the lofexidine 200 µg, 400 µg, and 800 µg doses, respectively. The corresponding observed mean C_{max} for each of these doses at the observed T_{max} were 339.83, 536.92, and 1058.14 pg/mL and appeared to be linear in relation to dose.

The mean maximal plasma concentrations for the multiple dose segments were observed at 3, 2, and 3 hours postdose for the lofexidine 200 µg, 400 µg, and 800 µg doses, respectively. The corresponding observed mean C_{max} for each of these doses at the observed T_{max} were 756.50, 2394.00, and 2407.00 pg/mL; however, there did not appear to be any linear relationship with dose. This lack of linearity may be due to the small number of subjects (N=8 and 4, respectively) in the lofexidine 400 and 800 µg multiple dosing segments. The 200 µg dose reached steady state on the third day of QID dosing, the 400 µg dose on the fourth day of QID dosing and the 800 µg dose achieved steady state on the second day of QID dosing.

Pharmacokinetics: The pharmacokinetics of lofexidine 200, 400, and 800 µg given under single dose conditions are in the table below.

Mean Pharmacokinetic Parameters for All Subjects in Each Treatment Period-Single Dose

Parameter (units)	Single Dose					
	200 µg		400 µg		800 µg	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
AUC ₍₀₋₅₎ (pg·hr/mL)	12	1155 ± 265	12	1837 ± 732	7	4209 ± 1567
AUC _(0-t_{1/2}) (pg·hr/mL)	12	5081 ± 1676	12	9184 ± 5453	7	20117 ± 8783
AUC _(0-∞) (pg·hr/mL)	12	6489 ± 2113	12	10868 ± 5906	7	22311 ± 9400
C_{max} (pg/mL)	12	365.9 ± 87.2	12	561.5 ± 223	7	1263.1 ± 331.2
T_{max} (hr)	12	3.70 ± 1.07	12	3.70 ± 1.07	7	3.40 ± 1.27
λ_z (1/hr)	12	0.06 ± 0.02	12	0.06 ± 0.03	7	0.06 ± 0.03
$T_{1/2}$ (hr)	12	11.32 ± 2.65	12	12.73 ± 3.68	7	12.42 ± 3.73
Cl/F ^a (L/hr)	12	30.1 ± 10.74	12	44.0 ± 29.32	7	37.0 ± 17.69
Dose Normalized AUC ₍₀₋₅₎	12	1155 ± 265	12	918 ± 366	7	1052 ± 392
Dose Normalized AUC _(0-t_{1/2})	12	6489 ± 2113	12	5434 ± 2953	7	5578 ± 2350
Dose Normalized C_{max}	12	365.9 ± 87.2	12	280.8 ± 111.5	7	315.8 ± 82.8

^a Calculated CL/F values at steady-state (Multiple Dose) are overestimates of the actual CL/F because of the unequal dosing intervals (5, 5, 5 & 9 hours) used with QID dosing.

The t_{max} and $t_{1/2}$ values were similar across doses. The values of t_{max} , C_{max} , $t_{1/2}$ and AUC_(0-inf) in the four subjects who completed all three dosing periods were similar to the all subjects' analysis. The C_{max} and AUC_(0-inf) appear to be linearly related with increases in doses in both the all subjects and four subjects' analyses. The pharmacokinetic parameters of lofexidine HCl 200, 400, and 800 µg given under multiple dose conditions are in the table below

Mean Pharmacokinetic Parameters for All Subjects in Each Treatment Period-Multiple Dose						
Parameter (units)	Multiple Dose					
	200 ug		400 ug		800 ug	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
AUC ₍₀₋₅₎ (pg·hr/mL)	12	3344 ± 1312	8	11126 ± 4865	4	10876 ± 7613
AUC _(0-t_{1/2}) (pg·hr/mL)	12	16961 ± 8331	8	61410 ± 30655	4	58247 ± 37270
AUC _(0-∞) (pg·hr/mL)	12	19403 ± 9245	8	69519 ± 39416	4	71508 ± 50504
C _{max} (pg/mL)	12	784.7 ± 280.2	8	2580.0 ± 884.7	4	2510.5 ± 1753.8
T _{max} (hr)	12	3.90 ± 1.51	8	2.80 ± 2.05	4	3.00 ± 0.82
λ _z (1/hr)	12	0.04 ± 0.01	8	0.03 ± 0.01	4	0.04 ± 0.01
T _{1/2} (hr)	12	17.12 ± 4.54	8	21.69 ± 7.13	4	20.18 ± 7.86
CL/F ^a (L/hr)	12	64.4 ± 36.83	8	40.6 ± 29.04	4	126.1 ± 133.55
Accumulation (Ratio)	12	3.00 ± 1.37	8	5.00 ± 1.03	4	3.10 ± 1.82
Dose Normalized AUC ₍₀₋₅₎	12	3344 ± 1312	8	5563 ± 2433	4	2719 ± 1903
Dose Normalized AUC _(0-t_{1/2})	12	19403 ± 9245	8	34760 ± 19708	4	17877 ± 12626
Dose Normalized C _{max}	12	784.7 ± 280.2	8	1290.0 ± 442.3	4	627.6 ± 438.5

^a Calculated CL/F values at steady-state (Multiple Dose) are overestimates of the actual CL/F because of the unequal dosing intervals (5, 5, 5 & 9 hours) used with QID dosing.

For the multiple dose segment, the mean calculated t_{max} for all subjects ranged from 2.8 to 3.9 hours postdose. There were no linear relationships of C_{max} and AUC_(0-∞) with increasing dose. There was substantial accumulation associated with QID dosing with the AUC after 5 days of dosing being 3 to 5 times its value following the single dose. The half-lives increased approximately 40% in the multiple dosing groups, as compared to following a single dose, ranging from 17.1 to 21.7 hours. This apparent t_{1/2} increase may be an artifact of the higher concentrations due to drug accumulation associated with multiple dosing and to the longer observation period utilized after the multiple dose phase (72 hours versus 48 hours). Similar findings were noted in the additional analysis of just the four subjects who completed all treatment periods and the all-subjects analysis except that C_{max} and AUC_(0-∞) in the lofexidine 400 µg group in the four-subjects analysis were approximately 20% lower compared to their respective values in the all-subject analysis.

Dose Proportionality: The dose-normalized AUC₍₀₋₅₎ parameter was determined to be dose proportional for both the single and the multiple doses. The dose-normalized AUC_(0-∞) as well as the dose-normalized C_{max} parameter were determined to be dose proportional for the multiple dose sequence. The dose-normalized AUC_(0-∞) was dose proportional for the single dose levels of 400 and 800 µg, while the dose-normalized C_{max} was dose proportional for the single dose levels of 200 and 400 µg.

SAFETY RESULTS:

Of the 12 subjects enrolled, all 12 completed the lofexidine 200 µg segment, four withdrew during and one after completing the lofexidine 400 µg segment. Three subjects withdrew during the lofexidine 800 µg segment. Four subjects completed all three treatment periods.

Overall, 11 of 12 subjects had at least one adverse event during the study. There did not appear to be any relationship between the type, incidence or frequency of adverse events and the lofexidine doses. There were a total of 196 adverse events and all were judged to be at least possibly related to lofexidine. Most of the adverse events were moderate in intensity (77%), with 15% being severe and 8% being mild. All adverse events resolved without sequelae. There were no serious adverse events.

Overall, the most common adverse events were in the system organ class, nervous system disorders followed by gastrointestinal disorders, vascular disorders, and psychiatric disorders. Of the nervous system disorders, the most common adverse events were somnolence and headache noted for all lofexidine dose levels. The most common adverse events in the gastrointestinal disorders were dry mouth and nausea seen at all lofexidine doses. Hypotension was the adverse event noted for vascular disorders in only the lofexidine 400 and 800 µg dose levels. Insomnia and anxiety were noted for the psychiatric disorders, but were only seen at the lofexidine 400 µg dose.

There were statistically significant decreases from baseline in the sitting systolic and diastolic blood pressures for all dose levels. Statistically significant decreases from baseline in sitting heart rates were noted for all dose levels, also.

No changes were found in the physical examinations compared to baseline. There were no clinically significant changes noted for any of the clinical laboratory tests. No clinically significant changes from baseline were seen in the ECGs for any dose. There were no significant changes in the QTc intervals from baseline for any dose levels.

CONCLUSION:

This study provided estimates for the pharmacokinetic parameters of lofexidine following single and multiple doses of 200, 400 and 800 µg. In the single and multiple dose segments, the times of maximal plasma concentration were similar, approximately 3-3.5 hours. The half-lives were similar across doses within the three single dose groups, range: 11.3-12.7 hours, and within the multiple dose groups, range: 17.1-21.7 hours. There was substantial accumulation associated with QID dosing with the AUC after 5 days of dosing being 3-5 times its value following the single dose. The apparent increase in the half-lives, of approximately 40%, noted following multiple dosing compared to a single dose may be an artifact of the higher concentrations achieved with QID dosing and the longer sampling schedule employed after the multiple dose sequence. Dose proportionality was demonstrated, or nearly so, for the AUCs and C_{max} for both the single and multiple doses.

The 200 µg dose, both as a single dose and in multiple doses over 5 days, was safe and well tolerated by these subjects. However, although higher doses were considered safe, tolerability was more limited. Following a single oral dose of 400 µg, one third of the 12 subjects withdrew or were removed from the study before completing all required blood draws. An additional subject was discontinued after completing chronic dosing with 400 µg and 3 more subjects discontinued during chronic dosing at 800 µg. Only 4 of the original 12 subjects completed all prescribed dosing. Ten of the 12 subjects who began the 400 µg sequence and all 7 of the subjects who received 800 µg experienced significant hypotension, although medical intervention was not required. Also, CNS side effects of somnolence and headache and the GI side effect of nausea were not well tolerated. Tolerability of Lofexidine in normal healthy volunteers appears to be more limited than in opioid dependent patients undergoing acute withdrawal, where 800 µg QID has been successfully used.

Date of the report: May 5, 2010, amended March 10, 2016

4.4.2 Study LX1-1003 (and -1003-1): Absolute BA and Mass Balance

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: A Single-center, Open-label, Two-Period, Two-Treatment, Randomized Sequence Study to Determine the Mass Balance and Absolute Bioavailability of a Single Oral Dose of ¹⁴ C-labeled Lofexidine Compared to a Single Intravenous Dose of Lofexidine		
Principal Investigator: Mark T Leibowitz, MD Investigators: Cynthia A Zamora, MD; Michael R. Natalino, MD, PA; Nancy K Hinitt, MD; Joe H Juren, MD; Jonathan Larson, MD; Steven Hinitt, MD, MPH, MPA; Hector Caraballo, MD; Wilhelm Muller, PA; Martha M Garza, MD; Therese Rizzo, MSN, FNP-BC		
Study center(s): Worldwide Clinical Trials Early Phase Services, LLC 2455 NE Loop 410, Suite 150 San Antonio, Texas 78217		
Publications (reference): None		
Studied period: First subject enrolled: 06 July 2011 Last subject completed: 20 August 2011	Phase of development: 1	
Objectives: <ul style="list-style-type: none"> • To determine the mass balance recovery of orally administered lofexidine HCl, • To determine the absolute bioavailability of a single oral dose of lofexidine compared to a single IV dose of lofexidine, and • To determine the tolerability of lofexidine oral solution and IV lofexidine. 		
Methodology: Study USWM-LX1-1003 was a single-center, open-label, 2-period, 2-treatment, randomized sequence-study in which 12 healthy subjects were scheduled to receive a single oral administration of an aqueous solution containing 400 µg lofexidine HCl plus a tracer amount of ¹⁴ C-lofexidine HCl (approximately 1.34 µg lofexidine HCl providing 280 nCi radioactivity) (Treatment A) and a single IV administration of lofexidine HCl 228 µg (equivalent to 200 µg lofexidine free base) in phosphate buffered saline (PBS) solution (Treatment B).		

<p>Subjects were screened within 28 days prior to study start. Only medically healthy subjects with clinically acceptable laboratory profiles and ECGs were enrolled in the study.</p> <p>Each subject received a single dose of Treatment A and a single dose of Treatment B in a randomized sequence, both administered open-label. Each treatment was administered following an overnight fast of at least 10 hours.</p> <p>Blood was drawn and urine was collected for clinical laboratory testing at screening, at each check-in, and at the end of the study. In addition, blood samples were obtained prior to dosing and postdose at selected times through 144 hours; pooled urine samples were collected for determination of radioactivity prior to dosing and postdose over selected time intervals through 144 hours; feces were collected for determination of radioactivity prior to dosing and, if possible, postdose up to 216 hours.</p> <p>In the assessment of mass balance in Study USWM-LX1-1003, multiple subjects failed to provide urine voids during collection intervals and these instances were not followed up on in a timely manner. Errors were also made in processing and analyzing the urine. Because of these factors, a decision was made to repeat the mass balance portion of the study under Protocol USWM -LX1-1003-1.</p> <p>Study USWM-LX1-1003-1 was a single-center, open-label, single-period follow-up study in which 6 healthy adult male subjects received a single oral administration of a solution containing nominally 400 µg lofexidine HCl plus a tracer amount of ¹⁴C-lofexidine HCl (approximately 1.2 µg lofexidine HCl providing 247 nCi radioactivity). The study was conducted in the same general manner as the mass balance portion of Study USWM-LX1-1003.</p>
<p>Number of Subjects (planned and analyzed):</p> <p>USWM-LX1-1003: Planned: 12; Enrolled: 12; Analyzed: PK 10, safety 12</p> <p>USWM-LX1-1003-1: Planned: 6; Enrolled: 6; Analyzed: 6</p>
<p>Diagnosis and main criteria for inclusion:</p> <p>Healthy adult, 18-50 years of age (inclusive), body mass index (BMI) between 18 and 30 kg/m² (inclusive), and a minimum weight of 50 kg. USWM-LX1-1003 included non-pregnant, non-breastfeeding females; USWM-LX1-1003-1 enrolled males only.</p>
<p>Test product, dose and mode of administration, batch number:</p> <p>USWM-LX1-1003 Treatment A (Test) and USWM-LX1-1003-1:</p> <p>Lofexidine oral solution</p> <p>Dose = solution containing approximately 400 µg lofexidine HCl and a tracer amount of ¹⁴C-lofexidine HCl</p> <p>USWM-LX1-1003: Lot 65041JUL11-01 USWM-LX1-1003-1: Lot 65041APR12-01</p>
<p>Reference therapy, dose and mode of administration, batch number:</p> <p>USWM-LX1-1003 Treatment B (Reference)</p> <p>Lofexidine intravenous (IV) solution</p> <p>Dose = 228 µg lofexidine HCl (equivalent to 200 µg lofexidine free base) in PBS administered IV via infusion pump at a rate of 1 mL/min (1 µg/min of lofexidine free base, or 1.14 µg/min of lofexidine HCl) for 200 min</p> <p>Lot: 19072011@8</p> <p>Duration of treatment:</p> <p>In Study USWM-LX1-1003, 2 single-dose treatments were administered with a washout period of at least 14 days between doses. In Study USWM-LX1-1003-1, a single dose was administered.</p>

<p>Criteria for evaluation:</p> <p>Pharmacokinetics:</p> <p>Blood samples were obtained at selected times through 144 hours; pooled urine samples were collected for determination of radioactivity using accelerator mass spectrometry (AMS) over selected time intervals through 144 hours; and feces were collected for determination of radioactivity using AMS for up to 216 hours.</p> <p>Lofexidine concentrations were assessed in plasma and urine (USWM-LX1-1003 only). Radioactivity was assessed in blood, urine, and feces. Radioanalysis samples were analyzed for lofexidine and its metabolites using accelerator mass spectrometry (AMS). Major radioactivity peaks were matched to lofexidine-related reference compounds to identify the major lofexidine-related compounds in plasma and urine (USWM-LX1-1003 only).</p> <p>Safety:</p> <p>Safety assessments included adverse events, laboratory parameters, vital signs, 12-lead (paper) electrocardiograms (ECGs), and Holter ECGs.</p>
<p>Statistical methods:</p> <p>Pharmacokinetics:</p> <p>In Study USWM-LX1-1003, plasma concentration-time data for lofexidine and ¹⁴C-lofexidine in plasma were analyzed by noncompartmental methods. Concentration-time data that were below the limit of quantification (BLQ) were treated as zero in the data summaries and descriptive statistics. The free base amounts of lofexidine were used for clearance, mass balance, and absolute oral bioavailability calculations. Concentrations of lofexidine in the various biomatrices are reported in terms of lofexidine free base.</p> <p>The following pharmacokinetic (PK) parameters were calculated: maximum drug concentration in plasma determined directly from individual concentration-time data (C_{max}), time to reach maximum concentration (T_{max}), observed terminal elimination rate constant (λ_z), observed terminal elimination half-life ($T_{1/2}$), area under the concentration-time curve from time zero to 6 hours postdose (AUC_{0-6}), area under the concentration-time curve from time zero to 72 hours postdose (AUC_{0-72}), area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), total systemic clearance after IV administration (CL), oral clearance (CL/F), volume of distribution after IV administration (V_d), volume of distribution after oral administration (V_d/F), and absolute oral bioavailability (F).</p> <p>Actual sample times were used for all PK and statistical analyses. Concentration-time data and PK parameters were summarized by analyte and treatment using descriptive statistics: n, mean, standard deviation, minimum, median, maximum, and percent coefficient of variation (CV%). In addition, the 90% confidence interval about the arithmetic mean for the absolute oral bioavailability was calculated using the standard error of the mean and the Student's t-distribution.</p> <p>In Studies USWM-LX1-1003 and USWM-LX1-1003-1, total radioactivity was determined by AMS in plasma, urine, and feces. Plasma samples were analyzed for combined lofexidine and metabolites by quantifying the radioactivity from the administered lofexidine present in plasma samples using AMS. ¹⁴C-lofexidine in urine was analyzed to determine urinary excretion of drug-related material per collection interval, total recovery, and percent of dose excreted in urine (Study USWM-LX1-1003) or urine and feces (Study USWM-LX1-1003-1).</p>
<p>Safety:</p> <p>AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 13.1. The incidence of treatment-emergent adverse events (TEAEs) was summarized by treatment, MedDRA system organ class, MedDRA preferred term, by investigator attribution of relationship to study drug and by severity.</p> <p>Changes from predose were summarized for laboratory parameters and vital signs; shift tables were also</p>

provided.

Holter ECG extractions were performed in duplicate from recordings made under resting conditions at predose and 3, 4, and 8 hours postdose. Change from predose in QTc with Fridericia's heart rate correction (QTcF) was the primary endpoint and change in QTc with Bazett's heart rate correction (QTcB) was a secondary endpoint. QTc intervals were analyzed descriptively and categorically (QTc interval prolongations > 450, > 480 and > 500 msec; QTc increases from predose > 30 and > 60 msec). Other secondary endpoints included change from predose in heart rate, BP, PR interval, and QRS duration.

SUMMARY – CONCLUSIONS

Results for both studies, USWM-LX1-1003 and USWM-LX1-1003-1, are summarized in this report.

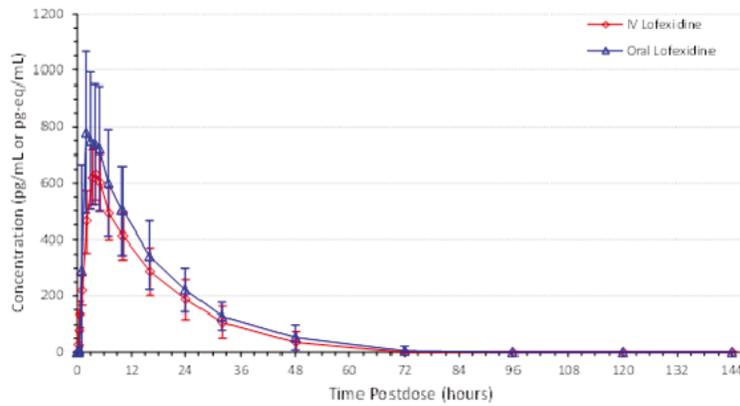
PHARMACOKINETIC RESULTS:

Lofexidine Plasma Concentrations and Pharmacokinetic Parameters:

In Study USWM-LX1-1003, 10 of 12 subjects were evaluable for PK analysis following both treatments. One subject discontinued from the study following the oral dose due to hypotension. A second subject was not evaluable for PK following the IV administration because the normal saline infusion and bolus injections administered in response to a hypotensive adverse event were administered into the same arm as was used for PK sampling, resulting in anomalous concentration results over a substantial portion of the PK observation window.

Mean lofexidine plasma concentration-time profiles after administration of lofexidine oral solution (Treatment A) and lofexidine intravenous solution (Treatment B) are illustrated in [Synopsis Figure 1](#) and [Synopsis Figure 2](#), and descriptive statistics for lofexidine plasma PK parameters are provided in [Synopsis Table 1](#). Lofexidine plasma concentration-time profiles for all subjects are illustrated in [Synopsis Figure 2](#) (Treatment A) and [Synopsis Figure 3](#) (Treatment B). After the administration of lofexidine oral solution, lofexidine plasma concentrations were relatively uniform between approximately 2 and 5 hours postdose and then followed an apparent first-order decline. After administration of lofexidine IV solution, peak lofexidine plasma concentrations were generally observed at the end of the infusion or the following sample and were followed by an apparent first-order decline. Concentrations remained above the assay lower limit of quantification (LLOQ) for 48 to 72 hours postdose. The mean (90% confidence interval) absolute bioavailability of lofexidine for the oral solution as based on the mean of the ratios in the study subjects for the oral to IV AUC_{inf} values was 0.7168 (0.5808, 0.8529) ([Synopsis Table 2](#)).

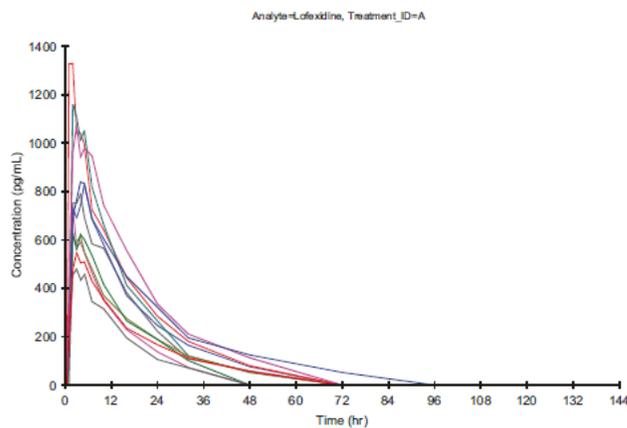
Synopsis Figure 1. Mean Lofexidine Plasma Concentration-Time Profiles After Administration of Oral Solution (Treatment A) and Intravenous Solution (Treatment B) (USWM-LX1-1003)



Note: Plasma concentrations below limit of quantification (50.0 pg/mL) were set to zero (0.00 pg/mL) in the data summaries. Error bars for A and B indicate the respective standard deviations.

Source: Figure 1 of Appendix 16.5

Synopsis Figure 2. Lofexidine Plasma Concentration-Time Profiles for All Subjects After Administration of the Oral Solution (Treatment A) (Study USWM-LX1-1003)



Note: Plasma concentrations below limit of quantification (50.0 pg/mL) were set to zero (0.00 pg/mL) in the data summaries.

Source: Figure 2 of Appendix 16.5

Synopsis Table 1. Summary of Plasma Pharmacokinetic Parameters of Lofexidine (USWM-LX1-1003)

Parameter	Treatment A Oral Solution				Treatment B IV Infusion (200 minutes)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	10	2.90	0.88	30.19	10	3.85	0.52	13.42
T _{max} (hr) median [range]	10	3.00 [2.00 – 4.00]			10	4.00 [3.33 – 5.00]		
C _{max} (pg/mL)	10	819	282	34.47	10	640	95.2	14.88
AUC ₀₋₆ (hr•pg/mL)	10	3541	1235	34.89	10	2789	445.1	15.96
AUC _{last} (hr•pg/mL)	10	13520	4977	36.83	10	10680	3112	29.14
AUC _{inf} (hr•pg/mL)	10	14860	5261	35.41	10	12030	3247	26.98
AUC _{Extrap} (%)	10	9.55	3.08	32.21	10	11.64	2.50	21.51
λ _z (hr ⁻¹)	10	0.0553	0.0121	21.80	10	0.0603	0.0141	23.43
T _{1/2} (hr)	10	13.18	3.40	25.76	10	12.05	2.71	22.50
T _{last} (hr)	10	45.60	11.96	26.22	10	39.20	9.58	24.43
C _{last} (pg/mL)	10	71.2	21.4	30.04	10	79.9	16.2	20.33
CL/F (L/hr) ^a	10	26.47	9.503	35.90	10	17.63	4.288	24.32
V _z /F (L) ^a	10	480.0	136.0	28.33	10	297.9	68.85	23.12

CV% = percent coefficient of variation; IV = intravenous; SD = standard deviation. Note: Full precision data used in pharmacokinetic analysis.

^a For CL/F and V_z/F for Treatment B (the IV infusion), the value for “F” is 1.

Source: Table 2 of Appendix 16.5

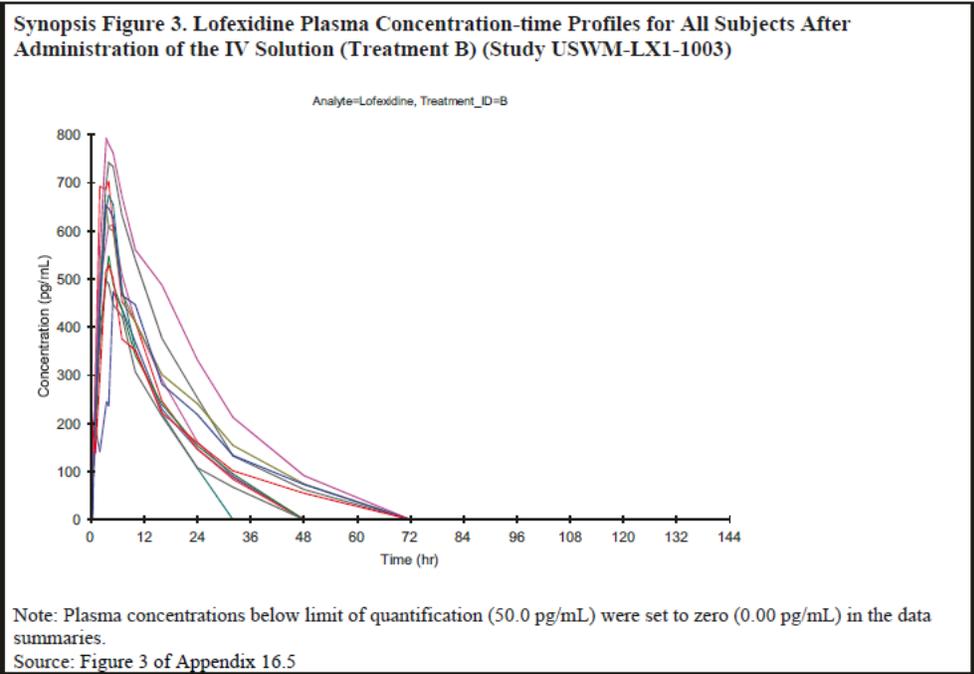
Synopsis Table 2. Absolute Oral Bioavailability of Lofexidine (USWM-LX1-1003)

F (AUC _{inf})					
n	Mean Ratio	SD	CV%	90% Confidence Interval	
				Lower	Upper
10	0.7168	0.2347	32.75	0.5808	0.8529

Source: Table 3 of Appendix 16.5

Mass Balance Recovery:

In Study USWM-LX1-1003, the mean recovery of radioactivity in urine after administration of 400 µg lofexidine HCl oral solution was 70.90% (Synopsis Table 3). Due to deficiencies in the collection and processing in the analysis of urine samples, the mass balance portion of the study was repeated in Study USWM-LX1-1003-1; in the repeat analysis, the mean recovery of radioactivity in urine over 144 hours was 93.47% and mean recovery of radioactivity in the feces over 216 hours was 0.92% (Synopsis Table 4). Total radioactivity recovery was 94.39% of the administered dose. The nearly complete recovery of lofexidine-related radioactivity in the urine indicates that essentially all of the lofexidine dose was absorbed following oral administration.



Synopsis Table 1. Summary of Plasma Pharmacokinetic Parameters of Lofexidine (USWM-LX1-1003)

Parameter	Treatment A Oral Solution				Treatment B IV Infusion (200 minutes)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	10	2.90	0.88	30.19	10	3.85	0.52	13.42
T _{max} (hr) median [range]	10	3.00 [2.00 – 4.00]			10	4.00 [3.33 – 5.00]		
C _{max} (pg/mL)	10	819	282	34.47	10	640	95.2	14.88
AUC ₀₋₆ (hr•pg/mL)	10	3541	1235	34.89	10	2789	445.1	15.96
AUC _{last} (hr•pg/mL)	10	13520	4977	36.83	10	10680	3112	29.14
AUC _{inf} (hr•pg/mL)	10	14860	5261	35.41	10	12030	3247	26.98
AUC _{Extrap} (%)	10	9.55	3.08	32.21	10	11.64	2.50	21.51
λ _z (hr ⁻¹)	10	0.0553	0.0121	21.80	10	0.0603	0.0141	23.43
T _{1/2} (hr)	10	13.18	3.40	25.76	10	12.05	2.71	22.50
T _{last} (hr)	10	45.60	11.96	26.22	10	39.20	9.58	24.43
C _{last} (pg/mL)	10	71.2	21.4	30.04	10	79.9	16.2	20.33
CL/F (L/hr) ^a	10	26.47	9.503	35.90	10	17.63	4.288	24.32
Vz/F (L) ^a	10	480.0	136.0	28.33	10	297.9	68.85	23.12

CV% = percent coefficient of variation; IV = intravenous; SD = standard deviation. Note: Full precision data used in pharmacokinetic analysis.

^a For CL/F and Vz/F for Treatment B (the IV infusion), the value for “F” is 1.

Source: Table 2 of Appendix 16.5

Synopsis Table 2. Absolute Oral Bioavailability of Lofexidine (USWM-LX1-1003)

F (AUC _{inf})					
n	Mean Ratio	SD	CV%	90% Confidence Interval	
				Lower	Upper
10	0.7168	0.2347	32.75	0.5808	0.8529

Source: Table 3 of Appendix 16.5

Mass Balance Recovery:

In Study USWM-LX1-1003, the mean recovery of radioactivity in urine after administration of 400 µg lofexidine HCl oral solution was 70.90% (Synopsis Table 3). Due to deficiencies in the collection and processing in the analysis of urine samples, the mass balance portion of the study was repeated in Study USWM-LX1-1003-1; in the repeat analysis, the mean recovery of radioactivity in urine over 144 hours was 93.47% and mean recovery of radioactivity in the feces over 216 hours was 0.92% (Synopsis Table 4). Total radioactivity recovery was 94.39% of the administered dose. The nearly complete recovery of lofexidine-related radioactivity in the urine indicates that essentially all of the lofexidine dose was absorbed following oral administration.

Synopsis Table 3: Percent Recovery of Radioactivity in Urine After Administration of 400 µg Lofexidine HCl and a Tracer Amount of ¹⁴C-Lofexidine HCl (USWM-LX1-1003)

Subject (b) (6)	Recovery (%)
	75.01
	60.04
	85.66
	61.91
	44.68
	80.89
	63.14
	25.38 ^a
	72.50
	31.79 ^a
	81.49
	83.70
Mean (SD)	70.90 (13.16)
Median (minimum, maximum)	73.76 (44.68, 85.66)
CV%	18.57

^a Subjects (b) (6) were not included in the summary statistics for urinary excretion because they had anomalously low urine excretion of lofexidine during some collection intervals.

Source: Table 6 of Appendix 16.5

Synopsis Table 4: Percent Recovery of Radioactivity in Urine and Feces After Administration of 390 µg Lofexidine HCl and a Tracer Amount of ¹⁴C-Lofexidine HCl (Study USWM-LX1-1003-1)

Subject (b) (6)	Urinary Recovery ^{a,b} (%)	Fecal Recovery ^{a, b} (%)
	90.98	0.95
	92.14	0.92
	94.14	0.86
	96.93	1.12
	93.30	1.00
	93.31	0.67
Mean (SD)	93.47 (2.02)	0.92 (0.15)
Median (minimum, maximum)	93.30 (90.98, 96.93)	0.93 (0.67, 1.12)

SD = standard deviation.

^a Percent of dose recovered, based on 341.9 µg free base dose (390 µg lofexidine HCl dose) was estimated as the mean of the lofexidine HCl content per vial presented in the Certificate of Analysis; see Appendix 16.1.6.

^b Nominally 400 µg of lofexidine HCl containing a tracer amount (247 nCi, 1.2 µg) of ¹⁴C-lofexidine HCl. Average assayed content of dose vials was 390 µg lofexidine HCl.

Source: Table 14.2.1 of Appendix 16.9, Table 14.2.2 of Appendix 16.9

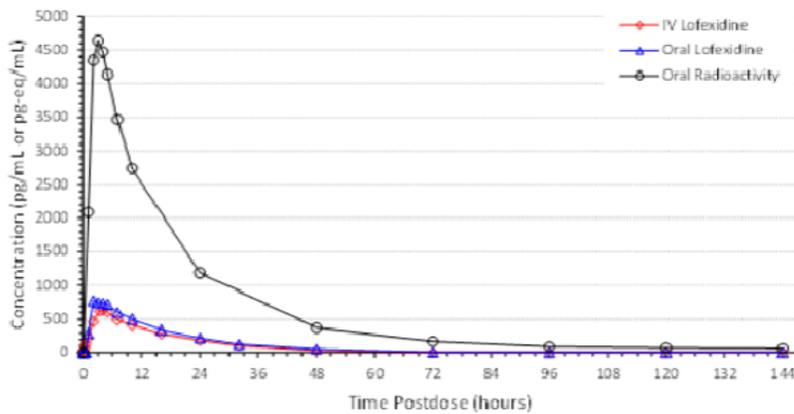
Radioactivity in Plasma:

Plasma concentrations and PK parameters of total radioactivity were assessed in both studies (USWM-LX1-1003 and USWM LX1-1003-1).

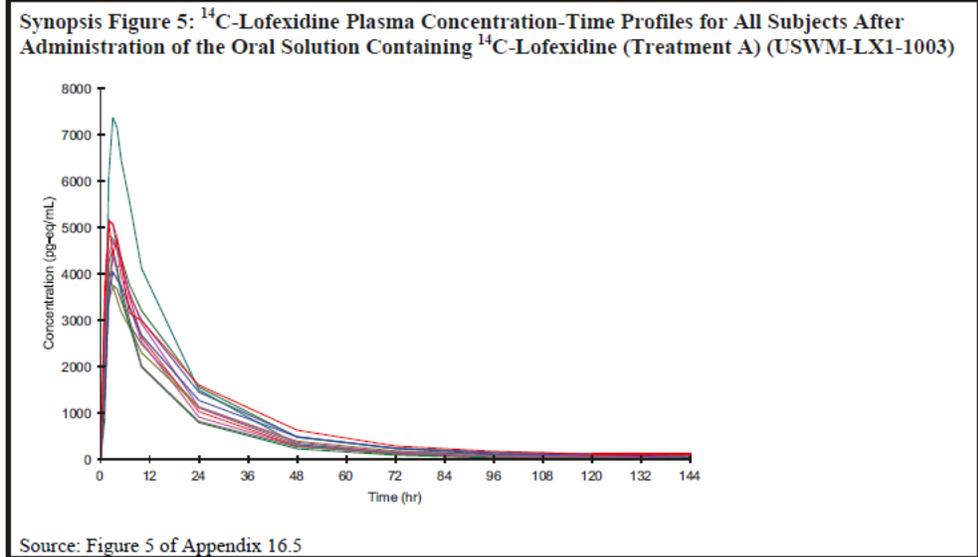
For Study USWM-LX1-1003, Synopsis Figure 4 illustrates the mean ¹⁴C-lofexidine and lofexidine plasma concentration-time profiles following administration of oral solution (Treatment A) and IV infusion (Treatment B) and Synopsis Figure 5 illustrates ¹⁴C-lofexidine plasma concentration-time profiles after Treatment A for all subjects. Total radioactivity plasma concentration-time data for Treatment A are summarized in Synopsis Table 5. Plasma PK parameters of total plasma radioactivity are summarized in Synopsis Table 6.

After the administration of 400 µg lofexidine HCl oral solution, plasma lofexidine concentrations and total radioactivity concentrations from ¹⁴C-lofexidine and its related metabolic products peaked and remained relatively uniform between approximately 2 and 5 hours postdose. This broad peak was followed by an apparent first-order decline through approximately 48 hours and then a less rapid elimination phase that was most apparent in the radioactivity concentration-time profile because of the greater sensitivity of the AMS methodology.

Synopsis Figure 4: Mean Total Radioactivity and Lofexidine Plasma Concentration-Time Profiles Following the Administration of Oral Solution (Treatment A) and the IV Infusion (Treatment B) (USWM-LX1-1003)



Source: Figure 4 of Appendix 16.5



Synopsis Table 5. Total Radioactivity Plasma Concentration-Time Data After Administration of Oral Solution Containing ¹⁴C-Lofexidine (Treatment A) (USWM-LX1-1003)

Time ^b (hours)	Treatment A ^a Lofexidine Oral Solution			
	n	Mean (pg-eq/mL)	SD (pg-eq/mL)	CV%
0.00	10	0.00	0.00	NC
1.00	10	2090	897	42.82
2.00	10	4340	906	20.87
3.00	10	4640	1050	22.54
4.00	10	4470	1040	23.34
5.00	10	4130	924	22.35
7.00	10	3470	812	23.40
10.00	10	2740	632	23.10
24.00	10	1190	287	24.07
48.00	10	376	122	32.56
72.00	10	173	63.4	36.72
96.00	10	94.7	47.4	50.03
120.00	10	75.4	29.0	38.50
144.00	10	64.6	37.0	57.21

CV% = percent coefficient of variation; NC = not calculated; SD = standard deviation.
^a Concentrations reported in pg-eq/mL to 3 significant figures; concentrations below limit of quantification set to zero (0.00 pg-eq/mL) in the data summarization.
^b While plasma samples taken at 5, 10, 20, and 30 minutes and 16 and 32 hours postdose, these samples were not analyzed for radioactivity.

Source: Table 4 of Appendix 16.5

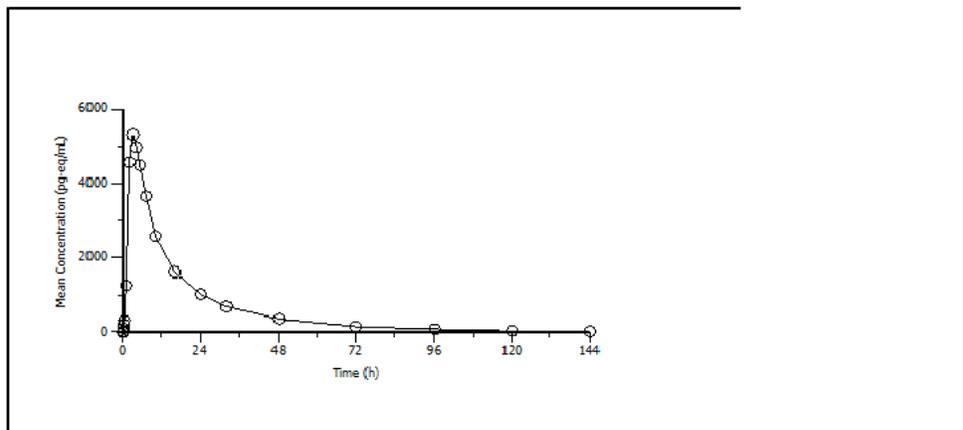
Synopsis Table 6. Plasma Pharmacokinetic Parameters of Total Radioactivity After Administration of Oral Solution Containing ¹⁴C-Lofexidine (Treatment A) (USWM-LX1-1003)

Parameter	n	Mean	SD	CV%
T _{max} (hr)	10	2.60	0.52	19.86
T _{max} (hr) (median [range])	10		3.00 [2.00-3.00]	
C _{max} (pg-eq/mL)	10	4740	1050	22.09
AUC ₀₋₆ (hr•pg-eq/mL)	10	21580	4395	20.37
AUC ₀₋₇₂ (hr•pg-eq/mL)	10	87440	17260	19.74
AUC _{last} (hr•pg-eq/mL)	10	94360	18390	19.48
AUC _{inf} (hr•pg-eq/mL)	10	98820	19470	19.71
AUC _{Extrap} (%)	10	4.35	4.44	102.18
λ _z (hr ⁻¹)	10	0.0276	0.0142	51.50
T _{1/2} (hr)	10	40.63	35.45	87.26
T _{last} (hr)	10	144.00	0.00	0.00
C _{last} (pg-eq/mL)	10	64.6	37.0	57.21
CL/F (L/hr)	10	3.669	0.7341	20.01
V _z /F (L)	10	205.9	171.6	83.35

Source: Table 5 of Appendix 16.5

For Study USWM-LX1-1003-1, [Synopsis Figure 6](#) illustrates the mean plasma total radioactivity-time profile for ¹⁴C-lofexidine following administration of oral solution, and total radioactivity plasma concentration-time data are summarized in [Synopsis Table 7](#). Plasma PK parameters of total plasma radioactivity are summarized in [Synopsis Table 8](#). In general, the PK profile of total radioactivity in plasma in the current Study USWM-LX1-1003-1 was comparable to that observed previously in Study USWM-LX1-1003. While the results from Study USWM-LX1-1003 are suggestive of a more prolonged terminal T_{1/2} (approximately 40 hours) than was quantified for the parent drug under single-dose conditions, the results from Study USWM-LX1-1003-1 indicate a terminal T_{1/2} of 21 hours, similar to the 12-13 hour T_{1/2} of lofexidine ([Synopsis Table 1](#)). The disagreement between the terminal radioactivity T_{1/2} results for the two studies may indicate between-subject variability in the handling of some minor metabolite or variability in the accessibility of lofexidine to some functionally deeper distribution compartment.

Synopsis Figure 6. Mean Plasma Total Radioactivity-Time Profile After Administration of 390 µg^a Lofexidine HCl and a Tracer Amount of ¹⁴C-Lofexidine HCl (USWM LX1 1003-1)



^a Nominally 400 µg of lofexidine HCl containing a tracer amount (247 nCi, 1.2 µg) of ¹⁴C-lofexidine HCl. Average assayed content of dose vials was 390 µg lofexidine HCl.
Source: Figure 14.2.3.2 of Appendix 16.9

Synopsis Table 7. Total Radioactivity Plasma Concentration-Time Data After Administration of 390 µg Lofexidine HCl and a Tracer Amount of ¹⁴C-Lofexidine HCl (USWM-LX1-1003-1)

Time (hours)	Lofexidine Oral Solution ^{a,b}			
	n	Mean (pg-eq/mL)	SD (pg-eq/mL)	CV%
0.00	6	0.00	0.00	NC
0.08	6	27.3	31.2	114.40
0.17	6	91.7	52.7	57.44
0.33	6	212	85.5	40.44
0.50	6	311	116	37.20
1.00	6	1260	664	52.61
2.00	6	4580	1580	34.41
3.00	6	5340	1670	31.21
4.00	6	5000	1460	29.09
5.00	6	4500	1210	26.90
7.00	6	3670	826	22.54
10.00	6	2580	427	16.55
16.00	6	1610	231	14.34
24.00	6	1030	233	22.72
32.00	6	686	179	26.07
48.00	6	354	123	34.84
72.00	6	148	73.9	49.82
96.00	6	78.5	34.3	43.74
120.00	6	31.5	37.2	118.01
144.00	6	20.0	31.3	156.43

CV% = percent coefficient of variation; NC = not calculated; SD = standard deviation.

^a Concentrations reported in pg-eq/mL to 3 significant figures; concentrations below limit of quantification set to zero (0.00 pg-eq/mL) in the data summarization.

^b Nominally 400 µg of lofexidine HCl containing a tracer amount (247 nCi, 1.2 µg) of ¹⁴C-lofexidine HCl. Average assayed content of dose vials was 390 µg lofexidine HCl.

Source: Table 14.2.3.1 of Appendix 16.9

Synopsis Table 8. Plasma Pharmacokinetic Parameters of Total Radioactivity After Administration of 390 µg Lofexidine HCl and a Tracer Amount of ¹⁴C-Lofexidine (USWM-LX1-1003-1)

Parameter	Oral Solution ^{a,b}			
	n	Mean	SD	CV%
T _{max} (hr)	6	3.00	0.63	21.08
T _{max} (hr) (median [range])	6		3.00 [2.00 – 4.00]	
C _{max} (pg-eq/mL)	6	5410	1640	30.25
AUC ₀₋₆ (hr•pg-eq/mL)	6	22570	6225	27.57
AUC ₀₋₇₂ (hr•pg-eq/mL)	6	80130	10580	13.20
AUC _{last} (hr•pg-eq/mL)	6	84350	10960	13.00
AUC _{inf} (hr•pg-eq/mL)	6	86100	11020	12.80
AUC _{Extrap} (%)	6	2.05	0.59	28.78
λ _z (hr ⁻¹)	6	0.0339	0.0071	20.86
T _{1/2} (hr)	6	21.17	4.19	19.78
T _{last} (hr)	6	116.00	23.60	20.34
C _{last} (pg-eq/mL)	6	56.9	9.39	16.50
CL/F (L/hr) ^c	6	4.031	0.5661	14.04
V _z /F (L) ^c	6	123.8	33.78	27.30
AUC ₀₋₇₂ /AUC _{inf}	6	0.9306	0.03718	3.99

CV% = percent coefficient of variation; SD = standard deviation.

^a Concentrations reported in pg-eq/mL to 3 significant figures; concentrations below limit of quantification set to zero (0.00 pg eq/mL) in the data summarization

^b Nominally 400 µg of lofexidine HCl containing a tracer amount (247 nCi, 1.2 µg) of ¹⁴C-lofexidine HCl. Average assayed content of dose vials was 390 µg lofexidine HCl.

^c Note: CL/F and V_z/F were calculated based on 341.9 µg free base dose (390 µg lofexidine HCl). The dose was estimated as the mean of the lofexidine HCl content per vial presented in the Certificate of Analysis; see Appendix 16.1.6).

Source: Table 14.2.3.3 of Appendix 16.9

Blood to Plasma Partitioning:

Concentrations of total radioactivity in whole blood, plasma, and RBCs as measured in samples collected 4 hours after administration of the oral solution are compared in [Synopsis Table 9](#). The radioactivity concentration in whole blood (3,160 pg-eq/mL) was less than that observed in plasma (4,560 pg-eq/mL). The actual hematocrit of individual subjects (for the study period in which the oral solution was administered) was used to estimate the radioactivity equivalents in the RBC and the RBC/plasma concentration was calculated. Based on the mean RBC/plasma ratio, the concentration of total radioactivity in RBCs averages 26.66% of that in plasma. Hence, RBCs do not preferentially bind lofexidine or its metabolites and do not appear to have a mechanism for preferential uptake of lofexidine.

Synopsis Table 9. Total Radioactivity in Whole Blood, Plasma, and Red Blood Cells at 4 Hours After Administration of Oral Solution Containing ¹⁴C-Lofexidine (Treatment A) (USWM-LX1-1003)

Subject	Whole Blood ^a (pg-eq/mL)	Plasma ^a (pg-eq/mL)	Hematocrit (%)	RBC ^{a,b} (pg-eq/mL)	RBC/Plasma (%)
(b) (6)	2680	4760	48.6	480	10.09
	2470	3890	45.6	776	19.95
	3010	4150	39.4	1260	30.28
	2750	4150	42.4	848	20.44
	2690	4060	43.2	889	21.89
	2050	3460	39.8	-82.7	-2.39
	5280	7160	38.7	2300	32.15
	3010	4780	45.2	864	18.08
	3320	4590	39.4	1370	29.77
	3570	4540	35.6	1820	39.98
	2690	3680	39.9	1200	32.58
	3590	4580	37.8	1960	42.82
n	9	9	9	9	9
Mean (SD)	3160 (869)	4560 (1040)	41.67 (3.60)	1230 (585)	26.66 (9.55)
Minimum	2470	3680	37.80	480	10.09
Median	2750	4150	39.90	1200	29.77
Maximum	5280	7160	48.60	2300	42.82
CV%	27.47	22.76	8.64	47.50	35.83

CV% = percent coefficient of variation; RBC = red blood cells; SD = standard deviation.
^a Concentrations reported in pg-eq/mL to 3 significant figures.
^b RBC concentrations estimated using percent RBC volume in whole blood (hematocrit), percent plasma volume in whole blood (100 – hematocrit), and known whole blood and plasma concentrations.
^c Subject (b) (6) was not included in the summary statistics; the actual hematocrit resulted in a negative estimate for RBC concentration.
^d Subjects (b) (6) were not included in the summary statistics because they were not evaluable for other pharmacokinetic comparisons.

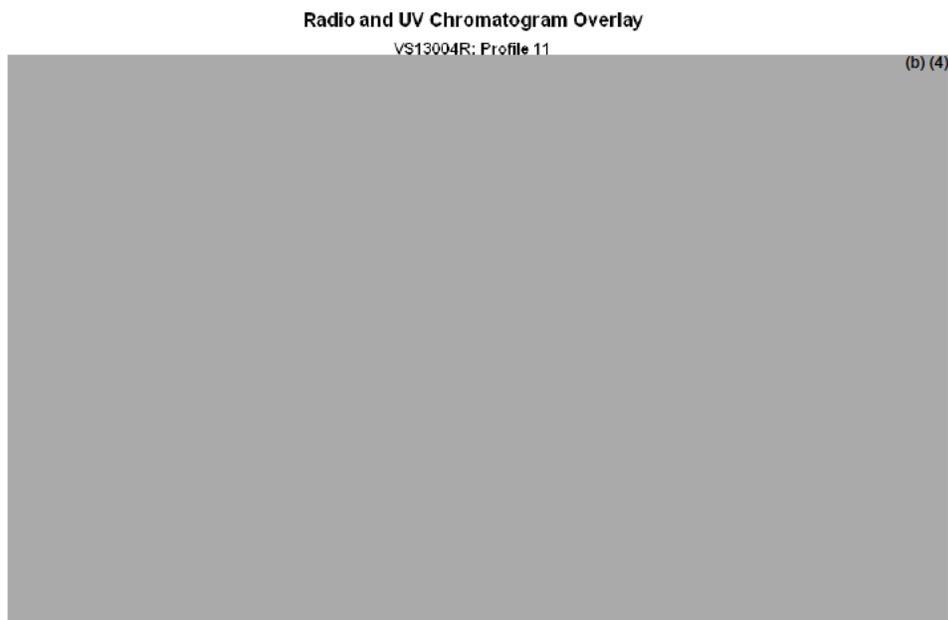
Source: Table 8 of Appendix 16.5

Metabolic Profiling:

Plasma samples collected 3 hours postdose following oral dosing were pooled to assess the metabolite profile in plasma at the approximate time of peak plasma concentrations. The radioactivity content of liquid chromatography fractions collected following ultra-performance liquid chromatography (UPLC) was assessed using AMS. The radiochromatogram and overlaid UV absorption chromatogram for plasma are shown in [Synopsis Figure 7](#), along with the identities of the major radioactivity peaks. The contributions of the various peaks to the total radioactivity are summarized in [Synopsis Table 10](#). The parent drug, lofexidine, accounted for 13.1% of the total plasma radioactivity, while the metabolites N-(2-aminoethyl)-2-(2,6 dichlorophenoxy) propanamide (LADP), 2-(2,6 dichlorophenoxy) propionic acid (LDPA), and 2,6-dichlorophenol (DCP) accounted for 24.5%, 17.2%, and 13.6%, respectively. None of the other peaks accounted for more than 5% of the plasma radioactivity. In urine, the parent drug, lofexidine,

accounted for 19.1% of the total radioactivity, while the metabolites LADP and LDPA accounted for 49.3% and 1.43%, respectively. DCP, a major metabolite in the plasma, was not detected in the urine, possibly because of its volatility. None of the other peaks accounted for more than 10% of the urine radioactivity.

Synopsis Figure 7. Radio and Ultraviolet Chromatogram Overlay of Profile 11 (Untreated Plasma—3 Hours) (USWM LX1-1003)



Source: Figure 7 of Appendix 16.5

Synopsis Table 10. Integrated Area of Radiochromatogram Plasma Peaks (percent of total on column radioactivity) (USWM-LX1-1003)				
Peak	Peak Retention in Time Window	Compound Area (ng-eq/mL)	Percent of Total Compound Area	Identity
P1	6.3-6.6	0.0339	2.13	Unknown
P2	7.4-7.5	0.00825	0.517	Unknown
P3	7.7-8.2	0.0323	2.02	Unknown
P4	8.4-8.9	0.209	13.1	Lofexidine
P5	9.3-9.8	0.391	24.5	LADP
P6	11.5-11.8	0.0518	3.24	Unknown
P7	11.8-12.1	0.0720	4.51	Unknown
P8	12.1-12.8	0.218	13.6	DCP
P9	13.2-13.6	0.275	17.2	LDPA
Total	0-14.0	1.29	80.9	Not applicable

DCP = 2, 6-dichlorophenol; LADP = N-(2-aminoethyl-2-(2,6 dichlorophenoxy) propanamide); LDPA = 2-(2,6 dichlorophenoxy) propionic acid.
 Source: Table 9 of Appendix 16.5

SAFETY RESULTS:

In Study USWM-LX1-1003, 9 of 12 subjects (75.0%) reported TEAEs. Most adverse events were mild or moderate, with severe adverse events reported for 2 subjects (both had severe hypotension). All TEAEs were considered possibly or probably related to study treatment. The most frequent adverse events were somnolence and hypotension, each reported in 7 subjects (58.3%). Four subjects had hypotension associated with both oral and IV treatments. All TEAEs resolved.

There were no deaths or other serious adverse events. One subject discontinued from the study due to severe hypotension after the oral treatment.

Adverse events in Study USWM-LX1-1003-1 were similar to those in Study USWM-LX1-1003.

In Study USWM-LX1-1003, mean BP decreased with both treatments by > 20 mmHg for both systolic and diastolic BP. Mean pulse also decreased from predose to postdose, with a maximum mean decrease of 11.9 bpm (4 hours postdose after Treatment A). In Study USWM-LX1-1003-1, mean systolic BP, diastolic BP, and pulse also decreased postdose.

Based on analysis of Holter ECGs from Study USWM-LX1-1003, lofexidine was associated with an increase in QTcF that correlated with lofexidine plasma concentration and did not correlate with heart rate. Mean increase in QTcF at 4 hours postdose was 16.0 msec with oral lofexidine and 17.9 msec with IV lofexidine. In Study USWM-LX1-1003-1, mean QTcF values decreased slightly to moderately, maximally 5.8 msec at 8 hours postdose.

Study exit clinical laboratory, 12-lead (paper) ECG, and physical examination evaluations were completed with no clinically significant findings.

CONCLUSIONS:

- Based on the mass balance investigation, the mean urinary recovery of lofexidine-derived radioactivity after oral administration of approximately 400 µg lofexidine HCl was 93.47% (over 144 hours) and mean fecal recovery was 0.92% (over 216 hours), for a total mean recovery of 94.39%. Essentially all orally administered lofexidine was absorbed.
- The mean (90% confidence interval) absolute bioavailability of a single oral dose of lofexidine compared with a single IV infusion of lofexidine was 0.7168 (0.5808, 0.8529).
- The principal lofexidine-related molecular species found in plasma were lofexidine, LADP, LDPA, and DCP, and the principal lofexidine-related molecules found in urine were lofexidine, LADP, and LDPA. The DCP contribution in urine and feces may have been underestimated due to losses during sample processing, because DCP is a volatile molecule over most of the pH range.
- Approximately half of the subjects experienced hypotension, which is consistent with the α_2 -adrenergic receptor agonist mechanism of action of lofexidine. Lofexidine was associated with mean increases in QTcF that correlated with increasing lofexidine plasma concentrations, with mean increases of approximately 16 to 18 msec 3 and 4 hours postdose. No serious AEs were reported.

Date of the report:

10 April 2017

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: A Single-center, Open-label, Single-period, Single-treatment Study to Determine the Mass Balance of a Single Oral Dose of ¹⁴ C-labeled Lofexidine		
Principal Investigator: Mark T. Leibowitz, MD Investigators: Cynthia A Zamora, MD; Michael R Natalino, MD, PA; Nancy K Hinitt, MD; Joe H Juren, MD; Jonathan Larson, MD; Steven Hinitt, MD, MPH, MPA; Hector Caraballo, MD; Wilhelm Muller, PA; Martha M Garza, MD; Therese Rizzo, MSN, FNP-BC		
Study center: Worldwide Clinical Trials Drug Development Solutions, Clinical Research Services (WCTCRS), 2455 NE Loop 410, Suite 150, San Antonio, Texas 78217		
Publications (reference): None		
Studied period: First subject enrolled: 30 May 2012 Last subject completed: 21 June 2012	Phase of development: 1	
Objectives: <ul style="list-style-type: none"> To determine the mass balance recovery of orally administered lofexidine HCl, and To determine the tolerability of lofexidine oral solution. 		
Methodology: Study USWM-LX1-1003-1 was a single-center, open-label, single-period follow-up to Study USWM-LX1-1003 in which 6 healthy adult male subjects received a single oral administration of an aqueous solution containing 400 µg lofexidine HCl plus a tracer amount of ¹⁴ C-lofexidine HCl (approximately 1.2 µg ¹⁴ C-lofexidine HCl providing 247 nCi radioactivity). Subjects were screened within 28 days prior to study start. Only medically healthy subjects with clinically acceptable laboratory profiles and ECGs were enrolled. Subjects were administered the treatment following an overnight fast of at least 10 hours. Blood was drawn and urine was collected for clinical laboratory testing at screening, at check-in, and at the end of the study. In addition, blood samples were obtained prior to dosing and postdose at selected times through 144 hours; pooled urine samples were collected for determination of radioactivity prior to dosing and postdose over selected time intervals through 144 hours; and feces were collected for determination of radioactivity prior to dosing and, if possible, postdose up to 216 hours. Subjects were administered IV normal saline at a continuous rate of 150 mL/hour from check-in until 1 hour prior to dosing.		

Number of Subjects (planned and analyzed):		
Planned: 6	Enrolled: 6	Analyzed: 6
Diagnosis and main criteria for inclusion: Healthy male, 18-50 years of age (inclusive), body mass index (BMI) between 18 and 30 kg/m ² (inclusive), and a minimum weight of 50 kg.		
Test product, dose and mode of administration, batch number: Nominally 400 µg of lofexidine HCl dissolved in water, containing a tracer amount (247 nCi, 1.2 µg) of ¹⁴ C-lofexidine HCl. Average assayed content of dose vials was 390 µg lofexidine HCl. Lot: 65041APR12-01		
Duration of treatment: A single dose was administered.		
Criteria for evaluation:		
Pharmacokinetics: Plasma, urine, and fecal samples were analyzed for ¹⁴ C content to determine the combined concentration of lofexidine and lofexidine-related metabolites in the samples of each of the biomatrices.		
Safety: Safety assessments included adverse events (AEs), laboratory findings, vital signs, 12-lead (paper) electrocardiograms (ECGs), and Holter 12-lead ECGs.		
Statistical methods:		
Pharmacokinetics: ¹⁴ C-lofexidine in urine and feces was analyzed to determine urinary excretion of drug-related material per collection interval, total recovery, and percent of dose excreted in urine and feces. Recoveries of radioactivity in the urine and the feces were expressed as percentages of the administered dose. Plasma samples were analyzed for lofexidine by quantifying the radioactivity from the administered lofexidine present in plasma samples using AMS. Total radioactivity PK in plasma were analyzed using noncompartmental methods.		
Safety: AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 13.1. The incidence of treatment-emergent adverse events (TEAEs) was summarized by treatment, MedDRA primary system organ class, MedDRA preferred term, by investigator attribution of relationship to study drug, and by severity. Changes from predose were summarized for laboratory parameters and vital signs; shift tables were also provided. Holter ECG extractions were performed in duplicate from recordings made under resting conditions at predose and 3, 4, 7, and 8 hours postdose. Change from predose in QTc with Fridericia's heart rate correction (QTcF) was the primary endpoint and change in QTc with Bazett's heart rate correction (QTcB) was a secondary endpoint. QTc intervals were analyzed descriptively and categorically (QTc interval prolongations > 450, > 480 and > 500 msec; QTc increases from predose > 30 and > 60 msec). Other secondary endpoints included change from predose in heart rate, BP, PR interval, and QRS duration.		

SUMMARY – CONCLUSIONS

PHARMACOKINETICS RESULTS:

Results for percent recovery of radioactivity in urine and feces data are presented for the individual subjects as well as summary statistics for the study population in [Synopsis Table 1](#). Mean recovery of radioactivity in the urine over 144 hours was 93.47% of the administered radioactivity, while mean recovery of radioactivity in the feces over 216 hours was 0.92%. Total radioactivity recovery was 94.39% of the administered dose. The nearly complete recovery of lofexidine-related radioactivity in the urine indicates that essentially all of the lofexidine dose was absorbed following oral administration.

Synopsis Table 1: Percent Recovery of Radioactivity in Urine and Feces After Administration of 390 µg Lofexidine HCl and a Tracer Amount of ¹⁴C-Lofexidine HCl

Subject	Urinary Recovery (%)	Fecal Recovery ^a (%)
(b) (6)	90.98	0.95
	92.14	0.92
	94.14	0.86
	96.93	1.12
	93.30	1.00
	93.31	0.67
Mean (SD)	93.47 (2.02)	0.92 (0.15)
Median (minimum, maximum)	93.30 (90.98, 96.93)	0.93 (0.67, 1.12)

SD = standard deviation.

^a Percent of dose recovered, based on 341.9 µg free base dose (390 µg lofexidine HCl dose) was estimated as the mean of the lofexidine HCl content per vial presented in the Certificate of Analysis; see Appendix 16.1.6. Source: Table 14.2.1, Table 14.2.2

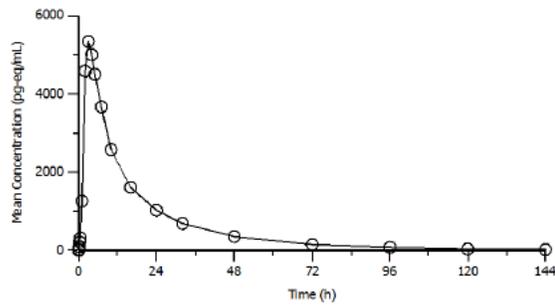
Total radioactivity plasma concentration-time data are summarized in [Synopsis Table 2](#) and the mean plasma total radioactivity-time profile is illustrated in [Synopsis Figure 1](#). PK parameters of total radioactivity in plasma are summarized in [Synopsis Table 3](#). In general, the PK profile of total radioactivity in plasma in the current study was comparable to that observed previously in Study USWM LX1-1003.

Synopsis Table 2. Total Radioactivity Plasma Concentration-Time Data After Administration of 390 µg Lofexidine HCl and a Tracer Amount of ¹⁴C-Lofexidine HCl

Lofexidine Oral Solution				
Time (hours)	n	Mean (pg-eq/mL)	(SD) (pg-eq/mL)	CV%
0.00	6	0.00	(0.00)	NC
0.08	6	27.3	(31.2)	114.40
0.17	6	91.7	(52.7)	57.44
0.33	6	212	(85.5)	40.44
0.50	6	311	(116)	37.20
1.00	6	1260	(664)	52.61
2.00	6	4580	(1580)	34.41
3.00	6	5340	(1670)	31.21
4.00	6	5000	(1460)	29.09
5.00	6	4500	(1210)	26.90
7.00	6	3670	(826)	22.54
10.00	6	2580	(427)	16.55
16.00	6	1610	(231)	14.34
24.00	6	1030	(233)	22.72
32.00	6	686	(179)	26.07
48.00	6	354	(123)	34.84
72.00	6	148	(73.9)	49.82
96.00	6	78.5	(34.3)	43.74
120.00	6	31.5	(37.2)	118.01
144.00	6	20.0	(31.3)	156.43

CV% = percent coefficient of variation; NC = not calculated; SD = standard deviation.
^a Concentrations reported in pg-eq/mL to 3 significant figures; concentrations below limit of quantification set to zero (0.00 pg-eq/mL) in the data summarization
 Source Data: Table 14.2.3.1

Synopsis Figure 1: Mean Plasma Total Radioactivity-Time Profile After Administration of 390 µg^a Lofexidine HCl and a Tracer Amount of ¹⁴C-Lofexidine HCl



^a Nominally 400 µg of lofexidine HCl containing a tracer amount (247 nCi, 1.2 µg) of ¹⁴C-lofexidine HCl. Average assayed content of dose vials was 390 µg lofexidine HCl.
Source Data: Figure 14.2.3.2

^b Note: CL/F and V_z/F were calculated based on 341.9 µg free base dose (390 µg lofexidine HCl). The dose was estimated as the mean of the lofexidine HCl content per vial presented in the Certificate of Analysis; see Appendix 16.1.6).
Source Data: Table 14.2.3.3

Synopsis Table 3: Plasma Pharmacokinetic Parameters of Total Radioactivity After Administration of 390 µg Lofexidine HCl and a Tracer Amount of ¹⁴C-Lofexidine HCl

Parameter	n	Oral Solution		
		Mean	SD	CV%
T _{max} (hr)	6	3.00	0.63	21.08
T _{max} (hr) (median [range])	6		3.00 [2.00 – 4.00]	
C _{max} (pg-eq/mL)	6	5410	1640	30.25
AUC ₀₋₆ (hr•pg-eq/mL)	6	22570	6225	27.57
AUC ₀₋₇₂ (hr•pg-eq/mL)	6	80130	10580	13.20
AUC _{last} (hr•pg-eq/mL)	6	84350	10960	13.00
AUC _{inf} (hr•pg-eq/mL)	6	86100	11020	12.80
AUC _{Extrap} (%)	6	2.05	0.59	28.78
λ _z (hr ⁻¹)	6	0.0339	0.0071	20.86
T _{1/2} (hr)	6	21.17	4.19	19.78
T _{last} (hr)	6	116.00	23.60	20.34
C _{last} (pg-eq/mL)	6	56.9	9.39	16.50
CL/F (L/hr)	6	4.031	0.5661	14.04
V _z /F (L) ^b	6	123.8	33.78	27.30
AUC ₀₋₇₂ /AUC _{inf}	6	0.9306	0.03718	3.99

CV% = percent coefficient of variation; SD = standard deviation.

^a Nominally 400 µg of lofexidine HCl containing a tracer amount (247 nCi, 1.2 µg) of ¹⁴C-lofexidine HCl.

Average assayed content of dose vials was 390 µg lofexidine HCl.

Source: Table 14.2.3.3

SAFETY RESULTS:

Four of 6 subjects (66.7%) reported TEAEs. The most frequent TEAE was hypotension, which was reported in 3 subjects (50.0%); all events of hypotension were mild. No other TEAE was reported in more than 1 subject. All TEAEs were considered mild or moderate, all were considered possibly or probably related to study treatment, and all resolved. There were no deaths, no other serious adverse events, and no discontinuations due to adverse events.

Mean systolic and diastolic BP decreased postdose, with a maximum decrease of up to 27.67 mm Hg for systolic BP and of 23.17 mm Hg for diastolic BP. Mean pulse also decreased from predose to postdose, with a maximum decrease of 17.67 bpm.

Based on analysis of Holter ECGs, mean QTcF values decreased slightly to moderately, maximally -5.8 msec at 8 hours postdose. No outlier values of QTc or change in QTc were found. Small changes to the PR interval and QRS duration were not considered clinically significant.

Study exit clinical laboratory, 12-lead (paper) ECG, and physical examination evaluations were completed with no clinically significant findings.

CONCLUSIONS:

- After administration of a nominal dose of 400 µg lofexidine HCl and a tracer amount of ¹⁴C-lofexidine HCl, the mean recovery in urine was 93.47% with low variability (2.16% coefficient of variation [CV]). The mean recovery in feces was 0.92% (16.61% CV). Total radioactivity recovery was 94.39% of the administered dose.
- In general, the PK profile of total radioactivity in plasma in the current study was comparable to that observed previously (Study USWM LX1-1003).
- Three of 6 subjects had TEAEs of hypotension. There were no unexpected AEs.

Date of the report:
10 April 2017

4.4.3 Study LX1-1004: Food Effect

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine HCl 200 µg tablet		
Name of Active Ingredient: Lofexidine HCl		
Title of Study: A Single-Dose, Open-Label, Randomized, Two-Way Crossover Food-Effect Study of Lofexidine 400 µg (2 x 200 µg) Tablets		
Investigators: Mark T. Leibowitz, M.D.; Cynthia A. Zamora, M.D.; Michael R. Natalino, M.D., P.A.; Nancy K. Hinit, M.D.; Joe H. Juren, M.D.; Jonathan Larson, M.D.; Steven Hinit, M.D., MPH, MPA; Charla Hutchens, BSN, WHNP-BC; Felicia Lauten, BSN, WHNP-BC; Wilhelm Muller, PA; Martha M. Garza, M.D.; Therese Rizzo, MSN, FNP-BC		
Study Center(s): Worldwide Clinical Trials Early Phase Services, LLC (WCT), 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217		
Publication: None		
Study Period (days): 16	Phase of Development: I	
Introduction to the Amendment: The purpose of the First Amendment to the Report is to provide the following revisions to the original report dated 03 September 2013.		
<ul style="list-style-type: none"> • Correction of page numbers in the List of Appendices and Tables of Contents in Sections 16.4 and 16.5. • Inclusion of a sponsor signatory page in Section 16.1.5. 		
Objectives: The objective of this single-dose, open-label, randomized, two-period, two-way crossover, food-effect study was to evaluate the effect of food on the rate of absorption and oral bioavailability of a test formulation of lofexidine HCl 400 µg (2 x 200 µg tablet) manufactured by US WorldMeds, LLC.		
Study Methodology: This was a single-dose, open-label, randomized, two-period, two-way crossover, food-effect study in which 12 healthy adult subjects were scheduled to receive two separate single-dose administrations of lofexidine HCl 400 µg (2 x 200 µg tablet). In one study period, subjects were administered the study treatment following an overnight fast of at least 10 hours. In the other study period, subjects fasted overnight for at least 10 hours then began consuming a Food and Drug Administration (FDA) standard high-calorie, high-fat breakfast meal 30 minutes prior to administration of the study drug. Each drug administration was separated by a washout period of at least seven days. Subjects that were discontinued for any reason (except for overall trial safety concerns) were to be replaced by back up volunteers.		

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine HCl 200 µg tablet		
Name of Active Ingredient: Lofexidine HCl		
Number of Subjects Planned: 12 Enrolled: 13 Analyzed: 12		
Diagnosis and Criteria for Inclusion: Healthy male or non-pregnant, non-breastfeeding female, 18-50 years of age (inclusive), Body Mass Index (BMI) between 18 and 30 kg/m ² (inclusive), and a minimum weight of 50 kg (110 lbs).		
Treatment A, Dose and Mode of Administration, Lot Number: Lofexidine HCl 400 µg Dose = 2 × 200 µg tablet orally administered under fasted conditions Lot: 94803V7191		
Treatment B, Dose, and Mode of Administration, Lot Number: Lofexidine HCl 400 µg Dose = 2 × 200 µg tablet orally administered under fed conditions Lot: 94803V7191		
Duration of Treatment: This was a two-way crossover study in which two single-dose treatments were administered according to a randomization schedule with a seven-day washout period between doses.		
Criteria for Evaluation: <u>Efficacy</u> : No efficacy evaluations were performed in this study. A summary of pharmacokinetic analyses is provided. <u>Safety</u> : The Investigator assessed safety using the following parameters: physical examinations, vital signs, clinical laboratory evaluations, Holter monitoring, 12-lead ECGs, and reported or observed adverse events.		
Statistical Methods: The following pharmacokinetic parameters were calculated: peak concentration in plasma (C _{max}), time to peak concentration (T _{max}), elimination rate constant (λ _z), terminal half-life (T _{1/2}), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC _{last}), area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC _{inf}), apparent clearance (CL/F), apparent volume of distribution (V _z /F), last quantifiable concentration (C _{last}), and time of last quantifiable concentration, (T _{last}). Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C _{max} , AUC _{last} , and AUC _{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. No significant food effect was declared if the lower and upper confidence intervals of the ratio of the parameters were totally within the 80% to 125% interval.		

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine HCl 200 µg tablet		
Name of Active Ingredient: Lofexidine HCl		

SUMMARY CONCLUSIONS

SAFETY RESULTS:

A total of 29 treatment-emergent AEs (TEAEs) were reported by 9 subjects over the course of the study (Table 14.3.3). There were no serious TEAEs or deaths during the course of the study. Of the 29 TEAEs reported, 11 were mild and 18 were moderate (Table 14.3.5). Twenty-seven (27) of the TEAEs were probably related to the study medication and the remaining 2 were unrelated (Table 14.3.6).

Table 12.1 Adverse event reporting:

Category	Number of Subjects Reporting %	
Any adverse events	9	69.2%
Mild adverse events	6	46.2%
Moderate adverse events	7	53.8%
Severe adverse events	0	0%
Serious adverse events	0	0%
Withdrawals due to treatment emergent adverse events	0	0%
Deaths	0	0%

*Table 14.3.2 incorrectly lists the single discontinued subject as being withdrawn due to an adverse event. Subject (b) (6) was discontinued in Period 1 by the Sponsor due to a single episode of vomiting within 8 hours of drug administration ($< 2 \times T_{max}$), because of the potential impact on the determination of oral bioavailability.

Source: Table 14.3.2, Table 14.3.5, Table 14.1.1

The most commonly reported postdose AEs were somnolence (n=7; 4 following Treatment A and 3 following Treatment B), hypotension (n=5; 3 following Treatment A and 2 following Treatment B), nausea (n=4; 2 following Treatment A and 2 following Treatment B), and pain in extremity (n=4; 3 following Treatment A and 1 following Treatment B). (Table 14.3.4)

In total, 16 AEs were reported following Treatment A and 13 following Treatment B. (Table 14.3.3)



Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine HCl 200 µg tablet	Volume: Page:	
Name of Active Ingredient: Lofexidine HCl		
<p>Five of the TEAEs were related to clinically significant abnormal vital sign evaluations. Subject (b) (6) was assessed with intermittent hypotension which was judged to be moderate and probably related to the study treatment by the Investigator. Subject (b) (6) was assessed with intermittent asymptomatic hypotension which was judged to be moderate and probably related to the study treatment by the Investigator. Subjects (b) (6) and (b) (6) were assessed with asymptomatic hypotension, which were judged to be moderate and probably related to the study treatment by the Investigator. Subject (b) (6) was assessed with intermittent hypotension, which was judged to be mild and probably related to the study treatment by the Investigator. (Listing 16.2.7)</p> <p>Narratives of the clinically significant episodes of intermittent and intermittent asymptomatic hypotension are provided in Section 12.3.2.</p> <p>No other clinically significant abnormalities in vital signs, laboratory evaluations, or physical exams were observed.</p> <p>No subject was withdrawn due to a treatment emergent adverse event. Subject (b) (6) was discontinued in Period 1 by the Sponsor due to a single episode of vomiting within 8 hours of drug administration ($< 2 \times T_{max}$), because of the potential impact on the determination of oral bioavailability.</p> <p>Refer to Table 14.3.6 for more detailed data regarding the relationships between observed AEs and the relative study treatment.</p> <p><u>CARDIAC SAFETY RESULTS:</u></p> <p>The following is excerpted from the conclusions section of the cardiac safety report provided by (b) (4). The full report is included in Appendix 16.7.</p> <p>In this two-way crossover food-effect study 12 healthy adult subjects received two separate single doses of lofexidine 400 µg in both fasting and post-prandial states. QT interval responses were corrected by both the Fredericia and Bazett corrections. Lofexidine appeared to prolong the mean QTcF versus Baseline by approximately 9 msec at peak (median 6.8 msec) in the fasted group; a similar effect was not observed under fed conditions. Overall, the QTc interval increased with plasma lofexidine concentration up to the maximum observed concentration of approximately 1 ng/mL. In one subject (Subject (b) (6) 4 hours postdose, fasted) a QTcF prolongation of 31 msec was observed coincident with almost the highest lofexidine concentration noted among all subjects. This may represent a heightened pharmacodynamic sensitivity in this small sample, but it cannot be ruled out that it may also represent a more "typical" concentration effect response in a larger population. Clinically non-significant sinus bradycardia was the only treatment emergent arrhythmia observed in this study.</p> <p>Although it can be concluded that no subject had a safety issue related to QT prolongation under either fed or fasted conditions during the 3, 4, and 8 hours postdose ECGs, due to the small study population and limited number of ECG data points, more definitive statistical conclusions cannot be drawn.</p>		



WORLDWIDE CLINICAL TRIALS
SCIENTIFICALLY MINDED • MEDICALLY DRIVEN

Document Control Number 3006001_am1
First Amendment to the Report
US WorldMeds Reference Number USWM-LX1-1004

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine HCl 200 µg tablet	Volume: Page:	
Name of Active Ingredient: Lofexidine HCl		
<p>Results from this 400 µg single dose study in normal volunteers may not be predictive of clinical experience because anticipated dosing in the target patient population will likely be up to 800 µg QID for 5 to 10 days, and significant drug accumulation leading to plasma concentrations several fold higher than achieved in this study is expected during that treatment time frame.</p> <p><u>PHARMACOKINETIC RESULTS:</u></p> <p>Data for 12 subjects who completed the study were included in the pharmacokinetic and statistical analyses. Results of the pharmacokinetic and statistical analyses are shown below in Synopsis Tables 1 and 2.</p>		

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine HCl 200 µg tablet		
Name of Active Ingredient: Lofexidine HCl		

Synopsis Table 1: Pharmacokinetic Parameters of Lofexidine

Parameter	Treatment A: (Fasted)			Treatment B: (Fed)		
	n	Mean	SD CV%	n	Mean	SD CV%
T _{max} (hr)	12	5.00 [3.00-7.00]		12	5.98 [2.00-10.00]	
C _{max} (pg/mL)	12	744	181 24.37	12	732	180 24.57
AUC _{last} (hr*pg/mL)	12	14160	3484 24.61	12	14230	4213 29.60
AUC _{inf} (hr*pg/mL)	11	15400	3890 25.25	12	16000	4768 29.80
AUC _{Estrap} (%)	11	10.43	4.20 40.28	12	10.96	3.01 27.48
λ _z (hr ⁻¹)	11	0.0525	0.0094 18.02	12	0.0513	0.0113 22.05
T _{1/2} (hr)	11	13.68	2.92 21.34	12	14.09	2.93 20.79
T _{last} (hr)	12	46.02	4.66 10.13	12	46.03	4.69 10.18
C _{last} (pg/mL)	12	96.3	64.9 67.38	12	85.1	28.2 33.18
CL/F (L/hr)	11	24.23	6.722 27.74	12	23.97	7.965 33.23
Vz/F (L)	11	463.6	92.60 19.97	12	474.9	155.4 32.72

Note: Full precision data used in pharmacokinetic analysis

T_{max} is presented as Median [Range]

Source data: Appendix 16.4

Synopsis Table 2: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Lofexidine

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Fed/Fasted)	90% CI ^c		Power	ANOVA CV%
	(Fed)	(Fasted)		Lower	Upper		
C _{max}	712.2506	724.2494	98.34	88.66	109.09	0.9685	14.08
AUC _{last}	13624.2459	13728.8575	99.24	91.02	108.20	0.9916	11.72
AUC _{inf}	14980.3511	14915.0232	100.44	90.53	111.43	0.9679	13.29

^a Geometric Mean was based on for Least Squares Mean of log-transformed parameter values

^b 90% Confidence Interval

Note: T_{1/2} and parameters based on extrapolation could not be calculated for all subjects; statistical analysis is based on n = 12 for C_{max}, AUC_{last}, and n = 11 for AUC_{inf}

Source data: Appendix 16.4

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine HCl 200 µg tablet	Volume: Page:	
Name of Active Ingredient: Lofexidine HCl		
<p>The 90% confidence interval of the ratio comparing the maximum exposure to lofexidine (C_{max}) lies totally within the accepted 80% to 125% limits establishing bioequivalence. The 90% confidence intervals of the ratios comparing cumulative exposure to lofexidine (AUC_{last} and AUC_{int}), lie totally within the accepted 80% to 125% limits establishing bioequivalence.</p> <p><u>CONCLUSIONS:</u></p> <p>The 400 µg dose was generally well tolerated and there were no significant safety issues in the study. Administration of lofexidine tablets with a high-fat meal does not have a detectable effect on the oral bioavailability of lofexidine compared to administration under fasting conditions. The rate and extent of lofexidine absorption from the oral tablets are not affected by administration in the presence or absence of food.</p>		
<p>Original Date of Report: 03 September 2013 First Amendment to the Report Date: 02 January 2014</p>		

4.4.4 Study LX1-1005-1 and -1005-2: Subjects receiving methadone

US WorldMeds, LLC
USWM-LX1-1005-1

209229

16 May 2016

2 SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: A Pilot, Multiple Ascending Dose Study to Assess the Safety, Tolerability, and Electrocardiographic Effects of Lofexidine When Administered Orally to Methadone Maintained Adult Subjects		
Investigator(s): Lynn R. Webster, MD		
Study center(s): PRA Health Sciences (formerly Lifetree Clinical Research), Salt Lake City, UT		
Date of first enrollment: 14 February 2012	Phase of development: 1	
Date of last completed: 05 April 2012		
<p>Objectives: The primary objective of this study was to assess QT corrected for heart rate (QTc) interaction effects between lofexidine HCl and methadone. The secondary objectives of this study were to evaluate the safety and tolerability of lofexidine hydrochloride (HCl) by evaluating and monitoring pharmacokinetics (PK), vital signs, and adverse events (AEs) when co-administered with methadone; and to describe effects on opiate withdrawal when lofexidine HCl was introduced following a 50% or 100% methadone dose reduction, as required to elicit a withdrawal response.</p>		
<p>Methodology: This was an open-label multiple ascending dose study to assess the safety, tolerability, and electrocardiographic effects of lofexidine HCl in 6 methadone-maintained adult subjects. The study included a Screening Visit, an Inpatient Treatment Visit, and a Follow-Up Visit. Subjects who were on a stable dose of methadone (80 to 120 mg/day) and who satisfied inclusion and exclusion criteria were eligible for the study. Within 21 days of the Screening Visit, subjects reported to the inpatient study facility to begin the Inpatient Treatment Visit, which lasted between 10 to 27 days. This visit included an inpatient check-in (1 day); Methadone Baseline (1 day); Initial Lofexidine Titration (up to 4 days); 1, 2 or 3 Lofexidine Plateaus (2 days each); Methadone Reduction (up to 11 days); and Methadone Re-Titration and Discharge (up to 4 days). The steps subjects proceeded through during the Inpatient Treatment Visit varied depending on subjects' ability to titrate to a 0.8 mg 4 times a day (QID) dose of lofexidine HCl (3.2 mg/day), and whether they experienced opiate withdrawal after reduction of their methadone dose. During the Methadone Baseline Phase subjects took a single daily dose of methadone at 1 PM and underwent baseline study assessments, including electrocardiogram (ECG) recording for baseline assessment and blood collection for methadone PK. The next day subjects proceeded to the Initial Lofexidine Titration Phase. Subjects continued their baseline methadone dose. Lofexidine HCl was initiated at 0.2 mg QID (0.8 mg/day) and titrated in daily increments of 0.2 mg QID to a target dose of 0.8 mg QID (3.2 mg/day), if tolerated by the subject. Lofexidine HCl doses were escalated daily, unless at any point the subject met protocol-defined dose-hold criteria, which triggered a reduction in dose to the previous highest tolerated dose. Once subjects had titrated to the 0.8 mg QID dose or their highest tolerated dose of lofexidine HCl had been reached, they proceeded to a 2-day Lofexidine Plateau Phase during which they continued to receive their baseline methadone dose. If a subject was not able to titrate up to 0.8 mg QID, the subject continued to receive their highest tolerated dose in equal increments (e.g., 0.2, 0.4, or 0.6 mg QID at 8 AM, 1 PM, 6 PM, 11 PM) for both days of the plateau. If a subject tolerated 0.8 mg QID lofexidine HCl, on the first day of the Lofexidine Plateau Phase the subject received 0.8 mg QID lofexidine HCl. On the second day of the Lofexidine Plateau Phase, the dosing</p>		

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Lofexidine hydrochloride	Volume:	
Name of Active Ingredient: Lofexidine hydrochloride	Page:	
<p>schedule was modified so that the subject received 0.8 mg lofexidine HCl at 8 AM, 1 mg at 1 PM, 0.6 mg at 6 PM and 0.8 mg at 11 PM (for a daily total of 3.2 mg); subjects also underwent ECG monitoring and blood collection for methadone and lofexidine PK.</p> <p>Subjects who were able to titrate to the 0.8 mg QID lofexidine HCl dose while receiving their full dose of methadone continued to receive the 0.8 mg QID lofexidine HCl dose while undergoing a 4-day methadone reduction at 50% of their baseline methadone dose to evaluate lofexidine's potential impact on withdrawal symptoms.</p> <p>Subjects who were unable to titrate to the 0.8 mg QID lofexidine HCl dose while receiving their full dose of methadone underwent a methadone dose reduction of 50%, or if necessary, a dose reduction of 100%, and continued lofexidine HCl titration by adding an incremental 0.2 mg QID to the previously established tolerated dose to attempt to reach the targeted 0.8 mg QID dose. In the 100% methadone reduction group, 25% of the initial methadone dose was to be started after 2 days, with daily dosing at 1 PM. During these subsequent titration attempts lofexidine HCl doses escalated daily unless a subject met protocol-defined dose-hold criteria, which triggered a reduction in dose to the previous highest tolerated dose and required the Lofexidine Plateau procedures described above to be repeated while the subject was maintained on their newly reduced methadone dose (e.g., 50% of their baseline methadone dose) and if 0.8 mg QID was not achieved with 50% reduction, Lofexidine Plateau procedures were performed again with 75% withdrawal of methadone (i.e., total methadone withdrawal initially, followed 2 days later by methadone administration once daily (QD) at 25% of the baseline dose). Subjects who were unable to titrate to a higher lofexidine HCl dose during the 50% Methadone Reduction or 100%/75% Methadone Reduction than the lofexidine HCl dose they had titrated to during the Initial Lofexidine Titration Phase (or the 50% methadone reduction) did not repeat the Lofexidine Plateau procedures.</p> <p>During methadone reduction (whether for subjects entering an experimental 4-day 50% withdrawal phase at the tolerated 0.8 mg QID lofexidine HCl dose or for subjects continuing lofexidine HCl titration at 50% or 100%/75% methadone reductions), assessments of opiate withdrawal were performed using the Clinical Opiate Withdrawal Scale (COWS) and the Short Opiate Withdrawal Scale (SOWS).</p> <p>Following completion of the Lofexidine Plateau Phase (repeated as necessary) and Methadone Reduction Phase, subjects began the Methadone Re-Titration and Discharge Phase, during which lofexidine HCl was discontinued (except to treat withdrawal symptoms as necessary) and methadone was re-titrated to the subject's starting dose (or to a higher or lower dose relative to baseline as medically indicated at the discretion of the Investigator). Following successful methadone re-titration and completion of study assessments, subjects were discharged from the inpatient study clinic.</p> <p>Subjects returned to the study clinic for a follow-up visit 7 days (±2 days) after clinic discharge for safety follow-up and AE collection. Subjects were discharged from the study at this time, unless they were medically unstable on their dose of methadone. Subjects could be medically followed at regular intervals, as determined by the Investigator, until the subject was considered sufficiently stable for study discharge.</p>		

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Subjects who withdrew consent or met any one of the following study termination criteria prior to completion of the study were withdrawn:		
<ol style="list-style-type: none"> 1. Cardiovascular events including the following: <ol style="list-style-type: none"> a. Systolic blood pressure (SBP) < 70 mmHg and > 20% below screen value* b. Diastolic blood pressure (DBP) < 40 mmHg and > 20% below screen value* c. Heart rate (HR) < 40 beats per minute (bpm) and > 20% below screen value* d. QTc > 500 msec or > 25% above screen value for both males and females* e. QT corrected using Fridericia's calculation (QTcF) > 500 msec; or QTcF > 480 msec with a concurrent increase in average QTcF value > 60 msec from the screening baseline f. Persistent increase in QTcF > 60 msec above baseline, or persistent QTcF ≥ 480 msec and ≤ 500 msec and normal electrolytes g. QRS duration > 120 msec, along with a 25% increase from baseline h. PR interval > 240 msec, along with a 25% increase from baseline i. Syncope j. Clinically significant arrhythmia (including telemetry indication of ventricular tachycardia, ventricular fibrillation, Torsade de Pointes, second degree atrioventricular block)* <p>*ECGs and vital signs could be repeated as appropriate to confirm values and rule out extraneous results.</p> 2. Serious medical problems thought to be related or unrelated to the study medications. 3. Intercurrent illness or medical complications that, in the opinion of the site Investigator, precluded safe administration of study medications. 		
At the time of termination from the study, subjects were discontinued from lofexidine HCl; however, they could remain inpatient for up to 4 days while their methadone maintenance dose was re-titrated to their pre-study maintenance (i.e., baseline) dose.		
Number of subjects (planned and analyzed): A sufficient number of subjects were planned to ensure that 6 subjects completed at least the first Lofexidine Plateau and 50% Methadone Reduction phases. Six subjects enrolled, received study medication, and were analyzed.		
Diagnosis and main criteria for inclusion: Inclusion Criteria were as follows: <ol style="list-style-type: none"> 1. Adult male and/or female, 18 to 60 years of age (inclusive). 2. Receiving methadone maintenance treatment for opioid dependence at a stable once-daily dose of 80 through 120 mg for at least 4 weeks prior to check-in for the Inpatient Treatment Visit. 3. Body mass index (BMI) ≥ 18 kg/m² and ≤ 35 kg/m². 4. Normal screening results or abnormal results that were deemed by the Investigator as clinically insignificant. 5. Able to understand and willing to sign an informed consent form (ICF). 6. Females practicing adequate birth control or of non-childbearing potential. Medically acceptable birth control methods for this study included intrauterine device (IUD); 		

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vasectomized partner (minimum of 6 months); post-menopausal (at least 2 years); surgically sterile (at least 6 months); double barrier (diaphragm with spermicide, condoms with vaginal spermicide); abstinence; implanted or intrauterine hormonal contraceptives in use for at least 6 consecutive months prior to study dosing and throughout the study duration; and oral, patch and injected hormonal contraceptives or vaginal hormonal device (i.e., NuvaRing®) in use for at least 3 consecutive months prior to study dosing and throughout the study duration.

Exclusion Criteria were as follows:

1. Abnormal cardiovascular exam at screening and before randomization, including any of the following:
 - clinically significant abnormal ECG (e.g., significant first degree atrioventricular block, complete left bundle branch block, second or third degree heart block, clinically significant arrhythmia, or QTc interval (machine-read) > 450 msec for males and > 470 msec for females)*
 - HR < 55 bpm or symptomatic bradycardia*
 - SBP < 95 mmHg or symptomatic hypotension*
 - DBP < 65 mmHg*
 - blood pressure (BP) > 155/95 mmHg*
 - change in orthostatic SBP, DBP, or HR > 25% below recumbent values
 - prior history of myocardial infarction (MI) or evidence of prior MI on ECG*
 - history of long QT syndrome or relative with this condition
 - history of syncopal episodes
 - intraventricular conduction delay with QRS duration > 120 msec
 - evidence of ventricular pre-excitation (e.g., Wolff Parkinson White syndrome)

*ECGs and vital signs may be repeated as appropriate in order to confirm values and rule out extraneous results.
2. History or presence of significant or clinically unstable cardiovascular (including atrial fibrillation, congestive heart failure, myocardial ischemia, and indwelling pacemaker), hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, psychiatric, neurologic, or dermatologic disease.
3. History or presence of any degree of chronic obstructive pulmonary disease.
4. History of suicidal ideations or depression requiring professional intervention including counseling or antidepressant medication.
5. Positive drug (urine)/alcohol (breath) test at screening or check-in excluding methadone. Subjects who had a positive test for heroin or benzodiazepines at the Screening Visit could be enrolled if the test for heroin was negative at check-in to the Inpatient Treatment Visit. Subjects who had a positive test for heroin or benzodiazepines at the Screening Visit had to sign an ICF at check-in to the Inpatient Clinic Visit.
6. Receiving methadone for pain management.
7. Positive test for human immunodeficiency virus (HIV) or hepatitis B surface antigen. Subjects with a positive test for hepatitis C virus antibodies could be enrolled if the

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<p>subject was asymptomatic.</p> <ol style="list-style-type: none"> 8. Estimated creatinine clearance < 80 mL/min at screening (Cockcroft-Gault formula). 9. Aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase > 3.0 x upper limit of normal at screening or check-in. 10. Amylase or lipase > 1.5 x upper limit normal at screening or check-in. 11. Clinically significant out-of-reference range clinical chemistry values, with particular attention to potassium, magnesium, and calcium. 12. History of hypotension. 13. History of hypersensitivity or allergy to clonidine or any clonidine analogue. 14. Use of any new prescription medication within 12 days prior to check-in. 15. Use of any over-the-counter medication, including herbal products, within the 5 days prior to check-in. Up to 2 grams per day of acetaminophen was allowed at the discretion of the Investigator/Investigator's designee. 16. Use of any drug known to affect QTc within 30 days prior to check-in (tobacco excluded). 17. Blood donation or significant blood loss within 30 days prior to check-in. 18. Plasma donation within 7 days prior to check-in. 19. Participation in another clinical trial within 30 days prior to check-in. 20. Females who were pregnant or lactating. 21. Any other condition or prior therapy, which in the opinion of the Investigator, made the subject unsuitable for this study. 		
<p>Test Product, Dose and Mode of Administration, Lot Number: Lofexidine HCl 0.2 mg tablets were used in this study. Subjects' doses were escalated daily up to 0.8 mg QID (3.2 mg/day) lofexidine HCl starting at 0.2 mg and proceeding stepwise through 0.4, 0.6, and 0.8 mg QID (1.6, 2.4 and 3.2 mg/day, respectively). QID dosing was at 8 AM, 1 PM, 6 PM, and 11 PM. Only one dose escalation per day was permitted. Lofexidine HCl doses were escalated daily unless at any predose vital signs or ECG assessment a subject met one of the following dose-hold criteria, which triggered a reduction in dose to the previous highest tolerated dose.</p> <p>Predose assessments for ascertaining if a dose hold was indicated are listed below and were performed while the subject was in a sitting and/or recumbent position:</p> <ul style="list-style-type: none"> • SBP < 90 mmHg and > 20% below screen value*; • DBP < 50 mmHg and > 20% below screen value*; • HR < 50 bpm and > 20% below screen value*; • QTcF increase > 60 msec from baseline • QTcF ≥ 480 msec and ≤ 500 msec • Symptoms of hypotension • Symptoms of bradycardia <p>Orthostatic assessments were performed after subjects had been standing for 3 minutes:</p> <ul style="list-style-type: none"> • SBP, DBP, or pulse > 25% below recumbent values. <p>*Vital signs could be repeated as appropriate in order to confirm values and rule out extraneous results.</p> <p>Lofexidine HCl tablets were administered orally with 240 mL room temperature water.</p>		

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The lot number for lofexidine HCl tablets was 94803V7191.		
Duration of Treatment: Up to 57 days (up to 21 days outpatient screening plus up to 27 days in-clinic, and 7±2 days follow-up).		
Reference Therapy, Dose and Mode of Administration, Batch Number: Commercially available oral methadone HCl was used in this study. Subjects continued the methadone maintenance formulation (oral solution or tablet) and dose they were using prior to enrollment (80 to 120 mg/day). During the Inpatient Treatment Visit, subjects' methadone dose was reduced by 50%, or 100% if necessary, to achieve lofexidine titration or to elicit opiate withdrawal. Before subjects were discharged from the study, their methadone dose was returned to their starting dose, or if in the medical opinion of the Investigator the subject merited a higher or lower dose of methadone relative to the baseline dose, the subject was discharged at the new dose instead of the baseline dose. Methadone tablets or solution was administered orally with 240 mL room temperature water.		
Criteria for Evaluation: <p>Electrocardiographic Assessments: An H12+™ digital Holter recorder was used to collect continuous ECGs during the Inpatient Treatment Visit. Holter recorder ECG extractions occurred in duplicate at scheduled time points during methadone and lofexidine HCl dosing. During ECG extractions, subjects remained in a supine position for at least 10 minutes prior to and through the duration of the 5-minute extraction. ECG evaluations for analysis were performed in a central ECG laboratory with the capacity for digital ECG signal processing. All ECGs for each subject were read by the same cardiologist. During the Methadone Baseline Day, subjects wore the Holter monitor continuously for 24 hours. During the remaining portion of the Inpatient Treatment Visit, subjects wore a Holter monitor throughout the day until 30 minutes after the final postdose collection time point, at which time the Holter monitor could be removed. Holter monitors were placed back on subjects approximately 1 hour prior to the 7 AM extraction to ensure that all required time points were collected. The Holter recorder ECG extraction window was planned so as to be completed by the time fingerprick PK samples and venous PK samples were collected at the nominal scheduled time point, as required according to the Schedule of Events. If vital signs were required at Holter/PK time points, they were done in advance of the 10 minute supine quiet period that preceded the 5 minute Holter recorder ECG extraction window.</p> <p>Clinical Opiate Withdrawal Scale Assessment: The COWS clinical assessment was used to evaluate symptoms of opioid withdrawal. The COWS was completed during the Methadone Baseline before methadone dosing. During the 50% and 100%/75% Methadone Reduction phases, 2 scheduled assessments were performed daily, one immediately prior to the 8 AM lofexidine HCl dose and the other between 11:00 and 11:30 AM. The COWS could also be completed at unscheduled time points as needed, at the Investigator's discretion throughout the treatment period (including the Methadone Re-Titration and Discharge Period).</p> <p>Short Opiate Withdrawal Scale Assessment: The SOWS clinical assessment was completed by subjects to assess symptoms of opioid withdrawal. The SOWS was completed at the same time COWS assessments were completed.</p> <p>Pharmacokinetic Assessments: Blood samples were collected at scheduled time points for PK analysis of methadone and lofexidine plasma concentrations. Blood samples for lofexidine analysis were obtained by fingerprick and blood samples for methadone were obtained by venipuncture.</p>		

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<p>Safety Assessments: AEs, physical and neurological examinations, 12-lead ECG, continuous ambulatory telemetry, vital signs, and clinical laboratory assessments (including hematology, chemistry, and urinalysis).</p>		
<p>Statistical Methods:</p> <p>Sample Size Determination: The sample size for this study was selected empirically and was not chosen for inferential purposes. The study size was chosen to provide pilot data and to confirm the feasibility of the experimental design.</p> <p>Study Analysis Data Sets: Four analysis populations were described in the Statistical Analysis Plan: a Safety Population, a PK Population, a QTc Population, and an intent-to-treat (ITT) Population. However, data from all 6 subjects were used for Safety analysis, electrocardiographic analysis, and PK analysis. The Safety Population, which was defined as all subjects who received at least 1 dose of study medication, was used for presentation of demographic and baseline characteristics, subject disposition, opiate withdrawal scales, and safety data.</p> <p>Electrocardiographic Analysis: Electrocardiographic data were intended to be exploratory, and no formal statistical analyses of the changes in QTc values were planned.</p> <p>Pharmacokinetic Analysis: Noncompartmental PK parameters for methadone and lofexidine were calculated. The maximum observed plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}) were determined as the maximum measured concentration and its associated time. The areas under the plasma concentration time curve from time 0 to 24 hours (AUC_{0-24}) and from time 0 to 5 hours, (AUC_{0-5}) were calculated using linear trapezoidal estimation. AUC_{0-24} was calculated for the methadone baseline only. AUC_{0-5} was calculated for all lofexidine and methadone profiles, including baseline.</p> <p>To determine the effect of lofexidine on methadone PK, the ratio of AUC_{0-5} for the same dose of methadone with and without lofexidine was calculated for each subject. A similar ratio was also calculated for C_{max}.</p> <p>Dose-normalized C_{max} and AUC_{0-5} for methadone were also calculated for each subject. The results were examined for evidence of a PK interaction.</p> <p>Safety Analysis: No formal statistical testing was performed on safety variables. The most current version of Medical Dictionary for Regulatory Activities (MedDRA) was used to classify all AEs with respect to system organ class and preferred term. Treatment-emergent AEs (TEAEs) were summarized. For clinical laboratory test results, descriptive statistics were used to summarize the observed results at each time point and the change from baseline, the number of subjects with a change relative to the normal range (i.e., shift tables), and the number of subjects with changes to clinically significant values. Descriptive statistics were used to summarize the observed results at each time point and the changes from baseline in vital signs.</p>		
<p>Electrocardiographic Results: ECG findings were nearly uniformly normal except for some lower HR values during baseline while on methadone alone, and further decreases in HR during lofexidine HCl treatment. QTcF values remained in the normal range with a few exceptions. PR intervals were normal and occasional values of QRS were slightly high. No morphology findings of clinical significance emerged during treatment.</p> <p>HR values were low during baseline and decreased markedly in 5 of the 6 subjects while on lofexidine HCl treatment. The minimum HR reached was 34 bpm and the greatest decrease from baseline was 50.0 bpm.</p>		

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<p>QTcF values increased moderately from baseline in 5 of 6 subjects over the course of the observations. While somewhat variable, QTcF increases were found at the majority of observations. The maximum changes in QTcF from baseline among all 6 subjects ranged from 5.0 to 31.5 msec. The single exception to the pattern was a subject with high baseline QTcF values on methadone alone who had stable or slightly decreasing values in QTcF during lofexidine HCl treatment.</p> <p>Analysis of subjects on Plateau Days grouped by total daily dose of lofexidine HCl, at either 100% or 50% of their baseline methadone, showed mean increases in QTcF from baseline at the majority of observations, with maximum mean values of change in QTcF for the 7 analysis groups ranging from 8.5 to 31.5 msec. The maximum mean increase was for a total daily dose of 2.4 mg lofexidine HCl at 100% methadone.</p> <p>Small increases in the QTcF with lofexidine HCl treatment were confirmed using concentration-QT analysis. The estimated mean change in QTcF from baseline was 2.4 msec at the highest observed lofexidine concentration, 7.68 ng/mL, and only 0.1 msec at the mean concentration of all lofexidine samples, 3.52 ng/mL. A positive correlation was also observed for change in the QTcF and methadone concentration. There was a negative correlation observed between the change in QTcF and increasing HR.</p> <p>Additional findings:</p> <ul style="list-style-type: none"> • In 2 subjects, 1 with high QTcF baseline values, 12 instances of QTcF > 450 msec were seen during lofexidine HCl treatment (1 subject had 7 instances and 1 subject had 5 instances) but in no case was any QTcF value > 480 msec; • There was a single increase in QTcF from baseline that exceeded 30 msec (31.5 msec) but the QTcF remained within the normal range (432 msec); • PR and QRS interval data were unremarkable; • There were no emergent clinically significant ECG morphologic changes. <p>Overall, during administration of lofexidine HCl added to methadone dosing in opiate-dependent subjects, ECG findings showed decreases in HR from already low values during baseline, and a trend for slight increases in QTcF. The QTcF values generally remained in the normal range. QT interval corrected using Bazett's method (QTcB) values were unreliable and did not follow the overall pattern seen for QTcF. Because of the over-correction inherent in Bazett's formula, decreasing HR values during active treatment compared to baseline resulted in erroneously lower values of QTcB after baseline. QTcB changes from baseline were without clear trends over the course of the observations and generally showed decreases rather than increases. The maximum and minimum changes in QTcB were 21.0 and -59.0 msec, respectively. These findings should be discounted, as the low HR values invalidated QTcB findings and also raised uncertainty about the QTcF findings because of possible similar limitations in the Fridericia correction at such low values of HR.</p>		
<p>Pharmacokinetic Results: The results for methadone at 100% and 50% of the baseline dose are shown in Table S-1. The baseline doses of methadone HCl ranged from 80 to 120 mg/day, with a mean of 97.5 mg/day. The results for lofexidine are shown in Table S-2 and are summarized by lofexidine dose.</p>		

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Table S-1: Pharmacokinetic Parameters for Methadone

Parameter	% of Baseline Methadone		n
		Mean ± SD	
C _{max} (ng/mL)	100%	557 ± 148	13 ^b
	50%	389 ± 93	6
C _{min} (ng/mL)	100%	323 ± 141	13 ^b
	50%	265 ± 105	6
AUC ₀₋₅ (ng•hr/mL)	100%	2,395 ± 706	13 ^b
	50%	1,749 ± 475	6
AUC ₀₋₂₄ (ng•hr/mL)	100%	9,276 ± 3,780	6
<u>C_{max} with Lofexidine</u>	(ratio)	100%	1.05 ± 0.15
<u>C_{max} without Lofexidine</u>			
<u>C_{min} with Lofexidine</u>	(ratio)	100%	1.35 ± 0.39
<u>C_{min} without Lofexidine</u>			
<u>AUC₀₋₅ with Lofexidine</u>	(ratio)	100%	1.07 ± 0.18
<u>AUC₀₋₅ without Lofexidine</u>			
NC _{max} (ng/mL/mg)	100%	5.75 ± 1.48	13 ^b
	50%	7.68 ± 1.78	6
NC _{min} (ng/mL/mg)	100%	3.29 ± 1.29	13 ^b
	50%	5.21 ± 1.83	6
NAUC ₀₋₅ (ng•hr/mL/mg)	100%	24.7 ± 6.9	13 ^b
	50%	34.5 ± 8.8	6
T _{max} (hr)	100% & 50%	3.12 ^a (1.22 - 6.15)	19
T _{min} (hr)	100% & 50%	0 ^a (0 - 10.1)	19
t _{1/2}	100%	25.3 ± 8.5	5

AUC₀₋₅ = area under the plasma concentration time curve from time 0 to 5 hours; AUC₀₋₂₄ = area under the plasma concentration time curve from time 0 to 24 hours; C_{max} = maximum observed plasma concentration; C_{min} = minimum observed plasma concentration; NAUC₀₋₅ = dose-normalized area under the plasma concentration time curve from time 0 to 5 hours; NC_{max} = dose-normalized maximum observed plasma concentration; NC_{min} = dose-normalized minimum observed plasma concentration; SD = standard deviation; T_{max} = time to maximum plasma concentration; T_{min} = time to minimum plasma concentration; t_{1/2} = apparent terminal elimination half-life

^a The values for T_{max} and T_{min} are median (range) and were for 100% and 50% combined.

^b The values for the parameters are an average from 13 concentration-time profiles collected from a total of six subjects: one 24-hour profile and one or two 5-hour profiles.

Table S-2: Pharmacokinetic Parameters for Lofexidine

Parameter	1.6 mg Lofexidine HCl/Day (Doses of 0.4 mg QID) n = 4	2.4 mg Lofexidine HCl/Day (Doses of 0.6 mg QID) n = 3	3.2 mg Lofexidine HCl/Day (Doses of 0.8, 1.0, 0.6, and 0.8 mg during day) n = 5
	Mean± SD	Mean± SD	Mean± SD
C _{max} (ng/mL)	3.54± 0.82	6.29± 1.94	6.69± 0.70
T _{max} (hr)	3.14 ^a (2.13 - 4.13)	1.13 ^a (0 - 2.13)	2.15 ^a (2.10 - 3.15)
C _{min} (ng/mL)	2.69 ± 0.45	4.50± 1.32	4.71± 0.77
T _{min} (hr)	0.32 ^a (0 - 3.12)	0.63 ^a (0.62 - 3.13)	0.65 ^a (0 - 1.17)
AUC ₀₋₅ (ng•hr/mL)	15.7± 2.9	25.8± 6.7	29.0± 3.9

AUC₀₋₅ = area under the plasma concentration time curve from time 0 to 5 hours; C_{max} = maximum observed plasma concentration; C_{min} = minimum observed plasma concentration; T_{max} = time to maximum plasma concentration; T_{min} = time to minimum plasma concentration

^a Values for T_{max} and T_{min} are median (range).

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<p>Opiate Withdrawal Results: Most mean COWS Total Scores were reduced from baseline at the postdose assessment after methadone reduction; however, the magnitude of the changes was modest, and there was a high degree of individual variability. No notable patterns were observed in mean COWS item scores or changes from baseline.</p> <p>Mean SOWS Total Score at baseline indicated minimal withdrawal symptoms (3.3 [standard deviation, SD 5.92]). Mean SOWS Total Scores were less than 5 through the 50% Methadone Reduction and Second Lofexidine Plateau. Most mean SOWS Total Scores were reduced from baseline at the postdose assessment; however, the magnitude of the mean changes was modest, and there was a high degree of individual variability (individual change from baseline to postdose ranged from -15 to +6). Most symptoms reported at baseline were mild, although for one subject, withdrawal symptoms at baseline were rated as moderate (score of 15). Severe withdrawal symptoms were reported by 2 subjects during 100% Methadone Reduction and 1 subject during 50% Methadone Reduction.</p> <p>The small sample size limits the conclusions that can be drawn from the COWS and SOWS data.</p>		
<p>Safety Results: There were no serious adverse events (SAEs) or withdrawals due to AEs and most events were mild in severity. Systolic BP, DBP, and pulse rates were reduced from baseline during the study. Two subjects experienced AEs of mild bradycardia; the bradycardia was considered at least possibly related to study treatment in 1 subject. There were no AEs of hypotension. Three subjects experienced 5 anxiety events, of which 4 events in 2 subjects were considered at least possibly related to study treatment. None of the subjects experienced insomnia. In patients undergoing opioid withdrawal and treated with lofexidine, insomnia and anxiety are still frequently seen. Overall, the concomitant administration of lofexidine with methadone was well-tolerated. There were no unexpected safety signals.</p>		
<p>Conclusions</p> <p>The ability to determine clear relationships between drug concentrations and cardiac repolarization effects was limited due to the small number of subjects and treatment doses that varied subject-by-subject. However, the methodology allowed collection of detailed interaction data of lofexidine HCl and methadone on both cardiac (especially QTc) and PK parameters of interest. With regard to QTc and other ECG parameters, there was no significant safety signal for lofexidine HCl up to 3.2 mg/day co-administered with methadone HCl at 80 to 120 mg/day in the small sample of 6 subjects. Further there was no indication of any influence of lofexidine on the PK of methadone.</p> <p>Most mean COWS and SOWS Total Scores were reduced from baseline at the postdose assessment after methadone reduction; however, the small sample size limits the conclusions that can be drawn from the COWS and SOWS data.</p> <p>Overall safety evaluations (including AEs, clinical chemistries and vital signs) did not identify any unexpected safety signals; most events were mild in severity and there were no SAEs or withdrawals due to AEs. The AEs detected were similar to those found in earlier studies with lofexidine HCl in the opioid-dependent population. Overall, the concomitant administration of lofexidine HCl with methadone was well tolerated.</p> <p>Date of the Report: 16 May 2016</p>		

2 SYNOPSIS

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Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Assess the Safety, Tolerability, and Electrocardiographic Effects of Lofexidine When Administered Orally to Methadone Maintained Adult Subjects		
Investigator(s): Lynn R. Webster, MD		
Study center(s): Lifetree Clinical Research / PRA Health Sciences, Salt Lake City, UT		
Date of first screening: 02 July 2012	Phase of development: 1	
Date of last follow-up: 19 December 2012		
Objectives: The primary objective of this study was to assess QTc interaction effects between lofexidine and methadone. The secondary objectives of this study were to evaluate the safety and tolerability of lofexidine by evaluating and monitoring pharmacokinetics (PK), vital signs and adverse events when co-administered with methadone; describe effects on opiate withdrawal when lofexidine is introduced following a 50% methadone dose reduction, as required to elicit a withdrawal response; and evaluate QTc interaction effects of lofexidine compared with placebo.		
Methodology: This was a randomized, double-blind, placebo-controlled multiple ascending dose study to assess the safety, tolerability, and electrocardiographic effects of lofexidine in methadone-maintained adult subjects. The study included a Screening Visit, an Inpatient Treatment Visit, and a Follow-Up Visit. Subjects were randomized in 3:1 ratio to receive up to 4 tablets of lofexidine hydrochloride (HCl) (0.2 mg/tablet) 4 times a day (QID) or 4 tablets matching placebo QID.		
Subjects who were on a stable dose of methadone HCl (80 to 120 mg/day) and who satisfied inclusion and exclusion criteria were eligible for the study. Within 21 days of the Screening Visit, subjects reported to the inpatient study facility to begin the Inpatient Treatment Visit which could last from approximately 11 to 21 days. This visit included an inpatient check-in (1 day), Methadone Baseline (1 day), Initial Lofexidine Titration (3 to 5 days), 1 or 2 Lofexidine Plateaus (2 to 4 days), Methadone Reduction (2 to 6 days) and Methadone Re-Titration and Discharge (2 to 4 days). The order of steps subjects proceeded through during the Inpatient Treatment Visit varied depending on whether subjects were able to titrate to the highest dose of lofexidine (or placebo) during the Initial Lofexidine Titration. The highest dose of lofexidine (or placebo) was 4 tablets QID (0.2 mg lofexidine HCl per tablet or placebo) for a total daily lofexidine HCl dose of 3.2 mg or 16 tablets of placebo.		
During the Methadone Baseline phase subjects took a single daily dose of methadone at 1 PM and underwent baseline study assessments including electrocardiogram (ECG) monitoring, blood collection for methadone PK, and opiate withdrawal assessments (Clinical Opiate Withdrawal Scale [COWS] and Short Opiate Withdrawal Scale [SOWS]). The next day subjects proceeded to		

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the Initial Lofexidine Titration phase. Subjects continued using their baseline methadone dose. Lofexidine HCl was initiated at 2 tablets (0.4 mg or placebo) QID and titrated in daily increments of a single tablet (0.2 mg or placebo) QID to 0.8 mg QID (or placebo), if tolerated by the subject. Lofexidine doses were escalated daily unless at any point the subject met protocol-defined dose hold criteria, which triggered a withholding of the next dose and possibly a reduction in dose to the previous highest tolerated dose (or to the 1 tablet dose, 0.2 mg or placebo, if subjects could not tolerate the initial 2 tablets). Once subjects had titrated to the highest dose (i.e., 0.8 mg QID) or once subjects' highest tolerated dose had been determined, they proceeded to a 2-day Lofexidine Plateau phase during which they continued to receive their methadone maintenance dose. If the subject was unable to titrate up to 4 tablets QID (0.8 mg QID or placebo), the subject continued to receive their highest tolerated dose in equal increments (e.g., 2 or 3 tablets QID at 8 AM, 1 PM, 6 PM, 11 PM) for both days of the plateau. If the subject tolerated 4 tablets QID (0.8 mg QID or placebo) on the first day they received the 4 tablets QID (0.8 mg QID or placebo) according to the normal dosing schedule. On the second day, the lofexidine dosing schedule was modified so that subjects received 0.8 mg at 8 AM, 1 mg at 1 PM, 0.6 mg at 6 PM, and 0.8 mg at 11 PM, for a total daily dose of 3.2 mg lofexidine HCl or placebo. On this second day of the Lofexidine Plateau phase, subjects underwent ECG monitoring and blood collection for methadone and lofexidine PK. COWS and SOWS assessments were performed on both days of the Lofexidine Plateau.

Subjects who were titrated to a daily dose of 3.2 mg (or placebo) while receiving their full dose of methadone underwent a 4-day methadone dose reduction of 50% while continuing to take lofexidine or placebo at a dose of 3.2 mg/day to evaluate the effects of lofexidine on methadone withdrawal signs and symptoms. These subjects who completed the initial Lofexidine Plateau at a dose of 3.2 mg/day lofexidine HCl (or placebo) and who reached a COWS score of 5 or greater prior to the fourth day of the reduced methadone dose administration were permitted to proceed early to Methadone Re-titration and Discharge at the Investigator's discretion. If the COWS score did not reach 5 by 4 days, the subject proceeded to Methadone Re-titration and Discharge.

Subjects who were unable to titrate to the highest lofexidine HCl dose (3.2 mg/day) or placebo while receiving their full dose of methadone underwent a methadone dose reduction of 50% for up to 6 days while continuing to receive their highest tolerated dose of lofexidine from the initial titration. On the fourth day (or earlier at the Investigator's discretion based on withdrawal response), lofexidine titration resumed by adding an incremental 0.2 mg lofexidine HCl (or placebo) per dose to the previously established tolerated dose up to the maximum 3.2 mg/day (or placebo). During these subsequent titration attempts, lofexidine (placebo) doses were escalated daily beginning on the fourth day of the reduction (or earlier based on discretion of the Investigator) unless in any event a subject met protocol defined dose-hold criteria, which triggered a missed dose and possibly a reduction in dose to the previous highest tolerated dose and required the Lofexidine Plateau procedures described above to be repeated while maintaining the subject on their newly reduced methadone dose (e.g., 50% of their maintenance dose). Subjects

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<p>who were unable to titrate to a higher lofexidine dose during the 50% Methadone Reduction than the dose they titrated to during the Initial Lofexidine Titration did not repeat the Lofexidine Plateau procedures.</p>		
<p>During Methadone Reduction (whether for subjects entering an experimental 4-day 50% withdrawal phase at the tolerated 3.2 mg/day lofexidine HCl dose [or placebo] or for subjects continuing lofexidine titration at 50% methadone reduction), COWS and SOWS assessments of opiate withdrawal were performed.</p>		
<p>Following completion of the Lofexidine Plateau (repeated as necessary) and Methadone Reduction, subjects began the Methadone Re-Titration and Discharge phase during which lofexidine or placebo was discontinued and methadone was re-titrated to the starting dose (or to a higher or lower dose relative to baseline as medically indicated at the discretion of the Investigator). Lofexidine could be used to treat withdrawal symptoms, if necessary. Following successful methadone titration and completion of study assessments, subjects were discharged from the inpatient study clinic.</p>		
<p>Subjects returned to the study clinic for a follow-up visit 7 days (\pm 2 days) following clinic discharge for safety follow-up and adverse event collection. Subjects were discharged from the study at this time unless they were medically unstable on their dose of methadone. Subjects could be medically followed at regular intervals, as determined by the Investigator, until the subject was considered sufficiently stable for study discharge.</p>		
<p>Number of subjects (planned and analyzed): A sufficient number of subjects were to be enrolled to ensure 24 subjects completed at least the first Lofexidine Plateau and 50% Methadone Reduction phases. Subjects who did not complete these phases were to be replaced. Twenty-seven subjects enrolled, received study medication, and were analyzed.</p>		
<p>Diagnosis and main criteria for inclusion:</p>		
<p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Adult male and/or female, 18 to 60 years of age (inclusive). 2. Receiving methadone maintenance treatment for opioid dependence at a stable once-daily dose of 80 through 120 mg for at least 4 weeks prior to check-in for the Inpatient Treatment Visit. 3. Body mass index \geq 18 and \leq 35 (kg/m²). 4. Normal screening results or abnormal results that have been deemed by the Investigator as clinically insignificant. 5. Able to understand and willing to sign an informed consent form (ICF). 6. Females practicing adequate birth control or of non-childbearing potential. Medically acceptable birth control methods for this study include intrauterine device (IUD); vasectomized partner (minimum of 6 months); post-menopausal (at least 2 years); 		

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<p>surgically sterile (at least 6 months); double barrier (diaphragm with spermicide, condoms with vaginal spermicide); abstinence; implanted or intrauterine hormonal contraceptives in use for at least 6 consecutive months prior to study dosing and throughout the study duration; and oral, patch and injected hormonal contraceptives or vaginal hormonal device (i.e., NuvaRing®) in use for at least 3 consecutive months prior to study dosing and throughout the study duration.</p> <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> Abnormal cardiovascular exam at screening and before randomization, including any of the following: <ul style="list-style-type: none"> clinically significant abnormal ECG (e.g., significant first degree atrioventricular block, complete left bundle branch block, second or third degree heart block, clinically significant arrhythmia, or QTc interval [machine read] greater than 450 msec for males and greater than 470 msec for females)* heart rate < 55 beats per minute (bpm) or symptomatic bradycardia* systolic blood pressure (SBP) < 95 mmHg or symptomatic hypotension* diastolic blood pressure (DBP) < 65 mmHg* blood pressure (BP) > 155/95 mmHg* change in orthostatic SBP, DBP, or heart rate >25% below recumbent values prior history of myocardial infarction (MI) or evidence of prior MI on ECG* history of long QT syndrome or relative with this condition history of syncopal episodes intraventricular conduction delay with QRS duration >120 ms evidence of ventricular pre-excitation (e.g., Wolff Parkinson White syndrome) <p>*ECGs and vitals could be repeated as appropriate in order to confirm values and rule out extraneous results.</p> History or presence of significant or clinically unstable cardiovascular (including atrial fibrillation, congestive heart failure, myocardial ischemia, indwelling pacemaker), hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, psychiatric, neurologic, or dermatologic disease. History or presence of any degree of chronic obstructive pulmonary disease. History of suicidal ideations or depression requiring professional intervention including counseling or antidepressant medication over the past 12 months. Positive drug (urine)/alcohol (breath) test at screening or check-in excluding methadone. Subjects who had a positive test for heroin or benzodiazepines at the Screening Visit could be enrolled if the test for heroin was negative at check-in to the Inpatient Treatment 		

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<p>Visit. Subjects who had a positive test for heroin or benzodiazepines at the Screening Visit signed an ICF at check-in to the Inpatient Clinic Visit.</p> <ol style="list-style-type: none"> 6. Receiving methadone for pain management. 7. Positive test for human immunodeficiency virus (HIV) or hepatitis B surface antigen (HbsAg). Subjects with a positive test for hepatitis C antibodies (HCV) could be enrolled if the subject was asymptomatic. 8. Estimated creatinine clearance < 80 mL/minute at screening (Cockcroft-Gault formula). 9. Aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase > 3.0 x upper limit of normal at screening or check-in. 10. Amylase or lipase > 1.5 x upper limit normal at screening or check-in. 11. Clinically significant out-of-reference range clinical chemistry values, with particular attention to potassium, magnesium, and calcium. 12. History of hypotension. 13. History of hypersensitivity or allergy to clonidine or any clonidine analogue. 14. Use of any new prescription medication within 12 days prior to check-in. 15. Use of any over-the-counter medication, including herbal products, within the 5 days prior to check-in. Up to 2 grams per day of acetaminophen was allowed at the discretion of the principal investigator/ principal investigator's designee. 16. Use of any drug known to affect QTc within 30 days prior to check-in (tobacco and methadone excluded). 17. Blood donation or significant blood loss within 30 days prior to check-in. 18. Plasma donation within 7 days prior to check-in. 19. Participation in another clinical trial within 30 days prior to check-in. 20. Females who were pregnant or lactating. 21. Participation in the lofexidine HCl pilot protocol USWM-LX1-1005-1. 22. Any other condition or prior therapy, which, in the opinion of the Investigator, would make the subject unsuitable for this study. 		
<p>Test Product, Dose and Mode of Administration, Lot Number: Lofexidine HCl 0.2 mg tablets were used in this study. Subjects were escalated daily up to 0.8 mg QID lofexidine HCl starting at 0.4 mg QID and proceeding stepwise through 0.6 and 0.8 mg QID. QID dosing was at approximately 8 AM, 1 PM, 6 PM, and 11 PM. Only one dose escalation per day was permitted. Lofexidine doses were escalated daily unless at any predose vital signs or ECG assessment the subject met one of the following dose hold criteria, which triggered a withholding of the next dose and possibly a reduction in dose to the previous highest tolerated dose.</p> <p>Assessments were performed while subject was in a sitting and/or recumbent position:</p>		

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<ul style="list-style-type: none"> • Systolic blood pressure <90 mmHg and >20% below baseline value*; • Diastolic blood pressure <50 mmHg and >20% below baseline value*; • Heart rate <50 bpm and >20% below baseline value*; • QT interval corrected using Fridericia’s method (QTcF) increase >60 msec from baseline • QTcF ≥480 msec and ≤500 msec • Symptoms of hypotension • Symptoms of bradycardia <p>Orthostatic assessments were performed after subject had been standing for 3 minutes:</p> <ul style="list-style-type: none"> • Systolic blood pressure, diastolic blood pressure, or pulse >25% below recumbent values. <p>*ECG and vitals could be repeated as appropriate in order to confirm values and rule out extraneous results.</p> <p>Lofexidine HCl tablets were administered orally with 240 mL room temperature water. The lot number for lofexidine HCl was 94803V7191.</p>		
<p>Duration of Treatment: Up to 51 days (up to 21 days outpatient screening plus up to 21 days in-clinic, and 7±2 days follow-up).</p>		
<p>Reference Therapy, Dose and Mode of Administration, Batch Number: Commercially available oral methadone HCl was used in this study. Subjects continued the methadone maintenance formulation (oral solution or tablet) and dose they were using prior to enrollment (80-120 mg/day). During the Inpatient Treatment Visit, subjects’ methadone dose was reduced by 50% to achieve lofexidine titration if necessary and to elicit opiate withdrawal. Before subjects were discharged from the study, their methadone was returned to their starting dose, or if, in the medical opinion of the Investigator, the subject merited a higher or lower dose of methadone relative to the baseline dose, the subject was discharged with the new dose instead of the baseline dose. Methadone HCl tablets or solution was administered orally with 240 mL room temperature water.</p>		
<p>Criteria for Evaluation:</p> <p><u>Electrocardiographic Assessments:</u> An H12™ digital Holter recorder was used to collect continuous ECGs during the Inpatient Treatment Visit. This recorder provides 12-lead data recorded on a compact flash memory card. Holter ECG extractions for heart rhythms were taken in duplicate at scheduled time points during methadone and lofexidine (or placebo) dosing. During ECG extractions, subjects remained in a supine position for at least 10 minutes prior to and through the duration of the 5-minute extraction. Subjects could be placed in semi-recumbent or in Trendelenburg’s position if indicated due to an adverse event. Lead checks were to be performed in each 10-minute supine pre-extraction window. Continuous Holter monitoring and</p>		

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<p>ECG extractions were performed during the Inpatient Treatment Visit at specified time points. During the Methadone Baseline day, subjects wore the Holter monitor continuously for 24 hours. During the remaining portion of the Inpatient Treatment Visit, subjects wore a Holter monitor throughout the day until 30 minutes after the final postdose collection time point, at which time the Holter monitor could be removed. Holter monitors were placed back on the subjects at a minimum 20 minutes prior to the 7 AM extraction to ensure that all required time points were collected. The extraction window was planned based on being immediately followed by fingerprick PK samples and venous PK samples occurring at the nominal time point, as required according to the Schedule of Events. If vital signs were required at Holter/ PK time points, they were done in advance of the 10-minute supine period prior to scheduled Holter extraction windows. During Methadone Baseline, a 24-hour post (1 PM) dose ECG extraction was required that overlapped with the 1 PM dosing on the Initial Lofexidine Titration Day. For this time point, the ECG extraction window was started at 23 hours, 55 minutes postdose (or 12:55 PM) and ended at the nominal time point when dosing was to occur (1 PM).</p> <p>Holter ECG evaluations for analysis were performed in a central ECG laboratory with the capacity for digital ECG signal processing. All ECGs for an individual subject were read by a single cardiologist.</p> <p><u>Clinical Opiate Withdrawal Score Assessment:</u> The Clinical Opiate Withdrawal Scale (COWS) is a clinical assessment that was used to evaluate signs and symptoms of opioid withdrawal. The COWS was completed each day immediately prior to the 8 AM lofexidine/placebo dose and between 11:00 and 11:30 AM. It could also be completed at unscheduled time points as deemed necessary by the Investigator. For subjects who titrated to a dose of 3.2 mg/day lofexidine HCl (or placebo) during the Initial Lofexidine Titration, if the COWS score reached 5 or greater prior to the fourth day of the reduced methadone dose administration, subjects could proceed early to Methadone Re-titration and Discharge at the Investigator's discretion. If the COWS score did not reach 5 by 4 days, then subject proceeded to Methadone Re-titration and Discharge.</p> <p><u>Short Opiate Withdrawal Scale Assessment:</u> The Short Opiate Withdrawal Scale (SOWS) is a clinical assessment that subjects completed to evaluate symptoms of opioid withdrawal. The SOWS was completed at the same time COWS assessments were completed.</p> <p><u>Pharmacokinetic Assessments:</u> Blood samples were collected at scheduled time points for PK analysis of methadone and lofexidine. Blood samples for lofexidine analysis were obtained by fingerprick and blood samples for methadone were obtained venously.</p> <p><u>Safety Assessments:</u> Adverse events, physical and neurological examinations, 12-lead electrocardiogram, continuous ambulatory telemetry, vital signs, and clinical laboratory assessments (including hematology, chemistry, and urinalysis) were collected.</p>		
<p>Statistical Methods:</p> <p><u>Sample Size Determination:</u> The sample size for this study was based on clinical and practical considerations and not on a formal statistical power calculation. The sample size is considered</p>		

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<p>large enough to indicate the presence or absence of a clinically relevant effect on ECG parameters by lofexidine when added as a concomitant medication in methadone-maintained patients. Sufficient subjects were enrolled in this study to ensure that 24 subjects completed at least the first Lofexidine Plateau and 50% Methadone Reduction phases.</p> <p>Study Analysis Data Sets: Four analysis populations were described in the Statistical Analysis Plan: a Safety Population, a PK Population, a QTc Population, and an Intent-to-Treat (ITT) Population. The Safety Population was defined as all subjects who receive at least one dose of study medication. The PK Population was defined as all lofexidine and placebo treated subjects with sufficient PK data to estimate one or more of the PK parameters. The QTc Population was defined as all subjects with Holter ECG data and matching lofexidine/placebo and methadone samples for at least one dose of lofexidine/placebo. The ITT Population was defined as all subjects enrolled in the study.</p> <p>The following groups were defined based on subjects' lofexidine titration pathway:</p> <ul style="list-style-type: none"> • Group A (Scenario 1): Subjects who underwent complete titration to the maximum lofexidine dose during 100% Methadone (3.2 LFX 100% MD for electrocardiographic evaluation) • Group B (Scenario 2): Subjects who underwent complete titration to the maximum lofexidine dose during 50% Methadone Reduction (3.2 LFX 50% MD) • Group C (Scenario 3): Subjects who were unsuccessful with lofexidine titration to reach the maximum lofexidine dose (1.6 LFX 50% MD, 2.4 LFX 50% MD). • Group D: Subjects who discontinued the study. <p>Electrocardiographic Analysis from Holter Monitors: Summary statistics were calculated for heart rate (HR), PR, QRS, QT interval corrected using Bazett's method (QTcB) and QTcF, for the analysis groups on the Plateau Days and Titration Days by time point. While no formal comparison was made, the discussion addresses differences between changes of intervals from baseline for the Analysis Groups on the Plateau Days and Titration Days by time point.</p> <p>Pharmacokinetic Analysis: Noncompartmental PK parameters for methadone and lofexidine were calculated. The maximum concentration, C_{max}, and time of maximum concentration, T_{max}, were determined as the maximum observed concentration and its associated sample collection time. The areas under the plasma concentration curve from 0 to 24 hours, AUC_{0-24}, and from 0 to 5 hours, AUC_{0-5}, were calculated using linear trapezoidal estimation. AUC_{0-24} was calculated for the methadone baseline only. AUC_{0-5} was calculated for Plateau Day lofexidine and methadone profiles and for methadone on Baseline Day.</p> <p>To determine the effect of lofexidine on methadone PK, the ratio of AUC_{0-5} for the same dose of methadone with and without lofexidine was calculated for each subject. Similar ratios were also calculated for C_{max}. Means and standard deviations were calculated, if possible, for the ratios of C_{max} and AUC_{0-5} for methadone with and without lofexidine.</p>		

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<p>The dose normalized versions of C_{max} and AUC_{0-5} for each subject were subjectively evaluated for evidence of a PK interaction. The evaluation was open-ended and subjective because of the variety of doses used for each drug and the small number of subjects.</p>		
<p>Safety Analysis: No formal statistical testing was performed on safety variables. The most current version of Medical Dictionary for Regulatory Activities (MedDRA) was used to classify all adverse events (AEs) with respect to system organ class and preferred term. Treatment-emergent AEs (TEAEs) were summarized. For clinical laboratory test results, descriptive statistics were used to summarize the observed results at each time point and the change from baseline, the number of subjects with a change relative to the normal range (i.e., shift tables), and the number of subjects with clinically significant changes. Descriptive statistics were used to summarize the observed results at each time point and the changes from baseline in vital signs. Side-by-side boxplots of sitting heart rate and blood pressure results and change from baseline for each treatment and treatment phase were provided in graphs over time, separately.</p>		
<p>Electrocardiographic (Holter) Results: Protocol LX1-1005-2 provided ECG results establishing the safety of lofexidine + methadone for all ECG measurements studied.</p>		
<p>There were several values of QTcF >450 msec in both placebo and lofexidine-treated subjects and during both Baseline (methadone only) and following study drug administration. One subject in the 3.2 mg lofexidine HCl (LFX) 100% methadone HCl (MD) group (Group A) had a QTcF = 489 msec, although the change from baseline was less than 30 msec (13 msec). No changes from baseline in QTcF were >30 msec. QTcB values were unreliable because of the low heart rate values and are not discussed in this report.</p>		
<p>Regression analysis of change from baseline in QTcF as a function of log concentration of lofexidine confirmed a slight increase in QTcF with increasing lofexidine concentration, with a slope of 3.45 but the p-value indicated that the slope was not statistically different from a slope of 0. The predicted change from baseline in QTcF at the maximal lofexidine plasma concentration (14.9 ng/mL) observed following multiple days of dosing at 3.2 mg/day was only 3.0 msec with an upper 2-sided 95% confidence bound of 7.6 msec.</p>		
<p>A general decrease in HR values was seen during Plateau Day observations in subjects receiving lofexidine, with the largest decrease being a mean change in HR of -17.2 bpm for the 3.2 LFX 100% MD group at the -0.2 hour time point. On Titration Days, values of HR also decreased, maximally for the 3.2 LFX 100% MD group by a mean of -14.7 bpm.</p>		
<p>QTcF showed slight increases on Plateau Days in lofexidine-treated subjects. The greatest increase was for the 3.2 LFX 100% MD group where mean QTcF increased 9.1 msec at -6 hours.</p>		
<p>Normal results were found for PR and QRS and no emergent diagnostic findings of importance were noted.</p>		
<p>The modest association between increasing lofexidine concentration and increases in the change of QTcF were well below the expected range of concern for repolarization abnormalities. QTcF</p>		

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outliers were minimal and diagnostic findings without indication of adverse repolarization effects.

Overall, no important ECG safety signal was detected in this small but well-studied population.

Pharmacokinetic Results: Lofexidine had no apparent effect on the pharmacokinetics of methadone. The results for the methadone pharmacokinetic parameters during the first lofexidine plateau were similar for the lofexidine and placebo groups. While there was a slight increase in methadone C_{max} and AUC_{0-5} from baseline (no lofexidine for either group) to the first plateau, which had doses of lofexidine HCl from 1.6 to 3.2 mg/day for the lofexidine group and no lofexidine in the placebo group, the increases from baseline to plateau were similar for both the placebo and lofexidine groups suggesting the increase was not related to a pharmacokinetic interaction between lofexidine and methadone. The slight increase in the steady-state methadone profiles during the course of the study may be related to greater compliance to the methadone dose while in the inpatient setting with the dose administered by the staff, and/or the shift in the timing of taking the methadone dose to 1 PM while participating in the study.

Fifteen of the 18 subjects in the lofexidine group and all seven of the subjects in the placebo group completed the lofexidine titration to 0.8 mg QID within three days. During the titrations, there were slight increases in mean methadone concentrations with time that affected both the lofexidine and placebo groups. Sixteen of the 18 subjects in the lofexidine group reached the targeted maximum dose (3.2 mg/day) while also receiving 100% of their original methadone maintenance dose. One of the lofexidine subjects reached the 3.2 mg/day target at 50% of the original methadone maintenance dose, while the remaining lofexidine subject's maximal tolerated dose was 2.4 mg/day even at 50% of the original methadone maintenance dose.

Two subjects in the lofexidine group had a second lofexidine plateau at 50% of the baseline methadone dose. The C_{max} and AUC_{0-5} values for methadone were less than the values at the first plateau, although there was some indication the decrease was not proportional to the decrease in dose.

Although the study was not designed to directly determine possible effects of methadone on lofexidine pharmacokinetics, there was no indirect evidence of any interaction. At the 100% methadone maintenance plateau, the inter-subject variabilities in C_{max} and AUC_{0-t} were less than 40%, indicating consistency across the range of methadone doses. The mean and median dose-normalized NC_{max} and $NAUC_{0-5}$ for lofexidine were similar across all doses, indicating linear pharmacokinetics for lofexidine.

The C_{max} and AUC_{0-5} values for lofexidine for the two subjects that required the 50% methadone dose reduction to reach their maximal lofexidine doses were within the ranges of values for all lofexidine subjects at 100% methadone maintenance dose. For the 5-hour sampling period during the second day of the plateaus, there was no distinct elimination phase and values for the apparent terminal elimination half-life ($t_{1/2}$) could not be calculated. However, the lofexidine profiles were consistent with the reported elimination half-life of 11 hours. Small increases in NC_{max} and $NAUC_{0-5}$ values for lofexidine between the first plateau at 100% methadone maintenance and the second plateau several days later at 50% methadone maintenance were consistent with reported

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<p>accumulation of lofexidine for up to four days.</p> <p>During the lofexidine titration phase, the lofexidine concentrations increased with increasing dose and duration of dosing.</p> <p>Opiate Withdrawal Results: The COWS and SOWS assessments were collected as pilot data related to potential efficacy of lofexidine to alleviate signs and symptoms from methadone withdrawal. Due to the variable and individualized nature of the two titration phases of the study, subjects even in the same treatment arm may have had different dosing and different number of days in each phase (e.g., due to dose holds), making interpretation of daily change scores for the COWS and SOWS assessments difficult.</p> <p>For both COWS and SOWS, mean scores were numerically lower for lofexidine subjects than for placebo subjects when the methadone dose was reduced by 50%.</p> <p>Change from 100% methadone (initial Lofexidine Plateau Day 2) was more than double for the placebo group compared with the lofexidine group for the COWS assessment and was more than triple for the placebo group compared with the lofexidine group for the SOWS assessment, though the differences did not reach statistical significance.</p>		
<p>Safety Results: There were no deaths in this study. One subject experienced an SAE and was withdrawn from the study during the Methadone Baseline phase prior to receiving lofexidine or placebo. The most common at least possibly related TEAEs were headache, orthostatic hypotension, dry mouth, somnolence, dizziness, constipation and insomnia. There were no SAEs that were TEAEs, no subjects discontinued due to TEAEs, and most events were mild in severity.</p> <p>Systolic blood pressure, diastolic blood pressure, and pulse rates were reduced from baseline during the study. Fifteen subjects (79%) who received lofexidine had AEs of orthostatic hypotension compared with none of the subjects who received placebo.</p> <p>AEs of potential interest include cardiac disorders, insomnia, and anxiety. Methadone and lofexidine have both been shown to have cardiovascular properties. Three subjects experienced cardiac disorders, all of which were bradycardia (2 lofexidine subjects and 1 placebo subject) and were considered possibly related to study treatment. All cardiac events were mild and resolved without any changes to study treatment. Three lofexidine subjects and 2 placebo subjects experienced anxiety; anxiety AEs were considered at least possibly related to study treatment for all these subjects. Insomnia was reported by 7 lofexidine subjects (at least possibly related for all 7 subjects) and 3 placebo subjects (at least possibly related for 2 subjects).</p> <p>Overall, the concomitant administration of lofexidine with methadone was well-tolerated. There were no unexpected safety signals.</p>		
<p>Conclusions:</p> <p>There were several values of QTcF >450 msec in both placebo and lofexidine-treated subjects,</p>		

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<p>and during both Baseline (methadone only) and following study drug administration. There were no changes from baseline in QTcF >30 msec. There was a slight increase in QTcF with increasing lofexidine concentration. The predicted change from baseline in QTcF at the maximal plasma concentration observed following multiple days of lofexidine HCl dosing at 3.2 mg/day was only 3.0 msec with an upper 2-sided 95% confidence bound of 7.6 msec.</p> <p>The modest association between increasing lofexidine concentration and increases in the change in QTcF were well below the expected range of concern for repolarization abnormalities. QTcF outliers were minimal and diagnostic findings were without indication of adverse repolarization effects.</p> <p>Overall, no important ECG safety signal was detected in this small but well-studied population. Lofexidine had no apparent effect on the PK of methadone. Lofexidine PK was consistent with dose proportionality.</p> <p>For both COWS and SOWS mean scores were numerically lower for lofexidine subjects than for placebo subjects when the methadone dose was reduced by 50%. The decreases were not statistically significant, although they showed a trend indicating a potential positive effect of lofexidine on ameliorating the signs and symptoms of methadone withdrawal.</p> <p>There were no deaths, SAEs or premature discontinuation due to TEAEs. Most AEs were mild in severity. The most common at least possibly related TEAEs were headache, orthostatic hypotension, somnolence, dizziness, constipation, insomnia, nausea, upper abdominal pain, and anxiety. There were no SAEs that were TEAEs, no subjects discontinued due to TEAEs, and most events were mild in severity. There were no unexpected safety signals.</p>		
Date of the Report: 09 March 2016		

4.4.5 Study LX1-1006: Subjects receiving buprenorphine

US WorldMeds, LLC
USWM-LX1-1006

201229

26 February 2016

2 SYNOPSIS

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Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Assess the Safety, Tolerability, and Electrocardiographic Effects of Lofexidine When Administered Orally to Buprenorphine-Maintained Adult Subjects		
Investigator(s): Lynn R. Webster, MD		
Study center(s): PRA Health Sciences (formerly known as Lifetree Clinical Research), Salt Lake City, UT		
Date of first screening: 07 March 2013	Phase of development: 1	
Date of last follow-up: 23 September 2013		
Objectives: The primary objective of this study was to assess lofexidine related effects on QT/QT corrected for heart rate (QTc) in subjects receiving buprenorphine (Suboxone) maintenance. The secondary objectives of the study were to evaluate the safety and tolerability of lofexidine by evaluating and monitoring pharmacokinetics (PK), vital signs, and adverse events (AEs) when co-administered with buprenorphine; to describe effects on opiate withdrawal when lofexidine is introduced following a 50% buprenorphine dose reduction, as required to elicit a withdrawal response; and to evaluate QTc interaction effects of lofexidine compared with placebo.		
Methodology: This was a randomized, double-blind, placebo-controlled multiple ascending dose study to assess the safety, tolerability, and electrocardiographic effects of lofexidine in 30 buprenorphine-maintained adult subjects. The study included a Screening Visit, an Inpatient Treatment Visit, and a Follow-Up Visit. Subjects were randomized in a 4:1 ratio to receive up to 4 tablets of lofexidine hydrochloride (HCl) (0.2 mg/tablet) four times a day (QID) or 4 tablets of matching placebo QID.		
Within 21 days of the Screening Visit, subjects reported to the inpatient study facility to begin the Inpatient Treatment Visit, which lasted between approximately 11 to 21 days. This visit included an inpatient check-in (1 day), Buprenorphine Baseline (1 day), Initial Lofexidine Titration (3 to 5 days), 1 or 2 Lofexidine Plateaus (2 to 4 days), Buprenorphine Reduction (2 to 6 days) and Buprenorphine Re-Titration and Discharge (2 to 4 days). The order of steps subjects proceeded through during the Inpatient Treatment Visit varied depending on whether subjects were able to titrate to the highest dose of lofexidine HCl (4 tablets [0.8 mg or placebo] QID for a total daily lofexidine HCl dose of 3.2 mg or 16 tablets of placebo).		
During the Buprenorphine Baseline Phase subjects took a single daily dose of buprenorphine at 2 PM. Buprenorphine Baseline Phase study assessments included electrocardiogram (ECG) monitoring, blood collection for buprenorphine PK, and opiate withdrawal assessments (Clinical Opiate Withdrawal Scale, COWS, and Short Opiate Withdrawal Scale, SOWS). Subjects proceeded to the Initial Lofexidine Titration Phase the next day while continuing on their baseline buprenorphine dose. Lofexidine HCl was initiated at 2 tablets (0.4 mg or placebo) QID and titrated in daily increments of a single tablet (0.2 mg or placebo) QID to a dose of 0.8 mg QID (or placebo), if tolerated by the subject. Lofexidine doses were escalated daily unless at any point the		

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<p>subject met protocol-defined dose hold criteria, which triggered a missed dose or a reduction in dose to the previous highest tolerated dose (or to the 1-tablet dose, 0.2 mg or placebo, if subjects could not tolerate the initial 2 tablets, 0.4 mg or placebo).</p> <p>Once subjects titrated to the highest dose (i.e., 4 tablets QID) or once the highest tolerated dose had been determined, subjects proceeded to a 2-day Lofexidine Plateau Phase during which they continued to receive their buprenorphine maintenance dose. Subjects who were unable to titrate up to 4 tablets QID (0.8 mg or placebo) continued to receive their highest tolerated dose in equal increments (e.g., 2 or 3 tablets QID at 8 AM, 1 PM, 6 PM, 11 PM) for both days of the plateau. Subjects who tolerated 4 tablets QID (0.8 mg QID or placebo) during the Initial Lofexidine Titration Phase received 0.8 mg QID (or placebo) on the first day of the Lofexidine Plateau according to the normal dosing schedule. On the second day, the lofexidine dosing schedule was modified, so that subjects received 0.8 mg lofexidine HCl at 8 AM, 1 mg at 1 PM, 0.6 mg at 6 PM and 0.8 mg at 11 PM, for a total daily dose of 3.2 mg lofexidine HCl or placebo. Subjects also underwent ECG monitoring and blood collection for buprenorphine and lofexidine PK on this second day of the Lofexidine Plateau Phase. COWS and SOWS assessments were performed on both days of the Lofexidine Plateau.</p> <p>Subjects who were titrated to a daily dose of 3.2 mg lofexidine HCl (or placebo) while receiving their full dose of buprenorphine underwent a 4-day buprenorphine dose reduction of 50% while continuing to take lofexidine HCl or placebo at 3.2 mg/day to evaluate the effects of lofexidine on any buprenorphine withdrawal signs and symptoms. Those subjects who completed the initial Lofexidine Plateau at a dose of 3.2 mg/day lofexidine HCl (or placebo) and who reached a COWS score of 5 or greater prior to the fourth day of the reduced buprenorphine dose administration may have proceeded early to Buprenorphine Re-Titration and Discharge at the Investigator's discretion. If the COWS score did not reach 5 within 4 days, the subject proceeded to Buprenorphine Re-Titration and Discharge.</p> <p>Subjects who were unable to titrate to the highest lofexidine dose (3.2 mg/day) or placebo while receiving their full dose of buprenorphine underwent a buprenorphine dose reduction of 50% for up to 6 days while continuing to receive their highest tolerated dose of lofexidine from the initial titration. On the fourth day (or earlier at the Investigator's discretion based on withdrawal response), lofexidine titration was resumed by adding an incremental 0.2 mg lofexidine HCl or 1 tablet of placebo per dose to the previously established tolerated dose up to the maximum 3.2 mg/day (or placebo). During these subsequent titration attempts, lofexidine (or placebo) doses were escalated daily beginning on the fourth day of the reduction (or earlier at the discretion of the Investigator), unless in any event a subject met any of the protocol defined dose-hold criteria, which triggered a missed dose or a reduction in dose to the previous highest tolerated dose and required the Lofexidine Plateau procedures described above to be repeated, while maintaining the subject on their newly reduced buprenorphine dose (e.g., 50% of their maintenance dose). Subjects who were unable to titrate to a higher lofexidine dose during the 50% Buprenorphine Reduction than the dose they had titrated to during the Initial Lofexidine Titration did not repeat the Lofexidine Plateau procedures.</p>		

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<p>During Buprenorphine Reduction (whether for subjects entering an experimental 4-day 50% withdrawal phase at the tolerated 3.2 mg/day lofexidine HCl dose [or placebo] or for subjects continuing lofexidine titration at 50% buprenorphine reduction), COWS and SOWS assessments of opiate withdrawal were performed.</p>		
<p>Following completion of the Lofexidine Plateau (repeated as necessary) and Buprenorphine Reduction, subjects began the Buprenorphine Re-Titration and Discharge Phase, during which lofexidine or placebo were discontinued and buprenorphine was re-titrated to the starting dose (or to a higher or lower dose relative to baseline as medically indicated at the discretion of the Investigator). Lofexidine could have been used to treat withdrawal symptoms, if necessary. Following successful buprenorphine titration and completion of study assessments, subjects were discharged from the inpatient study clinic.</p>		
<p>Subjects returned to the study clinic for a follow-up visit 7 days (± 2 days) following clinic discharge for safety follow-up and AE collection. Subjects were discharged from the study at this time unless they were medically unstable on their dose of buprenorphine. Subjects could have been medically followed at regular intervals, as determined by the Investigator, until considered sufficiently stable for study discharge.</p>		
<p>Number of Subjects (Planned and Analyzed): A sufficient number of subjects were to be enrolled to ensure 30 subjects completed at least the first Lofexidine Plateau and 50% Buprenorphine Reduction phases. Subjects who did not complete these phases were to be replaced only if they withdrew or were dropped from the study due to meeting withdrawal criteria for blood pressure (BP) and heart rate (HR) effects or a non-QT related AE (e.g., hemodynamic, central nervous system, administrative). Subjects who were withdrawn or dropped from the study due to an effect on the QT interval were not to be replaced and were to be considered analyzable. Thirty-one subjects enrolled, 30 of whom received lofexidine or placebo and were included in the PK and QTc populations. One subject was withdrawn during Buprenorphine Baseline (prior to any lofexidine administration) due to safety concerns from arrhythmia. All 31 subjects were included in the safety population.</p>		
<p>Diagnosis and Main Criteria for Inclusion:</p>		
<p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Adult male and/or female, 18 to 60 years of age (inclusive). 2. Receiving buprenorphine maintenance treatment (Suboxone or Subutex) for opioid dependence at a stable total daily dose of 16 to 24 mg for at least 4 weeks prior to check-in for the Inpatient Treatment Visit. 3. Body mass index ≥ 18 and ≤ 35 (kg/m²). 4. Normal screening results or abnormal results that were deemed by the Investigator to be clinically insignificant. 5. Able to understand and willing to sign an informed consent form (ICF). 6. Females practicing adequate birth control or of non-childbearing potential. Medically 		

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<p>acceptable birth control methods for this study included intrauterine device (IUD); vasectomized partner (minimum of 6 months); post-menopausal (at least 2 years); surgically sterile (at least 6 months); double barrier (diaphragm with spermicide, condoms with vaginal spermicide); abstinence; implanted or intrauterine hormonal contraceptives in use for at least 6 consecutive months prior to study dosing and throughout the study duration; and oral, patch and injected hormonal contraceptives or vaginal hormonal device (i.e., NuvaRing[®]) in use for at least 3 consecutive months prior to study dosing and throughout the study duration.</p> <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Abnormal cardiovascular exam at screening and before randomization, including any of the following: <ul style="list-style-type: none"> • clinically significant abnormal ECG (e.g., significant first degree atrioventricular block, complete left bundle branch block, second or third degree heart block, clinically significant arrhythmia, or QT interval corrected using Fridericia's correction (QTcF) (machine read) greater than 450 msec for males and greater than 470 msec for females) • HR < 55 bpm or symptomatic bradycardia • systolic blood pressure (SBP) < 95 mmHg or symptomatic hypotension • diastolic blood pressure (DBP) < 65 mmHg • BP > 155/95 mmHg • change in orthostatic SBP, DBP, or HR > 25% below sitting values • prior history of myocardial infarction (MI) or evidence of prior MI on ECG • history of long QT syndrome or relative with this condition • history of syncopal episodes • intraventricular conduction delay with QRS duration > 120 msec • evidence of ventricular pre-excitation (e.g., Wolff Parkinson White syndrome) 2. History or presence of significant or clinically unstable cardiovascular (including atrial fibrillation, congestive heart failure, myocardial ischemia, indwelling pacemaker), hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, psychiatric, neurologic, or dermatologic disease. 3. History or presence of any degree of chronic obstructive pulmonary disease. 4. History of suicidal ideations or depression requiring professional intervention including counseling or antidepressant medication over the past 12 months. 5. Positive drug (urine)/alcohol (breath) test at screening or check-in excluding buprenorphine. Subjects who had a positive test for heroin, tetrahydrocannabinol (THC), or benzodiazepines at the Screening Visit could be enrolled if the tests were negative at check-in to the Inpatient Treatment Visit. Subjects who had a positive test for heroin, THC, or benzodiazepines at the Screening Visit had to sign an ICF at check-in to the Inpatient Clinic Visit. 		

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<ol style="list-style-type: none"> 6. Receiving buprenorphine for pain management. 7. Positive test for human immunodeficiency virus (HIV) or hepatitis B surface antigen (HBsAg). Subjects with a positive test for hepatitis C virus (HCV) antibodies could be enrolled if the subject was asymptomatic. 8. Estimated creatinine clearance < 80 mL/minute at screening (Cockcroft-Gault formula). 9. Aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase > 3.0 x upper limit of normal (ULN) at screening or check-in. 10. Amylase or lipase > 1.5 x ULN at screening or check-in. 11. Clinically significant out-of-reference range clinical chemistry values, with particular attention to potassium, magnesium, and calcium. 12. History of hypotension. 13. History of hypersensitivity or allergy to clonidine or any clonidine analogue. 14. Use of any new prescription medication within 12 days prior to check-in. 15. Use of any over-the-counter medication, including herbal products, within the 5 days prior to check-in. Up to 3,200 mg per day of ibuprofen or up to 2 grams per day of acetaminophen was allowed at the discretion of the Principal Investigator or designee. 16. Use of any drug known to affect QTc within 30 days prior to check-in (tobacco and buprenorphine excluded). 17. Blood donation or significant blood loss within 30 days prior to check-in. 18. Plasma donation within 7 days prior to check-in. 19. Participation in another clinical trial within 30 days prior to check-in. 20. Females who were pregnant or lactating. 21. Participation in a prior study of lofexidine hydrochloride. 22. Any other condition or prior therapy that, in the opinion of the Investigator, would have made the subject unsuitable for this study. 		
<p>Test Product, Dose and Mode of Administration, Lot Number: Lofexidine HCl 0.2 mg tablets (Lot number 24004-3561) were administered orally with 240 mL of water at approximately 8 AM, 1 PM, 6 PM and 11 PM. Lofexidine HCl doses were escalated daily starting at 0.4 mg QID and proceeding through 0.6 mg QID, up to a maximum of 0.8 mg QID. Doses were escalated once daily unless at any pre-dose vital signs or ECG assessment the subject met one of the following dose-hold criteria, which triggered a withholding of the next dose or a reduction in dose to the previous highest tolerated dose:</p> <ul style="list-style-type: none"> • SBP < 90 mmHg and > 20% below baseline value*; • DBP < 50 mmHg and > 20% below baseline value*; • HR < 50 bpm and > 20% below baseline value*; • QTcF increase > 60 msec from baseline 		

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<ul style="list-style-type: none"> • QTcF >450 msec in males and >470 msec in females • Symptoms of hypotension • Symptoms of bradycardia <p>Orthostatic assessments were performed after the subject had been standing for 3 minutes:</p> <ul style="list-style-type: none"> • SBP, DBP, or pulse > 25% below recumbent values <p>*ECGs and vital signs were repeated as appropriate in order to confirm values and rule out extraneous results. Baseline values for vital signs and ECG readings were obtained at admission into the clinic.</p>		
<p>Duration of Treatment: Up to 51 days (up to 21 days outpatient screening plus up to 21 days in-clinic, and 7±2 days follow-up).</p>		
<p>Reference Therapy, Dose and Mode of Administration, Lot Number: Buprenorphine HCl with naloxone HCl (Suboxone®) film as maintenance therapy at a total daily dose of 16 to 24 mg, administered sublingually. Buprenorphine doses were administered once daily at approximately 2 PM so that peak buprenorphine plasma concentrations would coincide in time with peak lofexidine plasma concentrations from the lofexidine dose administered at approximately 1 PM. The Suboxone lot numbers used were M12GW101, A13GW103, B13GW101, B13GW103, B13GW107, C13GW102, C13GW108, D13GW104, E13GW107, E13GW111, F13GW103 (Suboxone 8/2 mg film); and M12DW104 and A13DW104 (Suboxone 2/0.5 mg film).</p> <p>Placebo tablets identical in appearance to lofexidine HCl 0.2 mg tablets were used (Lot number 21101V6941). Subjects received up to 4 placebo tablets QID for a total of 16 tablets per day. The dosing procedures for the placebo tablets were the same as for lofexidine.</p>		
<p>Criteria for Evaluation:</p> <p><u>Electrocardiographic Assessments:</u></p> <ul style="list-style-type: none"> • QTcF (primary endpoint) • QT interval corrected using Bazett's calculation (QTcB) (secondary endpoint) • ECG numeric variables: HR in units of beats per minute (bpm); and RR interval, PR interval, QRS duration, and QT in units of milliseconds • Change from baseline for ECG numeric variables • ECG morphology <p><u>Clinical Effect Assessment</u></p> <ul style="list-style-type: none"> • The COWS was used to evaluate signs and symptoms of opioid withdrawal. • The SOWS was used to evaluate symptoms of opioid withdrawal. The SOWS was completed at the same time COWS assessments were completed. 		

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<p>Pharmacokinetic Assessment:</p> <ul style="list-style-type: none"> • Buprenorphine, norbuprenorphine, and lofexidine concentrations • C_{max}: maximum observed plasma concentration for each analyte • T_{max}: time of maximum observed concentration for each analyte. If the maximum value occurred at more than one time point, T_{max} was defined as the first time point with this value. • AUC_{0-5}: area under the plasma concentration-time curve from 0 to 5 hours for lofexidine • AUC_{-1to4}: area under the plasma concentration-time curve from -1 to 4 hours for buprenorphine and norbuprenorphine <p>The following PK parameters were calculated for buprenorphine and norbuprenorphine during the Buprenorphine Baseline Phase:</p> <ul style="list-style-type: none"> • AUC_{-7to17}: area under the plasma concentration-time curve from -7 to +17 hours (equivalent to 0 to 24 hours, assuming steady-state) • λ_z: rate constant for the terminal elimination, calculated using values from 4 to 17 hours post-dose. • $t_{1/2}$: elimination half-life ($t_{1/2} = \ln(2) / \lambda_z$) • Cl/F: apparent clearance (plasma clearance/oral bioavailability) calculated as $Dose/AUC_{-7to17}$ for the parent compound, buprenorphine, only <p>To determine the effect of lofexidine or placebo on buprenorphine PK, the ratio of AUC_{-1to4} for the same dose of buprenorphine with and without lofexidine or placebo was calculated for each subject. Similar ratios were also calculated for C_{max}.</p> <p>Safety Endpoints:</p> <ul style="list-style-type: none"> • all AEs • changes in results of clinical laboratory tests, including routine serum chemistry, hematology, and urinalysis tests • changes in vital sign values • changes in ECG findings (i.e., changes from normal to abnormal and in other ECG endpoints) • continuous ambulatory telemetry <p>Exploratory Endpoints:</p> <ul style="list-style-type: none"> • changes in COWS results • changes in SOWS results 		

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<p>Statistical Methods:</p> <p>The sample size for this study was based on clinical and practical considerations and not on a formal statistical power calculation. A sufficient number of subjects were to be enrolled to ensure 30 subjects completed at least the first Lofexidine Plateau and 50% Buprenorphine Reduction phases. This sample size was considered large enough to indicate the presence or absence of a clinically relevant effect on ECG parameters by lofexidine when added as a concomitant medication in buprenorphine-maintained patients.</p> <p>Total COWS and SOWS scores were summarized with descriptive statistics for subjects by group (Subjects who underwent complete titration to maximum dose during 100% Buprenorphine [Group A] and subjects who underwent complete titration to maximum dose during 50% Buprenorphine Reduction [Group B]) and treatment (lofexidine/placebo) for all time points. Absolute score and change from Baseline 1 (lowest score prior to any lofexidine administration) and Baseline 2 (score at 3 to 3.5 hours post 8 AM dose on Lofexidine Plateau Day 2, 100% buprenorphine) were evaluated using descriptive statistics (mean, median, standard deviation [SD], minimum, maximum, number of subjects (N), average buprenorphine dose, and average lofexidine/placebo dose). An analysis of data combined across Groups A and B was also performed for certain time points. The difference between Lofexidine and Placebo changes from Baseline 1 and 2 was evaluated using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and the respective baseline (Baseline 1 or Baseline 2) as a covariate.</p> <p><u>Study Analysis Data Sets</u></p> <p>The Safety population was defined as all subjects who received at least one dose of study medication or buprenorphine.</p> <p>The PK population was defined as all lofexidine HCl- and placebo-treated subjects with sufficient PK data to estimate one or more of the PK parameters. In addition, all subjects who had at least one sample collected for lofexidine analysis were included in the listing and statistical summaries of concentrations.</p> <p>The QTc population included all subjects with Holter ECG data and matching lofexidine/placebo and buprenorphine samples for at least one dose of lofexidine/placebo.</p> <p>The intent-to-treat (ITT) population included all subjects enrolled in the study.</p> <p><u>Electrocardiographic Analysis:</u></p> <p>Summary statistics (N, mean, median, minimum, maximum and SD) were used to summarize HR, PR, QRS, QTcB and QTcF, for the analysis groups on the Plateau Days and Titration Days by time point.</p> <p>The number and percent of subjects meeting each of the following categorical analysis criteria were summarized for each ECG time point:</p> <ul style="list-style-type: none"> • Absolute QTcB and QTcF interval prolongations: <ul style="list-style-type: none"> QTc interval > 450 msec; QTc interval > 480 msec; QTc interval > 500 msec 		

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<ul style="list-style-type: none"> • Change from Baseline in QTcB and QTcF interval: QTc interval increases from Baseline > 30 msec; QTc interval increases from Baseline > 60 msec • PR interval > 200 msec and \geq 25% increase from Baseline • QRS interval > 120 msec and \geq 25% increase from Baseline <p>Emergent ECG morphologies were summarized by analysis groups on the Plateau Days and Titration Days for all time points combined. ECG findings included only those which were found after the Buprenorphine Baseline Phase.</p> <p>A linear mixed effects model was employed to analyze the relationship of QTcF with lofexidine, buprenorphine and norbuprenorphine concentrations, with the time-matched changes from Baseline in QTcF intervals as the dependent variable and the corresponding time-matched lofexidine \log_{10} concentration, the buprenorphine \log_{10} concentration, and the norbuprenorphine \log_{10} concentration as the independent variables. The initial model included the \log_{10} concentrations of lofexidine, buprenorphine and norbuprenorphine, along with their interaction. If the interaction term had a p-value > 0.10 it was to be assumed that there was no pharmacodynamic interaction between lofexidine and buprenorphine or between lofexidine and norbuprenorphine, and the interaction was to be dropped from the model. Based on the final model, individual regressions of ΔQTcF on \log_{10} lofexidine concentration, on \log_{10} buprenorphine concentration and on \log_{10} norbuprenorphine concentration were performed, with estimates of the mean change of QTcF from Baseline at various concentrations.</p> <p>The relationship between buprenorphine and norbuprenorphine and ΔQTcF was examined separately for the lofexidine-treated subjects and for the placebo-treated subjects.</p> <p>Change from baseline in QTcB and QTcF were presented graphically by analysis group for Plateau Days, along with values of Baseline and Plateau Day buprenorphine and norbuprenorphine plasma concentrations and the Plateau Day lofexidine plasma concentration.</p> <p>Correlations between time-matched changes from Baseline in QTcF and time-matched changes from Baseline in HR from the ECG were displayed graphically for all time points, for all lofexidine-treated subjects and separately for placebo-treated subjects, along with a fitted regression line based on a repeated measures regression.</p> <p><u>Pharmacokinetic Analysis:</u></p> <p>Descriptive statistics (mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum) were calculated for each PK parameter grouped by lofexidine total daily dose (including placebo) and by buprenorphine treatment or treatment stage (baseline, 100% and 50% of maintenance dose). Mean concentrations on Titration Days and on Plateau Days were presented graphically.</p> <p><u>Safety Analysis:</u></p> <p>No formal statistical analysis was performed for safety variables. Summaries of the number and percentage of subjects reporting an AE for each classification level as well as the number of</p>		

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<p>events reported were provided. The denominators for calculating the percentages were based on the number of subjects. Summaries were provided for the following classifications:</p> <ul style="list-style-type: none"> • Overall summary of AEs. • Summary of AEs by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and MedDRA preferred term. • Summary of AEs by MedDRA preferred term and study drug relationship in descending order. • Summary of AEs by MedDRA SOC, MedDRA preferred term, and study drug relationship for events leading to premature discontinuation from the study. <p>Descriptive statistics were used to summarize the observed results at each time point and the change from baseline in clinical laboratory test results by treatment group without formal statistical testing.</p> <p>Descriptive statistics were used to summarize the observed vital sign values at each time point and the change from baseline at each post-dose time point without formal statistical testing.</p>		
<p>Electrocardiographic Results:</p> <p>Mean QTcF values were normal during titration and on plateau days. Mean values of change of QTcF from Baseline for the lofexidine groups showed variable responses ranging from -17.3 to 12.3 msec across treatment phases. Placebo group mean QTcF values decreased consistently. QTcB values were unreliable because of the low heart rate values and are not discussed in this report.</p> <p>There were minimal numbers of outliers of QTcF. Only 2 subjects had a total of 6 QTcF values >450 msec, one subject in the lofexidine group and one subject in the placebo group; and both subjects had these increases both at Baseline (4 instances) and after study drug administration (2 instances). No values > 480 msec, or changes > 60 msec greater than Baseline were seen.</p> <p>A general decrease in HR for the lofexidine subjects was noted during Plateau, ranging from -22.3 bpm for the 3.2 LFX 50% BUP group (Group B) at 3 hours post-dose, to -3.5 bpm for 1.6 LFX 100% BUP immediately pre-dose. On Titration Days, values of HR also decreased, maximally for the 3.2 LFX 100% BUP group at the 4-hour time point, by a mean of -13.1 bpm. There were no decreases in HR for the placebo group.</p> <p>Normal values and no consistent changes from baseline were found for PR and QRS, and no other diagnostic findings of importance were noted.</p> <p>Concentration-QTcF curves for lofexidine, buprenorphine and norbuprenorphine showed small values for slopes, which were not statistically different from a slope of 0. The predicted value of change from baseline of QTcF at maximal concentration for lofexidine was -5.1 msec, with an upper 2-sided 95% confidence bound of -0.6 msec.</p>		

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product:	Volume:	
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<p>Pharmacokinetic Results:</p> <p><u>Buprenorphine and norbuprenorphine pharmacokinetics:</u></p> <p>Although there were possibly differences in the mean concentrations during the Buprenorphine Baseline Phase compared to Plateau Day, the intersubject variability (as shown by the SD values) was sufficiently large that no clear difference was established.</p> <p>There was little or no difference in buprenorphine concentrations between the buprenorphine plus lofexidine and buprenorphine plus placebo groups, indicating no effect of lofexidine on the pharmacokinetics of buprenorphine and norbuprenorphine.</p> <p>At the second Lofexidine Plateau at 50% buprenorphine maintenance plus 3.2 mg/day lofexidine HCl (3 subjects), the C_{max} and AUC_{0-4} values for buprenorphine and norbuprenorphine were approximately 50% of the values at the first plateau, indicating dose proportionality for buprenorphine.</p> <p><u>Lofexidine pharmacokinetics</u></p> <p>There were increases in lofexidine plasma concentrations with dose during the Lofexidine Titration indicating dose dependence of lofexidine concentrations, and with time while the lofexidine dose remained constant indicating that steady-state was not reached within the time frame of the observations. Mean lofexidine concentrations on the Lofexidine Plateau days were approximately 4 to 5 ng/mL and showed minimal fluctuation over the 5-hour dosing interval.</p> <p>For the first Lofexidine Plateau, the mean values for lofexidine C_{max} and AUC_{0-5} were lower for 1.6 and 2.4 mg/day treatments than for the 3.2 mg/day treatment, while the mean values for dose-normalized C_{max} (NC_{max}) and AUC_{0-5} ($NAUC_{0-5}$) were similar for all doses, consistent with dose proportionality. The second Lofexidine Plateau at 50% buprenorphine plus 3.2 mg/day lofexidine HCl had lofexidine C_{max} and AUC_{0-5} values similar to the lofexidine values at 100% buprenorphine plus 3.2 mg/day lofexidine HCl. Based on the results for both the dose-normalized and non-normalized parameters for the limited number of subjects in this study, it was concluded that the pharmacokinetic parameters for lofexidine were approximately linear when co-administered with buprenorphine.</p> <p>Opiate Withdrawal Results:</p> <p>The COWS and SOWS assessments were exploratory endpoints related to the potential efficacy of lofexidine to alleviate signs and symptoms of buprenorphine withdrawal. Both lofexidine and placebo groups' mean COWS and SOWS scores at baseline and at 50% buprenorphine reduction showed absence of withdrawal symptoms. Changes from baseline in COWS and SOWS scores following 50% buprenorphine reduction were not significantly different between lofexidine and placebo ($p > 0.05$). Since there was no significant withdrawal when the buprenorphine dose was lowered by 50% for 4-6 days in this study, the potential effect of lofexidine on buprenorphine withdrawal could not be evaluated.</p>		

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product:		
Name of Active Ingredient: Lofexidine hydrochloride		
<p>Safety Results:</p> <p>All 24 subjects receiving lofexidine (100%) experienced at least 1 TEAE for a total of 197 TEAEs, compared to 5 placebo subjects (83%), who experienced 13 TEAEs. All 24 subjects who received lofexidine experienced at least 1 TEAE that was considered at least possibly related to study drug (with a total of 158 possibly related TEAEs), compared to 3 placebo subjects (a total of 7 possibly related TEAEs).</p> <p>Overall, the most frequently reported TEAEs (in $\geq 30\%$ of subjects overall) occurring after administration of lofexidine or placebo classified by MedDRA SOC were gastrointestinal disorders (70% of subjects, overall), nervous system disorders (73%), psychiatric disorders (63%), and vascular disorders (50%). In the gastrointestinal disorders SOC, the most frequently reported TEAEs by preferred term (reported by $\geq 30\%$ of subjects overall) in subjects who received lofexidine and placebo, respectively, were dry mouth (58% and 0% of subjects); in the nervous system disorders SOC, somnolence (58% and 17%) and headache (50% and 33%); in the psychiatric disorders SOC, insomnia (50% and 33%) and withdrawal syndrome (42% and 0%); and in the vascular disorders SOC, orthostatic hypotension (42% and 17%).</p> <p>The majority of the most common TEAEs were experienced by subjects in both the lofexidine and placebo groups, with the exception of dry mouth and withdrawal syndrome. The majority of TEAEs were mild in severity. Nine subjects (38%) who received lofexidine, compared to 1 subject (17%) who received placebo experienced TEAEs that were moderate in severity. One subject who received lofexidine experienced a severe AE of oropharyngeal pain that was judged by the investigator to be unlikely related to the study drug.</p> <p>Ten subjects who received lofexidine experienced 24 events of orthostatic hypotension, 7 subjects experienced 21 events of hypotension, and 1 subject experienced 2 events of diastolic hypotension. In the placebo group, 1 subject experienced 1 event of orthostatic hypotension and no subject experienced AEs of hypotension or diastolic hypotension. All these events of hypotension were considered at least possibly related to the study drug.</p> <p>A total of 5 TEAEs in the cardiac disorders SOC were reported by 5 subjects (21%) in the lofexidine group. These included 2 subjects with bradycardia, and 1 subject each with palpitations, tachycardia, or ventricular extrasystoles. The TEAEs of bradycardia, palpitations, and tachycardia were considered at least possibly related to the study drug. None of these TEAEs were reported by subjects receiving placebo. Mean QTcF interval values showed no clinically significant changes in QTcF interval for the placebo and lofexidine groups, although there were 2 subjects (1 each in the lofexidine and placebo groups) with clinically significant changes in QTcF interval.</p>		
<p>Conclusions:</p> <p>ECG findings for all subjects at all dose levels showed no effects on QTc and no important safety signal overall, and there was no statistically significant association between lofexidine</p>		

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<p>concentrations and QTcF. The predicted value of change of QTcF at maximal concentration for lofexidine was -5.1 msec, with an upper 2-sided 95% confidence bound of -0.6 msec.</p> <p>Lofexidine had no apparent effect on the PK of buprenorphine. Lofexidine PK in the presence of buprenorphine was consistent with dose proportionality.</p> <p>There was no significant withdrawal in either the lofexidine or placebo group when the buprenorphine dose was reduced by 50%; therefore, the potential effect of lofexidine on buprenorphine withdrawal could not be evaluated.</p> <p>Overall, the concomitant administration of lofexidine with buprenorphine was well tolerated. There were no serious TEAEs, no withdrawals due to TEAEs, and no unexpected safety signals. Most TEAEs were mild. The concomitant administration of buprenorphine and lofexidine was, however, less well-tolerated than buprenorphine with placebo, as a higher percentage of subjects receiving lofexidine and buprenorphine experienced TEAEs, a higher number of TEAEs of moderate severity, and more TEAEs that were considered related to study drug than did subjects who were receiving buprenorphine and placebo.</p> <p>Date of the Report: 26 February 2016</p>		

4.4.6 Study LX1-1007: Hepatic Impairment

US WorldMeds, LLC
Clinical Study Report USWM-LX1-1007

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine Hydrochloride		
Name of Active Ingredient: Lofexidine Hydrochloride		
Title of Study: Single-dose Pharmacokinetic and Safety of Oral Lofexidine in Hepatically-Impaired Subjects		
Principal Investigator: Thomas Marbury, MD		
Study center(s): Orlando Clinical Research Center 5055 South Orange Avenue Orlando, FL 32809		
Publications (reference): None to date		
Studied period (years): Date first subject enrolled: 10 June 2014 Date last subject completed: 13 October 2014		Phase of development: I
Objectives: Primary: <ul style="list-style-type: none"> The primary objective of this study was to evaluate changes in lofexidine hydrochloride (HCl) pharmacokinetics (PK) associated with impaired hepatic function. Secondary: <ul style="list-style-type: none"> The secondary objective of this study was to evaluate the safety and tolerability of lofexidine HCl in hepatically-impaired subjects. 		
Methodology: This was a Phase 1, open-label, parallel-cohort, single-dose study of lofexidine in 24 subjects: 6 adult subjects with mild hepatic impairment (Child-Pugh score of 5 to 6), 6 adult subjects with moderate hepatic impairment (Child-Pugh score 7 to 9), 6 adult subjects with severe hepatic impairment (Child-Pugh score 10 to 15), and 6 reference healthy normal subjects with normal hepatic function with mean age, body mass index (BMI), and gender distribution targeted to be similar to the impaired hepatic function cohorts. Subjects who successfully completed screening reported to the inpatient facility at an appropriate time the evening before study drug administration (Day -1) to ensure a minimum 10-hour fast. The next morning (Day 1) while still fasting, subjects received a single, oral dose of 0.4 mg lofexidine HCl (2 × 0.2 mg tablets). Blood samples and pooled urine samples were collected at multiple time points over the next 144 hours.		

Number of subjects (planned and analyzed): 24 subjects were planned to be enrolled and all 24 were included in the Safety and PK populations
Diagnosis and main criteria for inclusion: Male or female subjects between 18 and 65 years old at enrollment with a BMI between 19 and 38 kg/m ² , inclusive were eligible to participate in the study and were assigned to 1 of the following 4 cohorts: <ul style="list-style-type: none">• <i>Matched reference subject:</i> normal hepatic function and free from other clinically significant illnesses or disease, and medical history, physical examination, laboratory results, and other tests consistent with health, as determined by the Investigator.• <i>Subject with mild hepatic impairment:</i> Child-Pugh hepatic dysfunction staging system score of 5 to 6 Points (Stage A) and medical history, physical examination, laboratory results, and other tests consistent with their hepatic impairment, as determined by the Investigator.• <i>Subject with moderate hepatic impairment:</i> Child-Pugh hepatic dysfunction staging system score of 7 to 9 Points (Stage B) and medical history, physical examination, laboratory results, and other tests consistent with their hepatic impairment, as determined by the Investigator.• <i>Subject with severe hepatic impairment:</i> Child-Pugh hepatic dysfunction staging system score of 10 to 15 Points (Stage C) and medical history, physical examination, laboratory results, and other tests consistent with their hepatic impairment, as determined by the Investigator.
Test product, dose and mode of administration, batch number: A single, oral dose of lofexidine HCl 0.4 mg (2 × 0.2 mg tablets); Lot number: 24004-3561
Duration of treatment: Duration of Treatment: 1 day (single dose) Duration of Participation: up to 36 days (including a 28-day Screening Period and 7 nights / 8 days inpatient confinement)
Reference therapy, dose and mode of administration, batch number: None.
Criteria for evaluation: <i>Sample collection for pharmacokinetic parameters:</i> Fingerstick samples for PK analysis were collected before lofexidine administration (0 hour) and at 0.25, 0.5, 1, 2, 3, 4, 5, 7, 10, 16, 24, 32, 48, 72, 96, 120, and 144 hours postdose. Additional venous blood samples for protein binding assessments were collected predose and 4 hours postdose. Urine samples were obtained from pooled urine collected from 0 to 3 hours, 3 to 6 hours, 6 to 12 hours, 12 to 24 hours, 24 to 48 hours, 48 to 96 hours, 96 to 120 hours and 120 to 144 hours postdose for PK analysis. <i>Safety:</i> Safety was assessed by reported adverse events (AEs), vital signs (blood pressure and pulse rate), clinical laboratory tests (chemistry, hematology, and urinalysis), 12-lead bedside electrocardiograms (ECGs) and 12-lead ambulatory (Holter monitor) ECGs, and physical examinations.
Statistical methods: <i>Pharmacokinetic methods:</i> Concentration-time data were analyzed by non-compartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantification (BLQ) were treated as zero in the data summarization and descriptive statistics. In the

PK analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all PK and statistical analyses.

Pharmacokinetic results of lofexidine were summarized by cohort using descriptive statistics including arithmetic mean, median, standard deviation (SD), minimum, maximum, coefficient of variation, 90% confidence interval (CI), and 95% CI; geometric mean and geometric mean coefficient of variation were reported for C_{max} and AUCs.

Pharmacokinetic parameters (area under the plasma concentration-time curve from time zero extrapolated to infinity [AUC_{inf}], apparent terminal elimination half-life [$T_{1/2}$], maximum plasma concentration [C_{max}], apparent systemic clearance [CL/F], and total amount of unchanged drug excreted in urine over all collection intervals [$Total A_e$]) were analyzed using an analysis of covariance (ANCOVA) model with factors for cohort, sex, age, body weight, and BMI. After including demographic factors into the ANCOVA model, differences in PK parameters between cohorts were identified via p-values.

Safety Analysis:

No formal testing was performed on safety variables.

Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA; version 16) was used to code all AEs with respect to System Organ Class and Preferred Term. All treatment-emergent AEs (TEAEs) were summarized by System Organ Class and Preferred Term by frequency and severity.

Summary tables were produced for all TEAEs and treatment-related TEAEs by cohort and overall. Subjects who discontinued because of an AE, who had nonfatal serious AEs (SAEs), or who died during the study were identified and listed, if applicable.

Laboratory Parameters

Descriptive statistics were used to summarize the observed results at each time point and the change from Baseline in clinical laboratory test results by hepatic impairment cohort. An additional summary was produced by cohort: the number of subjects with a change relative to the normal range (i.e., shift tables). Any clinically significant laboratory results (as determined by the Investigator) were to be captured as AEs.

Vital Signs

Descriptive statistics were used to summarize the observed vital sign values at each time point and the change from Baseline at each post-dose time point by cohort.

Physical Examinations

For each cohort and overall, the number and percentage of subjects are presented for each body system as normal or abnormal at Screening and Discharge. Significant changes from baseline in physical examination findings were to be reported as TEAEs.

Safety Electrocardiograms

Safety 12-lead ECG changes from baseline are presented in shift tables (i.e., normal to abnormal) by cohort. Safety 12-lead ECGs are presented in a data listing.

Holter Electrocardiogram

Holter (12-lead) ECG changes from baseline and categorical findings are presented by cohort.

Morphological findings are presented by subject. Holter ECG readings extracted in duplicate, are presented in data listings.

Prior and Concomitant Medication

The number and percentage of subjects who received each prior and concomitant medication are presented by cohort and overall.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS RESULTS:

Subject (b) (6) (female subject with normal hepatic function) received a 1-liter bolus of normal saline at 3.33 hours post-dose and a 1-liter infusion of normal saline at 250 mL/h starting at 4.87 hours post-dose. These interventions could potentially have had an impact on the lofexidine concentrations observed between 3 and 10 hours post-dose; the plasma lofexidine concentrations for Subject (b) (6) were slightly higher than those observed for other subjects in the normal hepatic function cohort. Therefore, the PK and statistical analysis results are presented with and without Subject (b) (6).

Plasma concentrations:

The first quantifiable plasma lofexidine concentrations were observed at 0.25 hours for subjects with moderate hepatic impairment (Cohort 3) and subjects with severe hepatic impairment (Cohort 4), and at 1.00 hour for subjects with normal hepatic function (Cohort 1) and subjects with mild hepatic impairment (Cohort 2).

Peak mean plasma lofexidine concentrations occurred between 1.00 hour and 3.00 hours post-dose. Peak mean lofexidine plasma concentrations were similar for subjects with normal hepatic function (Cohort 1), subjects with mild hepatic impairment (Cohort 2), and subjects with moderate hepatic impairment (Cohort 3), ranging from 0.683 ± 0.142 ng/mL (normal hepatic function; Cohort 1 excluding Subject (b) (6)) to 0.754 ± 0.193 ng/mL (mild hepatic impairment; Cohort 2). The peak of the mean lofexidine plasma concentrations for subjects with severe hepatic impairment (1.05 ± 0.277 ng/mL; Cohort 4) was approximately 50% higher than that for subjects with normal hepatic function (0.683 ± 0.142 ng/mL; Cohort 1 excluding Subject (b) (6)).

Pharmacokinetic parameters:

Median time to maximum lofexidine plasma exposure (T_{max} , C_{max}) occurred between 0.75 hours (subjects with severe hepatic impairment; Cohort 4) and 3.00 hours (subjects with normal hepatic function; Cohort 1 excluding Subject (b) (6)). Mean C_{max} values were similar for subjects with normal hepatic function (Cohort 1), subjects with mild hepatic impairment (Cohort 2), and subjects with moderate hepatic impairment (Cohort 3), ranging from 0.701 ± 0.123 ng/mL (normal hepatic function; Cohort 1 excluding Subject (b) (6)) to 0.795 ± 0.143 ng/mL (mild hepatic impairment; Cohort 2). The mean C_{max} for subjects with severe hepatic impairment (1.17 ± 0.296 ng/mL; Cohort 4) was approximately 67% higher than that for subjects with normal hepatic function (0.701 ± 0.123 ng/mL; Cohort 1 excluding Subject (b) (6)).

Mean area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration (AUC_{last}) values in subjects with mild hepatic impairment (13.29 ± 5.686 h•ng/mL; Cohort 2) were approximately 27% higher compared with subjects with normal hepatic function (10.46 ± 2.216 h•ng/mL; Cohort 1 excluding Subject (b) (6)). The mean AUC_{last} values for subjects with moderate hepatic impairment (19.83 ± 6.364 h•ng/mL; Cohort 3) was approximately 90% higher compared to that for subjects with normal hepatic function (Cohort 1 excluding Subject (b) (6)) the mean AUC_{last} value for subjects with severe hepatic impairment (31.77 ± 8.479 h•ng/mL; Cohort 4) was approximately 200% higher than that for subjects with normal hepatic function (Cohort 1 excluding Subject (b) (6)). A similar trend was observed for mean AUC_{inf} values.

Mean time of the last quantifiable concentration (T_{last}) values increased with the degree of hepatic impairment. The last lofexidine plasma concentrations were observed at a mean time of 30.40 hours for subjects with normal hepatic function (Cohort 1 excluding Subject (b) (6)), at 40.33 hours for subjects with mild hepatic impairment (Cohort 2), at 57.00 hours for subjects with moderate hepatic impairment (Cohort 3), and at 92.00 hours for subjects with severe hepatic impairment (Cohort 4).

Mean apparent $T_{1/2}$ values were similar for subjects with normal hepatic function (Cohort 1) and subjects with mild hepatic impairment (Cohort 2). Subjects with moderate and severe hepatic impairment had mean apparent $T_{1/2}$ values approximately 2.5 times and 3.2 times, respectively, that of subjects with normal hepatic function. As expected, $T_{1/2}$ values increased as the severity of hepatic impairment increased and mean apparent plasma lofexidine clearance values decreased as the severity of hepatic impairment increased. Mean apparent clearance, CL/F , values ranged from 9.991 L/hour for subjects with severe hepatic impairment (Cohort 4) to 26.35 L/hour for subjects with normal hepatic function (Cohort 1).

As previously noted, Subject (b) (6) (female subject with normal hepatic function) received a 1-liter bolus of normal saline at 3.33 hours postdose and a 1-liter infusion of normal saline at 250 mL/hour starting at 4.87 hours postdose as a treatment for hypotension. These interventions proved to have an impact on the lofexidine concentrations observed between 3 and 10 hours postdose. Maximum and total lofexidine exposure parameters reported for Subject (b) (6) were greater than those reported for other subjects in the normal hepatic function. This subject has been omitted in most of the discussed comparisons between hepatic function cohorts, but descriptive statistics are also provided with this subject included.

LOFEXIDINE HCl DOSING ADJUSTMENTS AND DIFFERENCES IN SYSTEMIC CLEARANCES:

The mean apparent systemic clearance values for the mild, moderate and severely impaired hepatic function cohorts were approximately 85%, 53% and 39% of the value for the normal hepatic function cohort, respectively. Available oral dosing options allow these desired dose reductions to be closely approximated by using 75% of the normal dose (the dose administered to subjects with normal hepatic function) in mildly hepatically impaired subjects, 50% of the normal dose in moderately hepatically impaired subjects, and 33.3 to 37.5% of the normal dose in the severely hepatically impaired subjects. If the desired clinical target for normal hepatic function subjects is 3.2 mg/day (0.8 mg 4 times daily [QID]) lofexidine HCl, then the dosage adjustments would be 2.4 mg/day (0.6 mg QID) in subjects with mild hepatic impairment, 1.6 mg/day (0.4 mg QID) in subjects with moderate hepatic impairment and 1.2 mg/day (0.4 mg 3 times daily [TID]) in subjects with severe hepatic impairment. If the desired clinical target for normal hepatic function subjects is 2.4 mg/day (0.6 mg QID) lofexidine HCl, then the dosage adjustments would be 1.8 mg/day (0.6 mg TID) in subjects with mild hepatic impairment, 1.2 mg/day (0.4 mg TID) in subjects with moderate hepatic impairment and 0.8 mg/day (0.2 mg QID) in subjects with severe hepatic impairment.

Lofexidine concentrations generally reach steady-state on Day 3 of treatment in subjects with normal lofexidine clearance. Simulations indicate that subjects with moderate or severe hepatic impairment may not reach their steady-state lofexidine plasma concentrations until 6 or 7 days after initiation of treatment. The time to reach steady-state can be shortened by use of a loading dose. Simulations indicate that an appropriate loading dose approach is to use 0.8 mg QID (3.2 mg/day) or 0.8 mg TID (2.4 mg/day) lofexidine HCl during the first 24 hours of treatment in subjects with moderate or severe hepatic impairment. The choice of QID or TID dosing for the loading dose day can be based on whether a QID or TID maintenance dosing schedule is planned.

The suggested dose adjustments for lofexidine HCl to compensate for decreased lofexidine clearance in hepatically-impaired subjects are summarized in [Synopsis Table 1](#) (if the targeted lofexidine plasma concentration is the higher 4 to 5 ng/mL) and [Synopsis Table 2](#) (if the targeted lofexidine concentration is the lower 3 to 4 ng/mL). The tables also indicate loading dose options determined by simulations that

could be utilized to shorten the time required for lofexidine plasma concentrations to reach steady-state. The loading dose approach on Day 1 results in steady-state plasma lofexidine concentrations being achieved by the second day or third day of treatment; the lower maintenance dose would be used from Day 2 of treatment onwards.

Synopsis Table 1: Summary of Clearance Ratios and Suggested Lofexidine HCl Doses by Hepatic Function When Targeting 4 to 5 ng/mL at Steady State

Hepatic Function	CL/F ^a	Clearance Ratio	Scaled Daily Dose (mg/day)	Clinical Daily dose (mg/day)	Dose and Schedule	Loading Dose ^b (for Day 1)
Normal ^c	23.22	1.0000	3.20	3.2	0.8 mg QID	–
Mild impairment	19.85	0.8547	2.74	3.2 2.4 2.4	0.8 mg QID 0.8 mg TID 0.6 mg QID	–
Moderate impairment	12.24	0.5272	1.69	1.8 1.6	0.6 mg TID 0.4 mg QID	0.8 mg QID
Severe impairment	8.97	0.3863	1.24	1.2	0.4 mg TID	0.8 mg QID 0.6 mg QID

Abbreviations: CL/F = apparent systemic clearance; HCl = hydrochloride; QID = 4 times daily; TID = 3 times daily

^a CL/F values from Table 8 of the PK Report.

^b Loading dose of 3.2 or 2.4 mg administered as divided doses over the first 24 hours of treatment.

^c Subject (b) (6) is excluded from calculated mean CL/F of normal hepatic function cohort
 Source: Dosage Adjustment Report, Table 10.1

Synopsis Table 2: Summary of Clearance Ratios and Suggested Lofexidine HCl Doses by Hepatic Function When Targeting 3 to 4 ng/mL at Steady State

Hepatic Function	CL/F ^a	Clearance Ratio	Scaled Daily Dose (mg/day)	Clinical Daily dose (mg/day)	Dose and Schedule	Loading Dose ^b (for Day 1)
Normal ^c	23.22	1.0000	2.40	2.4	0.6 mg QID	–
Mild impairment	19.85	0.8547	2.05	2.4 1.8	0.6 mg QID 0.6 mg TID	–
Moderate impairment	12.24	0.5272	1.27	1.2	0.4 mg TID	0.6 mg QID
Severe impairment	8.97	0.3863	0.93	0.8	0.2 mg QID	0.6 mg QID

Abbreviations: CL/F = apparent systemic clearance; HCl = hydrochloride; QID = 4 times daily; TID = 3 times daily

^a CL/F values from Table 8 of the PK Report.

^b Loading dose of 3.2 or 2.4 mg administered as divided doses over the first 24 hours of treatment.

^c Subject (b) (6) is excluded from calculated mean CL/F of normal hepatic function cohort.
 Source: Dosage Adjustment Report, Table 10.2

CARDIAC SAFETY RESULTS:

Electrocardiogram findings indicated normal findings for heart rate (HR), PR, and QRS values. Heart

rate-corrected QT interval (Fridericia's correction; [QTcF]) findings, the primary correction method, showed moderate increases of QTcF from Baseline following lofexidine HCl administration. These were greatest for the subjects with severe hepatic impairment at 3 and 4 hours post-dose and for the moderate impairment cohort at 8 hours post-dose. The maximum mean increase was 21.1 msec at 4 hours post-dose for the severe impairment subjects. Mean values of change were >10 msec for all hepatic impairment cohorts at 4 hours post-dose, for the moderate and severe cohorts at 3 hours post-dose, and for the moderate cohort at 8 hours post-dose. Normal hepatic function subjects consistently had lower mean values of QTcF change at all time points with none \geq 5 msec.

Outlier values of QTcF were noted in 5 of 6 subjects in the severe hepatic impairment cohort. Change from Baseline in QTcF was found to be significantly positively correlated with concentration of lofexidine with a predicted change of QTcF of 19.4 msec at the maximum observed concentration of 1.21 ng/mL.

One subject in the normal hepatic function cohort had a single observation of Atrial Fibrillation and 2 subjects in the severe impairment cohort had non-specific T wave changes, one of whom also had markedly prolonged QTcF values.

SAFETY RESULTS:

There were no deaths and no SAEs during the study. No subjects discontinued the study because of TEAEs. Overall, 29.2% of subjects (7/24 subjects) experienced 10 TEAEs. Only 12.5% of subjects (3/24 subjects) reported TEAEs that were considered related to treatment and 2 subjects in the normal hepatic function cohort reported severe TEAEs of orthostatic hypotension.

Vital sign changes were consistent with known effects of lofexidine, including decreases in SBP and DBP and decreases in pulse which were more pronounced upon standing. The decreased blood pressure and pulse appeared to be more exaggerated and prolonged in subjects with severe hepatic impairment. In general, there were more events of orthostatic hypotension in the subjects with normal hepatic function compared to the subjects with mild, moderate, or severe hepatic impairment and the 2 subjects reported TEAEs of orthostatic hypotension had normal hepatic function. Results from clinical laboratory tests, physical examinations, safety ECGs, and concomitant medication use showed no safety concerns.

CONCLUSIONS:

- No significant differences in AUC_{inf} , C_{max} , $T_{1/2}$, CL/F, and Total A_e were observed between subjects with normal hepatic function and subjects with mild hepatic impairment.
- Significant increases in exposure and decreases in systemic clearance were observed between subjects with normal hepatic function and subjects with moderate or severe hepatic impairment generally becoming more pronounced as the severity of hepatic impairment increased.
- The larger AUC values, decreased CL/F, and increased $T_{1/2}$ observed in the moderate and severe hepatic impairment cohorts indicate that drug accumulation with repeated dosing will likely be greater for these subjects, relative to subjects with normal hepatic function, given the QID dosing regimen anticipated for clinical use.
- **DOSAGE AND ADMINISTRATION:** Dosage should be reduced in patients with hepatic impairment. Regardless of hepatic function (mild, moderate, or severe impairment), a loading dose of lofexidine HCl 0.6 mg QID (low dose) or 0.8 mg QID (high dose) for one day may be used to shorten the time required to reach lofexidine steady-state concentrations. Reduce the maintenance dose of lofexidine HCl for patients with hepatic impairment according to the following table. Monitor blood pressure closely in patients with hepatic impairment.

Level of Hepatic Impairment	Child-Pugh Score	Lofexidine HCl Maintenance Dose	
Mild Impairment (Class A)	5 to 6	Low Dose	0.6 mg TID
		High Dose	0.6 mg QID
Moderate Impairment (Class B)	7 to 9	Low Dose	0.4 mg TID
		High Dose	0.4 mg QID
Severe Impairment (Class C)	10 to 15	Low Dose	0.2 mg QID
		High Dose	0.4 mg TID

- In each of the hepatically-impaired cohorts, a set of lofexidine loading doses can be used to shorten the time required for lofexidine steady-state concentrations to be reached. Use of 0.8 mg QID (or the lower dose alternative of 0.6 mg QID) for the first day of treatment is sufficient to bring the subjects to near steady-state concentrations (3.5– 5 ng/mL, or the lower dose alternative of 2.5 – 4 ng/mL) by Day 2 or Day 3 of treatment. A loading dose approach is especially recommended for subjects with moderate or severe hepatic impairment.
- A reduced dose of lofexidine HCl should be considered in subjects with hepatic impairment who are being treated concomitantly with a strong CYP2D6 inhibitor. Preliminary evidence suggests a further halving of the recommended maintenance dose based on the degree of hepatic impairment.
- There were no deaths and no SAEs during the study. No subjects discontinued the study because of TEAEs.
- Overall, 29.2% of subjects (7/24 subjects) experienced 10 TEAEs. Only 12.5% of subjects (3/24 subjects) reported TEAEs that were considered related to treatment and 2 subjects in the normal hepatic function cohort reported severe TEAEs of orthostatic hypotension.
- Vital sign changes were consistent with known effects of lofexidine, including decreases in SBP and DBP and decreases in pulse which were more pronounced upon standing. The decreased blood pressure and pulse appeared to be more exaggerated and prolonged in subjects with severe hepatic impairment but were not symptomatic. In general, there were more events of orthostatic hypotension in the subjects with normal hepatic function compared to the subjects with mild, moderate, or severe hepatic impairment and the 2 subjects reported TEAEs of orthostatic hypotension had normal hepatic function.
- Results from clinical laboratory tests, physical examinations, safety ECGs, and concomitant medication use showed no safety concerns.
- Lofexidine administration to hepatically-impaired subjects was associated with prolongation of the QTc interval compared to Baseline and compared to subjects with normal hepatic function. This effect was generally greater with increasing degree of the hepatic impairment. A statistically significant relationship was observed between increasing lofexidine concentrations and increases in the change from Baseline of QTcF.

Date of the report: February 22, 2017

4.4.7 Study LX1-1008 and -1012: Renal Impairment

US WorldMeds, LLC
 Clinical Study Report USWM-LX1-1008

4250358

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine Hydrochloride		
Name of Active Ingredient: Lofexidine Hydrochloride		
Title of Study: Single-Dose Pharmacokinetics and Safety of Oral Lofexidine in Renally-Impaired Subjects		
Principal Investigator: Thomas Marbury, MD		
Study center: Orlando Clinical Research Center 5055 South Orange Avenue Orlando, FL 32809		
Publications (reference): None to date		
Studied period (years): Date first subject enrolled: 10 November 2014 Date last subject completed: 11 February 2015		Phase of development: I
Objectives: Primary: <ul style="list-style-type: none"> The primary objective of this study was to determine if end-stage renal disease (ESRD) affects the plasma pharmacokinetics (PK) of orally administered lofexidine. Secondary: <ul style="list-style-type: none"> The secondary objective of this study was to evaluate the safety and tolerability of lofexidine in ESRD subjects on hemodialysis. 		

<p>Methodology:</p> <p>This was a Phase 1, open-label, parallel-group, single-dose study of lofexidine in 16 subjects: 8 adult subjects with ESRD maintained on hemodialysis (3 times per week) and 8 healthy normal subjects confirmed to have normal renal function (NRF) defined as creatinine clearance (CL_{cr}) > 90 mL/min. The NRF subjects were recruited as 1:1 matches with each ESRD subject, being matched for gender, age (± 10 years), and body mass index (BMI; $\pm 15\%$). NRF and ESRD subjects were confined to an inpatient facility from the day before dosing to 144 or 156 hours (a total of 7 to 8 nights and 8 to 9 days) after dosing, respectively.</p> <p>Subjects who successfully completed screening reported to the inpatient facility at an appropriate time the evening before study drug administration (Day -1) to undergo pre-dose study procedures.</p> <p>The next morning (Day 1), all subjects received breakfast (approximately 6 hours before planned lofexidine HCl dosing) and then ESRD subjects began and completed their hemodialysis session prior to dosing. All subjects received a single, oral dose of 0.4 mg lofexidine hydrochloride (HCl) (2×0.2 mg tablets), dosed with 240 mL of water, the timing of which was approximately the same time for both NRF and ESRD subjects. Because ESRD subjects were maintained on 3 times per week dialysis, lofexidine HCl was administered near the beginning of a 3-day, between-dialysis interval.</p>
<p>Number of subjects (planned and analyzed):</p> <p>16 subjects were planned to be enrolled and all 16 were included in the Safety and Pharmacokinetic (PK) populations</p>
<p>Diagnosis and main criteria for inclusion:</p> <p>Diagnosis and Main Criteria for Inclusion: Male or female subjects between 18 and 75 years old at enrollment with a BMI between 18 and 38 kg/m² were eligible to participate in the study. Other inclusion criteria included:</p> <ul style="list-style-type: none">• <i>NRF matched subject:</i> $CL_{cr} \geq 90$ mL/min as estimated by Cockcroft and Gault or if clinically indicated by a 24-hour urine CL_{cr} test; gender, age (± 10 years), and BMI ($\pm 15\%$) matched to their ESRD subject• <i>ESRD subject:</i> Receiving adequate maintenance hemodialysis (at least 3 times a week) for at least 3 months prior to Day -1 (i.e., approximate $Kt/V > 1.1$ based on subject's nephrologist and Investigator)
<p>Test product, dose and mode of administration, batch number:</p> <p>A single dose of lofexidine HCl 0.4 mg (2×0.2 mg tablets); Lot number: 24004-3561</p>
<p>Duration of treatment:</p> <p>Duration of Treatment: 1 day (single dose)</p> <p>Duration of Participation:</p> <ul style="list-style-type: none">• <i>NRF matched subject:</i> up to 36 days (including up to a 28-day Screening Period and 7 nights / 8 days of inpatient confinement)• <i>ESRD subject:</i> up to 37 days (including up to a 28-day Screening Period and 8 nights / 9 days of inpatient confinement)
<p>Reference therapy, dose and mode of administration, batch number:</p> <p>None.</p>

Criteria for evaluation:

Sample collection pharmacokinetic parameters:

Finger stick blood samples were collected for PK analysis at multiple time points over 144 hours (NRF subjects) or 156 hours (ESRD subjects) after dosing. Two venous blood samples were collected from each subject for lofexidine protein binding analyses (and possible future lofexidine metabolite analysis), 1 sample 0 to 60 minutes before dosing and the other 4 hours post-dose.

Urine samples were obtained from pooled urines collected from 0 to 3 hours, 3 to 6 hours, 6 to 12 hours, 12 to 24 hours, 24 to 48 hours, 48 to 72 hours, 72 to 96 hours, and 96 to 144 hours post-dose. Pooled urine samples were collected from ESRD subjects as available according to the same schedule.

Arterial and venous blood samples from the arterial-venous (A-V) shunt were collected for PK analysis from ESRD subjects at 0.5, 1.5, 2.5, and 3.5 hours into each of the two, 4-hour hemodialysis sessions. Finger stick blood samples were also collected from the hand contralateral to the arm used for the dialysis A-V shunt at these same time points. Pooled dialysate effluent from ESRD subjects was collected during the two, 4-hour hemodialysis sessions over the following intervals: 0 to 1 hour, 1 to 2 hours, 2 to 3 hours, and 3 to 4 hours.

Safety:

Safety was assessed by reported adverse events (AEs), vital signs (blood pressure and pulse rate), clinical laboratory tests (chemistry, hematology, and urinalysis), 12-lead safety ECGs, 12-lead Holter ECGs, and physical examinations.

Statistical methods:

Pharmacokinetic methods:

Concentration-time data were analyzed by non-compartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantification (BLQ) were treated as zero in the data summarization and descriptive statistics. In the PK analysis, BLQ concentrations were treated as zero from time zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all PK and statistical analyses.

Differences in C_{max} , AUC_{0-32} , AUC_{inf} , and $T_{1/2}$ between NRF and ESRD subjects were assessed using analysis of variance (ANOVA). The Wilcoxon signed rank test was used for nonparametric comparisons of T_{max} and $T_{1/2}$ values; significant differences were defined a priori as $p < 0.05$. Additionally, scatterplots were generated for individual PK parameters C_{max} , AUC_{0-32} , AUC_{inf} , $T_{1/2}$, and CL/F by study population (NRF or ESRD) to visually identify potential trends dependent on renal impairment. Descriptive statistics were used to summarize lofexidine concentrations at each time point and PK parameters by renal function cohort. By-subject PK profiles are presented graphically.

Safety analysis:

No formal statistical testing was performed on safety variables.

Adverse events

The Medical Dictionary for Regulatory Activities (MedDRA; version 16) was used to code all AEs with respect to system organ class and preferred term. All treatment-emergent AEs (TEAEs) were summarized by system organ class and preferred term by frequency and severity.

Summary tables were produced for all (TEAEs) and treatment-related TEAEs by cohort and overall. Subjects who discontinued because of an AE, who had nonfatal serious AEs (SAEs), or who died during the study were identified and listed, if applicable.

Laboratory parameters

Descriptive statistics were used for continuous laboratory parameters at screening and discharge for each cohort and overall. Changes from baseline were calculated and presented by cohort and overall. Shift tables were constructed for all laboratory parameters by cohort and displayed the number and percentages of subjects with values that were low, normal, or high at baseline compared with low, normal, or high at discharge. Clinically significant values were identified. A listing of clinically significant laboratory values is provided.

Electrolyte parameters collected during the study are presented using descriptive statistics. Shift tables are provided.

Vital signs

Descriptive statistics were used to summarize the observed vital sign values at each time point by cohort and overall. Individual changes from pre-dose to each subsequent time point post-dose were calculated for each cohort and overall using descriptive statistics.

Physical examinations

The number and percentage of subjects with normal or abnormal physical examination results at screening and discharge are presented.

Safety electrocardiograms

The number and percentage of subjects with normal or abnormal ECG overall interpretation is presented. Shift tables were constructed to display the number and percentage of subjects with normal or abnormal results at Day 1 (pre-dose) compared with Day 1 (3.5 hours post-dose) and discharge.

Holter electrocardiogram

Summary statistics (N, mean, median, minimum, maximum, and standard deviation) for Holter (12-lead) ECG changes from baseline and categorical findings are presented by cohort. Morphological findings are presented by subject. Holter ECG readings extracted in duplicate are presented in data listings

Prior and concomitant medication

The number and percentage of subjects for each prior and concomitant medication are presented by cohort and overall.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

Plasma concentrations:

The first quantifiable plasma lofexidine concentrations were observed at 0.5 hours for ESRD subjects and NRF subjects.

The peak mean plasma lofexidine concentrations occurred at 3 hours post-dose for both NRF subjects and ESRD subjects. Peak mean lofexidine plasma concentrations were similar for NRF subjects and ESRD subjects (0.887 ± 0.194 ng/mL and 0.910 ± 0.145 ng/mL, respectively). Lofexidine concentrations observed for NRF subjects were below the limit of quantification approximately 24 hours earlier than in ESRD subjects. The last quantifiable lofexidine concentrations occurred between 32 hours and 72 hours post-dose for NRF subjects and between 48 hours and 96 hours post-dose for ESRD subjects.

The impact of dialysis on the overall PK of lofexidine during a typical 4-hour dialysis was minimal; the drop in lofexidine plasma concentrations produced during the dialysis session was transient, with a rebound to nearly predialysis concentrations after re-equilibration within a few hours following completion of the dialysis cycle. Lofexidine concentrations showed a drop of approximately 25% within the first half-hour of starting dialysis (67 hours post-dose), however, on completion of the 4-hour dialysis session, lofexidine concentrations rebounded between 71 hours and 76 hours post-dose to nearly the concentration expected if there had been no dialysis.

Pharmacokinetic parameters:

Median time to maximum lofexidine plasma exposure (C_{max}) for subjects with normal renal function and ESRD subjects occurred at T_{max} values of 3.0 hours and 2.5 hours, respectively. Mean C_{max} values were similar for NRF subjects and ESRD subjects (0.915 ± 0.217 ng/mL and 0.954 ± 0.160 ng/mL, respectively).

Since all subjects in both renal function groups had lofexidine concentrations greater than the lower limit of quantitation (LLOQ) out to at least 32 hours post-dose, the exposures prior to 32 hours were compared for the ESRD and NRF groups. An approximately 35% increase in overall lofexidine exposure through 32 hours post-dose (AUC_{0-32}) was observed for ESRD subjects compared with that of NRF subjects (17.83 ± 2.656 h•ng/mL and 13.25 ± 3.669 h•ng/mL, respectively). An approximately 71% increase in AUC_{inf} was observed for ESRD subjects compared with NRF subjects. Mean T_{last} occurred approximately 30 hours later for ESRD subjects compared with NRF subjects (76.95 hours and 46.00 hours, respectively).

Overall mean clearance reported for NRF subjects was greater than that reported for ESRD subjects (19.85 ± 5.994 L/h and 11.10 ± 2.156 L/h, respectively). The ESRD subjects had a mean CL/F that was approximately 56% of the mean CL/F of the NRF subjects.

Overall, individual $T_{1/2}$ values for ESRD subjects were within the range of the individual $T_{1/2}$ values estimated for NRF subjects, although mean apparent $T_{1/2}$ was approximately 7 hours longer for ESRD subjects compared with NRF subjects (26.41 hours and 19.34 hours, respectively) representing an approximately 37% prolongation in the mean $T_{1/2}$ associated with ESRD.

Mean lofexidine clearance during the first dialysis session was approximately 5-6 L/h; approximately half of the mean overall plasma CL/F value reported for ESRD subjects (11.10 L/h). The 4-hour dialysis session removed an average of 2.86 μ g of lofexidine, less than 1% of the 351 μ g lofexidine free base administered, but approximately 5%-6% of the lofexidine body load at the start of the dialysis session 67 hours postdose (body load at start of dialysis session estimated as $351 \mu\text{g} \cdot C_{67}/C_{max} = 50.4 \mu\text{g}$).

DOSE ADJUSTMENT IN ESRD SUBJECTS:

The apparent clearance for ESRD subjects in this study was approximately 56% of the value for NRF subjects (11.10 L/h vs. 19.85 L/h), leading to the conclusion that the daily dose in ESRD subjects should be approximately 56% of the daily dose in NRF subjects for comparable daily exposures to be achieved. Available oral dosing options allow this desired dose reduction to be closely approximated by using 50% of NRF subjects' dose in ESRD subjects. If the desired clinical target for NRF subjects is 3.2 mg/day (0.8 mg QID) lofexidine HCl, then a reduced dose in ESRD subjects of 1.6 mg/day (0.4 mg QID) would provide comparable lofexidine exposure; if the desired clinical target for NRF subjects is 2.4 mg/day (0.6 mg QID) lofexidine HCl, then a reduced dose in ESRD subjects of 1.2 mg/day (0.4 mg TID) would provide comparable lofexidine exposure.

CARDIAC SAFETY RESULTS:

Holter ECG findings showed differences between the groups with ESRD subjects having higher mean values at Baseline compared with NRF subjects for each of the ECG intervals. Heart rate was 18.9 bpm higher, PR interval was 5.8 msec longer, QRS value was 17.8 msec longer, and QTcF was borderline abnormal and 46.8 msec longer in ESRD subjects.

Based on the primary correction method, the mean QTcF for ESRD subjects increased from a borderline abnormal value of 451.7 msec at Baseline to a maximum of 463.2 msec at 4 hours post-dose. This represented a mean increase of 11.5 msec. At 8 hours post-dose, the mean QTcF was 441.2 msec, representing a mean decrease of -10.5 msec. While changes of QTcF from Baseline were similar for the NRF and the ESRD subjects, the NRF subjects had normal values of mean QTcF throughout the evaluation period.

QTcF categorical assessments indicated prolonged values were present in a majority of ESRD subjects but in none of the NRF subjects. Incidence for ESRD subjects was 6 of 7 (85.7%) with QTcF >450 msec and 2 of 7 (28.6%) with values >480 msec. It should be noted that at Baseline, 3 of 7 (42.9%) ESRD subjects had values of QTcF >450 msec and 1 of 7 (14.3%) had QTcF >480 msec.

A statistically positive relationship was observed between lofexidine plasma concentrations and change in QTcF in both groups; the effect was greater for the ESRD group. The predicted change in QTcF was 9.6 msec at the ESRD C_{max} of 0.914 ng/mL (upper 2-sided 95% confidence bound of 23.8 msec).

Findings for HR, PR interval, and QRS interval were unremarkable and changes from Baseline were similar for both renal function groups. Non-specific ST change was observed in one subject in the ESRD group.

A single dose of lofexidine HCl 0.4 mg administered to ESRD subjects and to NRF subjects was associated with increases in QTcF. The increase of QTcF from Baseline was positively correlated with increasing concentration of lofexidine. Nearly identical and modest increases in QTcF were noted in ESRD subjects and NRF subjects. The remainder of the ECG findings were unremarkable except for the uniformly longer ECG interval values at Baseline for ESRD subjects compared to NRF subjects.

SAFETY RESULTS:

There were no deaths and no SAEs during the study. No subjects discontinued the study because of TEAEs. Overall, 50.0% of subjects (8/16 subjects) experienced 9 TEAEs, all of which were considered related to study drug; 7 (77.7%) of the 9 events, one severe, were hypotension, a known effect of lofexidine. More subjects with NRF reported a TEAE than did subjects with ESRD (62.5% versus 37.5%, respectively).

Changes in SBP and DBP measurements were as expected for treatment with lofexidine. Results from clinical laboratory tests, physical examinations, safety ECGs, and concomitant medication use showed no safety concerns.

CONCLUSIONS:

- Mean C_{max} values were similar for NRF subjects and ESRD subjects, indicating no changes in maximum lofexidine exposure with renal impairment.
- Lofexidine exposure through 32 hours post-dose, as measured by AUC_{0-32} , was approximately 38% greater for ESRD subjects compared to NRF subjects.
- Lofexidine exposure as measured by AUC_{inf} , was approximately 75% greater for ESRD subjects compared to NRF subjects, indicating that dosage adjustment of lofexidine HCl may be warranted in patients with ESRD.
- Quantifiable lofexidine concentrations were present in systemic circulation for ESRD subjects for approximately 24 hours longer than for NRF subjects.
- Lofexidine concentrations showed a noticeable drop during the first dialysis session (67 hours to 71 hours post-dose). However, the concentration rebound following discontinuation of the dialysis session appeared to be nearly complete. The impact of a standard dialysis session, which removed approximately 1% of the administered dose, will be minimal in a setting of accidental or intentional lofexidine overdose. However, in patients with reduced systemic clearance, such as patients with ESRD or severe hepatic impairment, the lofexidine elimination half-life may be shortened by 1/5 to 1/3 during dialysis and there may be some benefit provided by a substantially prolonged dialysis treatment.

- Dosing of lofexidine in ESRD subjects does not require special scheduling associated with the dialysis session; no redosing is required to compensate for lofexidine lost during a standard dialysis session.

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- There were no new safety concerns identified in subjects with ESRD.

Date of the report:

February 27, 2017

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: Single-Dose Pharmacokinetics and Safety of Oral Lofexidine In Renally-Impaired Subjects		
Investigator: Thomas Marbury, MD		
Study center(s): Orlando Clinical Research Center, 5055 South Orange Avenue, Orlando, FL 32809		
Publications (reference): None		
Studied period (years): Date first subject enrolled: 08 February 2016 Date last subject completed: 16 July 2016		Phase of development: 1
Objectives: The primary objective of this study was to evaluate changes in lofexidine pharmacokinetics (PK) associated with impaired renal function. The secondary objective of this study was to evaluate the safety and tolerability of lofexidine in subjects with renal impairment.		
Methodology: This was a Phase 1, open-label, parallel-group, single-dose study of lofexidine. The plan was to enroll 6 subjects each with normal renal function, mild renal impairment, moderate renal impairment, and severe renal impairment not requiring dialysis. The normal renal function cohort was to comprise a similar distribution of sex, age, and body mass index (BMI) as the impaired renal function cohorts. Subjects were confined to an inpatient facility from the evening before dosing to 120 hours after dosing, for a total of 6 nights and 7 days. Subjects who successfully completed screening reported to the inpatient facility at an appropriate time the evening before study drug administration (Day -1) to ensure a minimum 10-hour fast. The next morning (Day 1) while still fasting, subjects received a single oral dose of 0.4 mg lofexidine HCl (2 × 0.2 mg tablets).		

<p>Fingerstick blood samples were collected for PK analysis at multiple time points over the next 120 hours. Venous blood samples were collected for protein binding analysis and possible future metabolite analysis within 2 hours before lofexidine administration and at 4 hours postdose. Urine aliquots from pooled urine samples were collected for PK analysis at 0-3 hours, 3-6 hours, 6-12 hours, 12-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours postdose.</p> <p>Safety assessments included treatment-emergent adverse events (TEAEs), vital signs (blood pressure and pulse), clinical laboratory tests (chemistry, hematology, and urinalysis), 12-lead safety ECGs, Holter electrocardiograms (ECGs), and physical examinations.</p>
<p>Number of subjects (planned and analyzed):</p> <p>24 planned; 23 analyzed (normal renal function, 6; mild renal impairment, 6; moderate renal impairment, 6; severe renal impairment, 5)</p>
<p>Diagnosis and main criteria for inclusion:</p> <p>Adults 18 to 79 years of age with a BMI between 19 and 38 kg/m², inclusive, with mean age, BMI, and sex distribution targeted to be similar across the 4 cohorts. The normal renal function cohort enrolled healthy subjects with eGFR \geq 90 mL/min/1.73 m². The renal impairment cohorts enrolled subjects whose medical history, physical examination, and laboratory tests were consistent with their renal impairment and whose pre-existing medical conditions were anticipated to be stable. Renal impairment was defined as follows: mild impairment: eGFR 60-89.99 mL/min/1.73 m²; moderate impairment: eGFR 30-59.99 mL/min/1.73 m²; severe renal impairment: eGFR <30 mL/min/1.73 m².</p>
<p>Test product, dose and mode of administration, batch number:</p> <p>Lofexidine HCl 0.2 mg tablets, dose = 0.4 mg (2 \times 0.2 mg tablets), Lot 33405-5588.</p>
<p>Duration of treatment:</p> <p>Single dose</p>
<p>Reference therapy, dose and mode of administration, batch number:</p> <p>Not applicable</p>
<p>Criteria for evaluation:</p> <p>Pharmacokinetics:</p> <p>Fingerstick blood samples were collected for PK analysis at multiple time points up to 120 hours postdose. Urine aliquots from pooled urine samples were collected for PK analysis at 0-3 hours, 3-6 hours, 6-12 hours, 12-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours postdose. Venous blood samples were collected for assessment of protein binding and for possible future metabolite analysis.</p> <p>Safety:</p> <p>Safety assessments included adverse events, laboratory parameters, vital signs, physical examinations, 12-lead (paper) electrocardiograms (ECGs), and Holter ECGs.</p>
<p>Statistical methods:</p> <p>Pharmacokinetics:</p> <p>Plasma lofexidine concentration-time data were analyzed using noncompartmental methods. The following PK parameters were calculated: maximum drug concentration in plasma determined directly from individual concentration-time data (C_{max}), time to reach maximum concentration (T_{max}), observed terminal elimination rate constant (λ_z), observed terminal elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{last}), area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), the percentage of AUC_{inf} in plasma based on extrapolation (AUC_{extmp} [%]); the</p>

last plasma concentration determined directly from individual concentration-time data (C_{last}), time of the last quantifiable plasma concentration (T_{last}), apparent total body clearance after oral administration (CL/F), apparent total body clearance (CL), apparent volume of distribution (V_z/F), amount of lofexidine excreted in urine (A_e), total amount of lofexidine excreted in urine (total A_e), renal clearance (CL_R), nonrenal clearance after oral administration (CL_{NR}/F), nonrenal clearance (CL_{NR}), and percentage of free (unbound) fraction of lofexidine ($F_u[\%]$). PK results were summarized by cohort (normal renal function, and mild, moderate, and severe renal impairment) using descriptive statistics.

(b) (4)
(b) (4)

Safety:

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0. The incidence of TEAEs was summarized by treatment, MedDRA system organ class, MedDRA preferred term, by investigator attribution of relationship to study drug and by severity. Changes from predose were summarized for laboratory parameters and vital signs; shift tables for laboratory values were also provided.

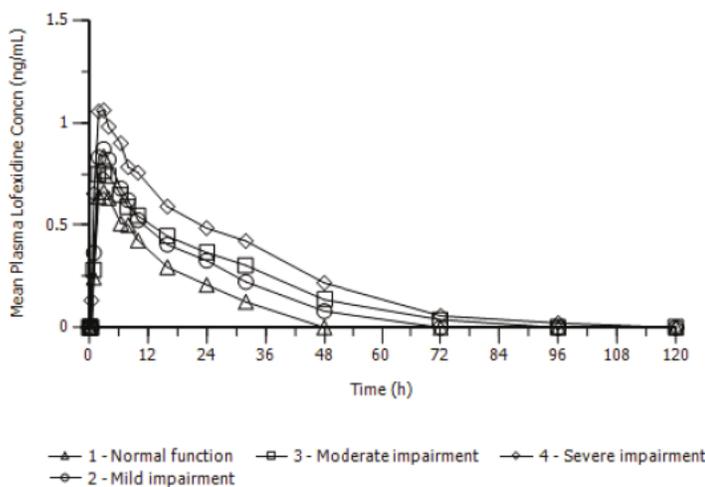
Twelve-lead Holter ECGs were extracted before lofexidine administration, and 3, 4, and 8 hours postdose. Change from predose in QTc with Fridericia's heart rate correction ($\Delta QTcF$) was the primary endpoint. Secondary endpoints were change from baseline in HR, PR, QRS, RR, and QT intervals; categorical outliers for QTcF, heart rate, PR, and QRS; categorical analysis for T-wave and U-wave morphology; and relationship between plasma concentration of lofexidine and $\Delta QTcF$.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS RESULTS:

Overall, mean lofexidine plasma concentrations were highest for subjects with severe renal impairment, followed by those observed for subjects with mild renal impairment, moderate renal impairment, and lowest for subjects with normal renal function (Synopsis Figure 1). The highest mean plasma lofexidine concentrations were 1.06 ± 0.179 ng/mL at 3.00 hours for the severe renal impairment cohort, 0.761 ± 0.154 ng/mL at 3.00 hours for the moderate renal impairment cohort, 0.870 ± 0.181 ng/mL at 3.00 hours for the mild renal impairment cohort, and 0.661 ± 0.0864 ng/mL at 3.00 hours for the normal renal function cohort.

Synopsis Figure 1. Mean Lofexidine Plasma Concentration-time Profiles After Oral Administration of Lofexidine HCl 0.4 mg to Subjects with Normal Renal Function and Subjects With Mild, Moderate, or Severe Renal Impairment



Source: Pharmacokinetic Report, Appendix 16.5, Figure 1

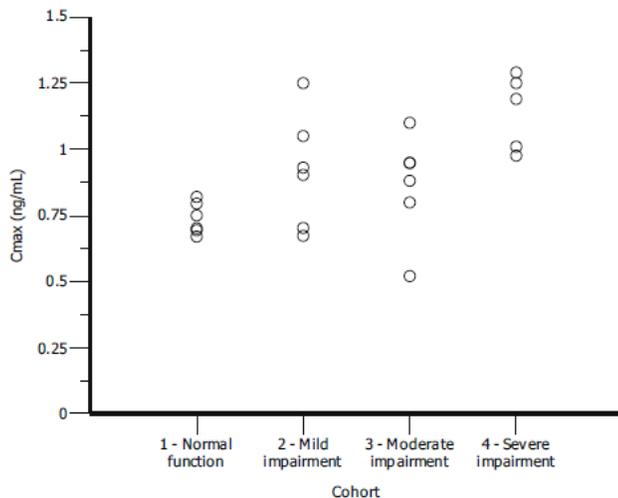
Mean C_{max} (Synopsis Figure 2), AUC_{inf} (Synopsis Figure 3), and $t_{1/2}$ increased with severity of renal impairment (Synopsis Table 1). Mean clearance (CL/F) decreased with increasing severity of renal impairment (Synopsis Figure 4).

Synopsis Table 1. Plasma Pharmacokinetic Parameters of Lofexidine After Oral Administration of Lofexidine HCl 0.4 mg to Subjects with Normal Renal Function and Subjects With Mild, Moderate, or Severe Renal Impairment

Time (h)	Cohort 1: Normal Renal Function (N = 6)			Cohort 2: Mild Renal Impairment (N = 6)			Cohort 3: Moderate Renal Impairment (N = 6)			Cohort 4: Severe Renal Impairment (N = 5)		
	Mean (ng/mL)	SD (ng/mL)	CV (%)	Mean (ng/mL)	SD (ng/mL)	CV (%)	Mean (ng/mL)	SD (ng/mL)	CV (%)	Mean (ng/mL)	SD (ng/mL)	CV (%)
T_{max} (h)	2.83	0.98	34.70	2.84	0.74	26.11	3.43	1.79	52.11	2.20	0.84	38.03
C_{max} (ng/mL)	0.739	0.0600	8.12	0.918	0.216	23.57	0.866	0.196	22.63	1.14	0.142	12.44
AUC_{last} (h•ng/mL)	10.28	1.855	18.04	16.18	4.412	27.27	19.22	4.003	20.83	27.98	5.781	20.66
AUC_{inf} (h•ng/mL)	13.53	3.102	22.92	19.48	3.609	18.53	23.42	3.751	16.02	32.82	5.489	16.73
AUC_{Extrap} (%)	23.36	4.75	20.34	17.98	9.82	54.59	18.37	5.67	30.87	15.13	3.54	23.38
λ_z (h^{-1})	0.0502	0.0092	18.27	0.0446	0.0056	12.59	0.0343	0.0054	15.64	0.0319	0.0053	16.59
$t_{1/2}$ (h)	14.24	2.87	20.15	15.74	1.99	12.65	20.63	3.39	16.44	22.29	4.22	18.94
T_{last} (h)	30.67	3.27	10.65	42.67	8.26	19.36	53.33	15.73	29.50	62.40	21.47	34.40
C_{last} (ng/mL)	0.154	0.0362	23.45	0.143	0.0422	29.53	0.144	0.0432	29.92	0.156	0.0430	27.50
CL/F (L/h)	26.94	5.466	20.29	18.53	3.391	18.30	15.29	2.376	15.54	10.89	1.530	14.05
CL (L/h)	19.31	3.918	20.29	13.28	2.431	18.30	10.96	1.703	15.54	7.806	1.097	14.05
V_z/F (L)	535.5	32.54	6.08	423.7	109.1	25.74	448.8	61.13	13.62	343.3	25.09	7.31

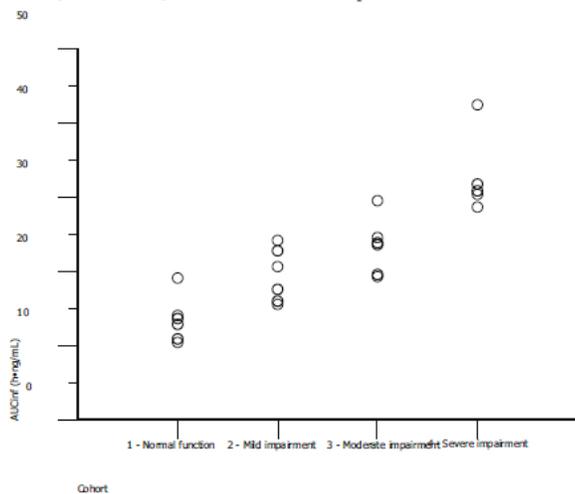
Note: CL/F, CL, and V_z/F values were calculated using lofexidine free base dose (0.3507 mg) and represent the overall CL/F, CL, and V_z/F calculated using data from the entire pharmacokinetic profile.
 Source data: Pharmacokinetic Report, Appendix 16.5, Table 2

Synopsis Figure 2. Scatter Plot of Individual Lofexidine C_{max} Values After Oral Administration of Lofexidine HCl 0.4 mg to Subjects with Normal Renal Function and Subjects With Mild, Moderate, or Severe Renal Impairment



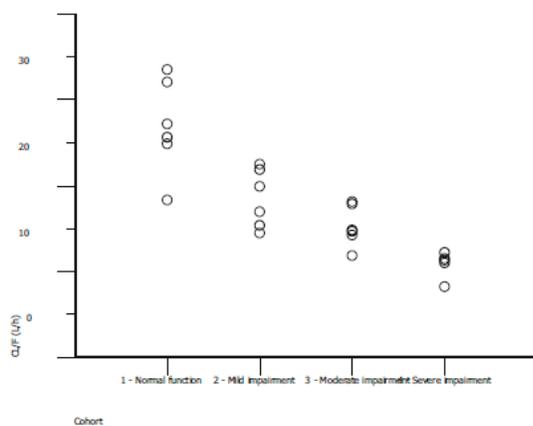
Note: Two patients in the moderate impairment cohort had very similar C_{max} values (0.948 and 0.949 ng/mL); therefore, the symbols for these two patients overlap in this figure
Source: Pharmacokinetic Report, Appendix 16.5, Figure 2

Synopsis Figure 3. Scatter Plot of Individual Lofexidine AUC_{inf} Values After Oral Administration of Lofexidine HCl 0.4 mg to Subjects With Normal Renal Function and Subjects With Mild, Moderate, or Severe Renal Impairment



Source: Pharmacokinetic Report, Appendix 16.5, Figure 3

Synopsis Figure 4. Scatter Plot of Individual Lofexidine CL/F Values After Oral Administration of Lofexidine HCl 0.4 mg to Subjects with Normal Renal Function and Subjects With Mild, Moderate, or Severe Renal Impairment



Note: CL/F values were calculated using lofexidine free base dose (0.3507 mg) and represent the overall CL/F calculated using data from the entire pharmacokinetic profile

Source: Pharmacokinetic Report, Appendix 16.5, Figure 4

Mean total amount of the administered lofexidine dose recovered in urine (total Ae) was highest for subjects with mild (68.45 µg) and moderate (66.53 µg) renal impairment followed by subjects with normal renal function (43.12 µg) and subjects with severe renal impairment (39.77 µg). Mean percent of the dose recovered in urine (%total Ae) ranged from 11.34% in subjects with severe renal impairment to 19.52% in subjects with mild renal impairment.

Mean renal clearance (CL_R) was similar for subjects with normal renal function (3.207 L/h), mild renal impairment (3.587 L/h), and moderate renal impairment (2.845 L/h), but was substantially decreased in subjects with severe renal impairment (1.255 L/h). Mean non-renal clearance values ($CL_{NR/F}$) decreased with increasing severity of renal impairment, ranging from 23.73 L/h in subjects with normal renal function to 9.636 L/h in subjects with severe renal impairment.

SAFETY RESULTS:

The proportion of subjects with TEAEs was similar across cohorts: 4 subjects (66.7%) with normal renal function, 4 subjects (66.7%) with mild renal impairment, 5 subjects (83.3%) with moderate renal impairment, and 3 subjects (60.0%) with severe impairment. Fifteen subjects (65.2%) experienced at least one TEAE considered related to study drug; the frequency of related TEAEs did not increase with increasing severity of renal impairment. The most frequently reported TEAEs were orthostatic hypotension, hypotension, dizziness, and flank pain. AEs of orthostatic hypotension or hypotension were reported in 67%, 50%, 50%, and 20% of subjects in the normal renal function mild impairment, moderate impairment, and severe impairment cohorts, respectively. All of these AEs were considered related to study drug.

Most adverse events were mild. Moderate and severe TEAEs were not reported at higher rates in subjects with renal impairment as compared with subjects with normal renal function. No subject died or experienced other serious AEs during the study and no subject discontinued due to an AE.

At baseline and as expected, there was a trend for higher mean blood urea nitrogen (BUN) in cohorts with higher renal impairment, with mean values of 12.50, 19.17, and 24.67, and 54.40 mg/dL in subjects with normal renal function and with mild, moderate, and severe impairment, respectively. Mean BUN levels remained fairly constant from baseline to 24 hours postdose. Overall, changes in laboratory parameters were small and not clinically meaningful.

Mean blood pressure and pulse decreased in all 4 cohorts after lofexidine administration. Mean decrease in vital sign values was not more pronounced with increasing renal impairment. In the first 12 hours after dosing, the maximum mean decrease in standing systolic blood pressure was -35.8 mmHg (normal renal function cohort, 6 hours postdose). The maximum mean decrease in standing diastolic blood pressure in the first 12 hours was -20.5 mmHg (normal renal function cohort, 6 hours postdose). Mean pulse also decreased. The maximum mean change in standing pulse was -10.7 bpm (mild renal impairment cohort, 7.5 hours postdose). For all 4 cohorts, blood pressure and pulse returned to near baseline values by 6 days postdose.

Based on Holter ECGs, a small heart rate reduction was seen in all cohorts postdose, ranging between -12 bpm and -5 bpm without clear relation to time after dosing. A relatively small effect on the QTcF interval was seen in the normal renal function and mild impairment groups, whereas the effect on $\Delta QTcF$ was larger in the moderate and severe renal impairment cohorts at all postdosing timepoints. The largest mean $\Delta QTcF$ was 18.0 msec at 4 hours postdose in the moderate renal impairment cohort and 21.3 msec at 4 hours postdose in the severe renal impairment cohort. One subject in the severe renal impairment cohort had a QTcF > 480 msec. One subject in the severe renal impairment cohort had a $\Delta QTcF$ > 60 msec. A relatively steep and statistically significant slope of the relationship between lofexidine plasma concentrations and $\Delta QTcF$ was observed. Within the limitations of this study, the predicted mean $\Delta QTcF$ effect using this model can be estimated to between 7 msec and 16 msec at lofexidine plasma levels between 0.7 ng/mL and 1.1 ng/mL. No effect

of lofexidine at these doses and concentrations was observed on cardiac conduction (PR and QRS intervals) or T-wave morphology.

CONCLUSION:

- Overall, maximum and total lofexidine exposure in plasma increased with increasing severity of renal impairment. Mean C_{max} , AUC_{last} , $AUC_{in\infty}$ and $t_{1/2}$ increased with increasing severity of renal impairment, and mean CL/F , V_z/F , and CL_{NR}/F decreased with increasing severity of renal impairment. Mean CL_R was similar for subjects with normal renal function, mild renal impairment, or moderate renal impairment, but was substantially decreased in subjects with severe renal impairment.
- Approximately half of the subjects experienced hypotension, which is consistent with the α_2 adrenergic receptor agonist mechanism of action of lofexidine. Neither the frequency or severity of hypotension changed with increasing levels of renal impairment. There were no serious AEs or discontinuations due to AEs. A relatively small prolongation effect on the QTcF interval was seen in the normal and mild renal impairment groups after lofexidine administration, whereas the effect was greater in the moderate and severe renal impairment groups.

Date of the report: 25 May 2017

4.4.8 Study LX1-1009: DDI with Naltrexone

US WorldMeds, LLC
Clinical Study Report Synopsis USWM-LX1-1009

209229

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: Assessment of the Effect of Naltrexone on Lofexidine Single Dose Pharmacokinetics in Healthy Subjects		
Principal Investigator: George Atiee, MD		
Study center(s): Worldwide Clinical Trials, San Antonio, TX		
Publications (reference): None to date		
Studied period (months): 2.5 Date first subject enrolled: 08 May 2015 Date last subject completed: 22 July 2015	Phase of development: I	
Objectives: Primary: <ul style="list-style-type: none"> To determine the effect of naltrexone on the single dose pharmacokinetics (PK) of the oral lofexidine formulation Secondary: <ul style="list-style-type: none"> To determine the effect of lofexidine on the steady-state PK of oral naltrexone 		
Methodology: This was a Phase 1, open-label, single-arm study. Two single doses of lofexidine (the first on Day 1 and the second on Day 11) and multiple daily doses of naltrexone (from Days 4 to 13) were administered to 24 adult healthy subjects. Subjects were confined to an inpatient facility for a total of 14 nights and 15 days. Subjects who successfully completed screening reported to the inpatient facility (Day -1) at an appropriate time to undergo pre-dosing study procedures. The next morning (Day 1) after an overnight fast, at approximately 8 AM, all subjects received the first single, oral dose of 0.4 mg lofexidine hydrochloride (HCl) (2 x 0.2 mg tablets), taken with 240 mL of water (no food). A standardized meal was served 1.5 hours after the lofexidine dose. The lofexidine dose was followed by a 74-hour (± 5 minutes) interval before initiation of naltrexone daily dosing on Day 4 at approximately 10 AM. The first naltrexone administration on Day 4 was a dose of approximately 25 mg (1/2 tablet of naltrexone 50 mg), with subsequent doses of 50 mg once daily on Days 5 to 13. Naltrexone daily doses were taken at the same time of day (± 10 minutes on Days 4-9, 12 and 13; ± 5 minutes on Days 10 and 11) with food to reduce the incidence of nausea. On Day 11, the second single dose of 0.4 mg lofexidine HCl was administered at approximately 8 AM in a fasted state on a background of steady-state naltrexone and followed by the daily administration of the naltrexone dose (50 mg) at approximately 10 AM. The actual clock time for administering the lofexidine and naltrexone doses was allowed to be staggered for logistic purposes as long as the dosing times for each drug were standardized for all treatment days, and the 2-hour (± 5 minutes) interval was maintained between the		

<p>lofexidine and naltrexone doses on Day 11. A meal was served approximately 1.5 hours after the lofexidine dose and 0.5 hours before the naltrexone dose. The daily administration of naltrexone dose (50 mg) continued on Day 12 and Day 13.</p> <p>After each administration of lofexidine on Day 1 and Day 11, fingerstick blood samples were collected for lofexidine PK analysis before dosing and after dosing at multiple time points over a 72-hour period. Each fingerstick blood sample (0.5 mL) was collected in a microtainer containing dipotassium ethylenediaminetetraacetic acid (K₂EDTA) anticoagulant. On Days 10 and 11, venous blood samples were collected for naltrexone and 6β-naltrexol PK analysis before naltrexone dosing and after dosing at multiple time points over a 24-hour period. Each venous blood sample (6 mL) was collected in a blood collection tube containing K₂EDTA anticoagulant.</p>
<p>Number of subjects (planned and analyzed): Planned: adequate number in order to obtain 24 who completed the study; Enrolled: 24; Analyzed: 24</p>
<p>Diagnosis and main criteria for inclusion: Male or female between the ages of 18-60 years with a body mass index (BMI) between 18 and 35 kg/m² were eligible to participate in the study. Other inclusion criteria included:</p> <ul style="list-style-type: none"> • If female: <ul style="list-style-type: none"> – was required to be using contraception if of childbearing potential or was required to be surgically sterile; and – could not be lactating. • Subject was in good health based on medical history, physical exam, laboratory profile, and electrocardiogram (ECG) as judged by the Investigator. • If subject smoked, subject had to agree to limit smoking while in the study to not more than 10 cigarettes per day. • Provided written informed consent before participation in the study, and an appropriate Health Insurance Portability and Accountability Act form was signed and dated.
<p>Test product, dose and mode of administration, batch number: Lofexidine Hydrochloride (HCl): Two single doses of lofexidine HCl (dose = 0.4 mg [2 x 0.2 mg tablets]); first dose administered on Day 1 and the second dose administered on Day 11; Lot: 33405-5588 Naltrexone HCl: Ten doses; 25 mg (1/2 tablet) administered on Day 4 and 50 mg (1 tablet) daily, administered on Days 5-13; Lot: 1170X91970</p>
<p>Duration of treatment: 14 day study; 11 days of study drug administration (Day 1, then Days 4 through 13)</p>
<p>Reference therapy, dose and mode of administration, batch number: not applicable to this study</p>
<p>Criteria for evaluation:</p> <p>Pharmacokinetics: The following PK parameters were estimated for the 3 analytes: maximum plasma drug concentration (C_{max}), time to reach maximum plasma drug concentration (T_{max}), observed terminal rate constant (λ_z), apparent terminal elimination half-life (T_{1/2}), area under the plasma drug concentration-time curve from time zero to 24 hours postdose (AUC₀₋₂₄) (naltrexone and 6β-naltrexol only), area under the plasma drug concentration-time curves from time zero to time of the last quantifiable concentration (AUC_{last}) (lofexidine only), area under the plasma drug concentration-time curve from time zero extrapolated to infinity (AUC_{inf}) (lofexidine only), the percentage of AUC_{inf} based on extrapolation (AUC_{Extrap} [%]) (lofexidine only), the last quantifiable plasma drug concentration (C_{last}), time to the last quantifiable plasma drug concentration (T_{last}), and apparent total body clearance</p>

after oral administration (CL/F).

Safety: Safety was assessed by recording adverse events (AEs), measuring vital signs (blood pressure and pulse rate) and clinical laboratory tests (coagulation, chemistry, hematology, and urinalysis), recording 12-lead safety and Holter ECGs, and performing physical examinations.

Statistical methods:

Disposition, Demographics, and Exposure: Two analysis data sets were defined: the PK analysis data set included all subjects with sufficient PK data to estimate at least C_{max} or AUC_{0-24} for lofexidine and naltrexone, alone and in combination (i.e., the PK population) and the safety analysis set included all subjects who received at least 1 dose of study drug (i.e., the safety population). For each population, subject disposition is summarized by the number and percentage of subjects who completed or discontinued. Protocol deviations were categorized and are provided in a data listing. Demographic and baseline characteristics are summarized for both populations. For exposure, the lofexidine and naltrexone dose administration date and times are provided in a data listing.

Pharmacokinetic Analysis: Concentration-time data of lofexidine, naltrexone, and 6 β -naltrexol were used in the PK analysis. Pharmacokinetic results of lofexidine, naltrexone, and 6 β -naltrexol for C_{max} and AUCs are summarized by Study Day using descriptive statistics including arithmetic mean, median, standard deviation, minimum, maximum, coefficient of variation, and geometric mean.

Comparison of the log-transformed PK parameters C_{max} , AUC_{inf} , and AUC_{last} for lofexidine and C_{max} and AUC_{0-24} for naltrexone and 6 β -naltrexol across treatments were performed using an analysis of variance (ANOVA) model and the 2 one-sided t-tests procedure. The ratios of the geometric means (lofexidine + naltrexone vs. lofexidine or naltrexone alone) and 90% confidence intervals (CI) were reported. Specifically, lofexidine C_{max} , AUC_{inf} , or AUC_{last} were compared for Days 11-13 (lofexidine + naltrexone) vs. Days 1 - 3 (lofexidine alone). Naltrexone and 6 β -naltrexol C_{max} and AUC_{0-24} were compared for Day 11 (lofexidine + naltrexone) vs. Day 10 (naltrexone alone). No significant drug-drug interaction would be concluded if the reported 90% CI fell entirely within the 80% to 125% interval.

Safety Analysis: The AE summary includes only treatment-emergent adverse events (TEAEs). The Medical Dictionary for Regulatory Activities (version 18.0) was used to classify all AEs with respect to system organ class and preferred term. Summary tables are provided for all TEAEs by system organ class and preferred term for all study phases and each treatment phase (i.e., lofexidine alone/washout [Days 1-3]; naltrexone alone [Days 4-10]; and lofexidine plus naltrexone [Days 11-14]). Additionally, TEAEs are presented by relationship to study drug and by maximum severity.

For clinical laboratory tests, vital sign measurements, and 12-lead safety ECGs, descriptive statistics were used to summarize the observed results at screening, check-in (Day -1, if appropriate), post-treatment time points, and change from baseline (defined as the last assessment before the first dose) to each post-treatment time point. Clinically significant abnormalities are listed, if applicable. The safety analysis includes pairing centrally read Holter ECGs with the PK samples; these data are reported in a separate Cardiac Safety Report.

Demographic Results:

A total of 24 subjects participated and all completed the study. All 24 subjects were included in the safety analysis set and PK analysis set. In this study, the PK and Safety Populations were the same.

No major protocol deviations were documented. A total of 34 minor protocol deviations occurred in 16 subjects (66.7%).

Most subjects were male (66.7%) and not Hispanic or Latino (62.5%). Of the 24 subjects, 50% were White and 37.5% were Black or African American. Mean age was 35.6 years and ranged from 20 to 51 years. The majority of subjects never smoked (79.2%). Mean height was 169.98 cm and ranged from 152.5 to 184.0 cm. Mean weight was 75.13 kg and ranged from 46.2 to 101.5 kg. Mean BMI was

25.92 kg/m² and ranged from 19.9 to 31.9 kg/m².

All 24 subjects received the protocol-specified doses of lofexidine and naltrexone.

Pharmacokinetic Results:

Overall, mean lofexidine concentrations were similar after administration of lofexidine alone (highest concentration of 1.08 ± 0.353 ng/mL at 2.00 hours) and lofexidine + naltrexone (highest was 1.06 ± 0.284 ng/mL at 3.00 hours). Lofexidine T_{max} was delayed by approximately 1.00 hour in the presence of naltrexone. The presence of naltrexone did not significantly affect the single dose PK of lofexidine.

Mean naltrexone concentrations were higher after administration of naltrexone alone (highest was 13.2 ± 7.32 ng/mL at 1.00 hour) compared to lofexidine + naltrexone (highest was 8.57 ± 6.26 ng/mL at 3.00 hours). Naltrexone T_{max} was delayed by approximately 2.00 hours in the presence of lofexidine. Co-administration of lofexidine and naltrexone resulted in a reduction of approximately 36% in naltrexone C_{max} and a slight reduction of approximately 8% in naltrexone AUC₀₋₂₄ compared to naltrexone alone. The alteration in steady-state PK of oral naltrexone was statistically significant in the presence of lofexidine.

Mean 6β-naltrexol concentrations were higher after administration of naltrexone alone (95.4 ± 49.4 ng/mL at 1.00 hour) compared to lofexidine + naltrexone (72.6 ± 33.3 ng/mL at 3.00 hours). In the presence of lofexidine, 6β-naltrexol T_{max} was delayed by approximately 2.78 hours. Co-administration of lofexidine and naltrexone resulted in a reduction of approximately 19% in 6β-naltrexol C_{max}; AUC₀₋₂₄ values were similar across treatments. The alteration in maximum 6β-naltrexol exposure was statistically significant in the presence of lofexidine; overall 6β-naltrexol exposure was not affected.

Safety Results:

All 24 subjects (100.0%) experienced at least one TEAE. No subjects died or experienced other SAEs during the study and no subjects discontinued due to an AE.

The most common TEAEs were hypotension (83.3%), somnolence (45.8%), dry mouth (16.7%), nausea (16.7%), orthostatic hypotension (12.5%), dizziness (12.5%), and vomiting (12.5%). The pattern and incidence of treatment-related TEAEs was similar to all TEAEs reported. All TEAEs reported were considered by the Investigator to be either mild or moderate in severity; no TEAEs were considered to be severe.

Across treatment phases, 87.5% of subjects experienced a TEAE during the lofexidine alone phase, 41.7% had a TEAE during the naltrexone alone phase, and 70.8% had a TEAE during the lofexidine + naltrexone phase. During the lofexidine alone treatment phase, hypotension (62.5%), somnolence (25.0%), and orthostatic hypotension (12.5%) were commonly observed, whereas, during the naltrexone alone phase, nausea (16.7%) and vomiting (12.5%) were more commonly observed. During the lofexidine + naltrexone treatment phase, hypotension (66.7%), somnolence (20.8%), and dry mouth (16.7%) were observed most commonly. The TEAEs occurring during the lofexidine alone treatment phase were consistent with known effects of lofexidine. The TEAEs reported during the lofexidine + naltrexone treatment phase showed no unexpected pattern or difference in incidences than those observed during the lofexidine alone or naltrexone alone phases.

When systolic and diastolic blood pressure were assessed, notable decreases from predose values were observed for the lofexidine alone and lofexidine + naltrexone treatment phases but not the naltrexone alone phase. Mean changes from predose values for pulse measurements were minimal.

The decreases in systolic and diastolic blood pressure were clinically meaningful and reflect the AEs observed, with hypotension reported in 83.3% of subjects. Additionally, orthostatic hypotension was reported in 12.5% of subjects. It should be noted, however, that decreased blood pressure is also an anticipated pharmacologic effect due to the alpha-2 agonist properties of lofexidine.

Clinically relevant findings were not observed in results from clinical laboratory tests, physical

examinations, 12-lead safety ECGs, or concomitant medications. Although sinus bradycardia and first degree atrioventricular block were reported as abnormalities with the 12-lead safety ECGs, no treatment-emergent pattern was observed and the Investigator did not consider any reported abnormalities to be clinically significant. The results of pairing Holter ECG data with PK samples showed no adverse cardiac safety signal when lofexidine and naltrexone were administered concomitantly in this study.

Conclusion:

The following conclusions are based on the results of this study:

- The presence of naltrexone did not significantly alter the single dose PK of lofexidine.
- The alteration in steady-state PK of oral naltrexone was statistically significant in the presence of lofexidine; T_{max} was delayed for both naltrexone and 6 β -naltrexol and overall exposure of naltrexone was slightly reduced.
- Lofexidine was, in general, well tolerated in this study. No deaths, SAEs, or discontinuations due to AEs occurred.
- No unexpected safety concerns were observed when lofexidine and naltrexone were administered concomitantly.

Date of the report: 14 March 2017

4.4.9 Study LX1-1010: Effect of Paroxetine on Lofexidine PK

US WorldMeds, LLC
 Clinical Study Report Synopsis USWM-LX1-1010

201729

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride	Volume: Page:	
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: Lofexidine Pharmacokinetics in the Presence of Paroxetine, A Strong CYP2D6 Inhibitor, in Healthy Volunteers		
Principal Investigator: George Atiee, MD		
Study center(s): Worldwide Clinical Trials, San Antonio, TX		
Publications (reference): None to date		
Studied period (months): 2 Date first subject enrolled: 20 January 2016 Date last subject completed: 23 March 2016		Phase of development: I
Objectives: Primary: <ul style="list-style-type: none"> To compare the pharmacokinetics (PK) of, and exposure to, lofexidine in healthy normal volunteers when lofexidine was administered alone or with steady-state paroxetine, a strong CYP2D6 inhibitor Secondary: <ul style="list-style-type: none"> To establish the safety and tolerability of a single dose of lofexidine when administered concomitantly with paroxetine 		
Methodology: This was a Phase 1, open-label, single sequence study in healthy subjects to compare the PK of lofexidine given alone and then concomitantly with paroxetine. Subjects received a single oral dose of 0.4 mg lofexidine hydrochloride (HCl) (2 x 0.2 mg tablets) on Day 1. Following a 72-hour washout period, subjects then received paroxetine HCl 20 mg (1 x 20 mg tablet) once daily (QD) on Days 4-6, 40 mg (2 x 20 mg tablets) QD on Days 7-19, 20 mg (1 x 20 mg tablet) QD on Day 20, and 10 mg (1 x 10 mg tablet) QD on Days 21-22. On Day 13, a second dose of lofexidine HCl 0.4 mg (2 x 0.2 mg tablets) was given 2 hours after the paroxetine dose was administered. All treatments were given with approximately 240 mL (8 fluid ounces) of room temperature water after a standardized light breakfast (approximately 500 calories and 30% fat) following an overnight fast with the exception of the paroxetine dose on Day 13, which preceded food by 1.5 hours. Other than Day 13, no food was allowed until 4 hours after study drug was administered. Fingertstick and venous blood samples were collected before each lofexidine dose administration (predose) and after each lofexidine dose administration for PK analysis of lofexidine. Each fingertstick blood sample (0.5 mL) was collected in a microtainer containing dipotassium-ethylenediaminetetraacetic acid (K ₂ -EDTA) anticoagulant. Each venous blood sample (6 mL) was collected in a blood collection tube containing K ₂ -EDTA anticoagulant. After the dose of study drug on Day 13, PK blood collection continued until Day 20. In addition, timed urine samples		

were collected at selected times throughout the study and reserved for analysis, if needed. Blood samples for genotyping were obtained from subjects prior to the first dose of lofexidine.
<p>Number of subjects (planned and analyzed): Planned: sufficient number of subjects in order to obtain at least 22 who completed the study; Enrolled: 24; Analyzed: 24</p>
<p>Diagnosis and main criteria for inclusion: Male or female between the ages of 18-60 years with a body mass index (BMI) between 18 and 35 kg/m² (inclusive) were eligible to participate in the study. Other inclusion criteria included:</p> <ul style="list-style-type: none"> • Subject was in good health based on medical history, physical exam, laboratory profile, and electrocardiogram (ECG) as judged by the Investigator. • If female: <ul style="list-style-type: none"> – could not be lactating, and – was required to be postmenopausal, surgically sterile, or using an acceptable form of birth control. • If subject smoked, subject had to agree to limit smoking while in the study to not more than 10 cigarettes per day. • Provided written informed consent before participation in the study, and signed and dated an appropriate Health Insurance Portability and Accountability Act form. • Subject was willing and able to remain in the study unit for the entire duration of the confinement period.
<p>Test product, dose and mode of administration, batch number: Lofexidine HCl: Two single doses of lofexidine HCl (dose = 0.4 mg [2 x 0.2 mg tablets]); first dose administered on Day 1 and the second dose administered on Day 13; Lot: 33405-5588 Paroxetine HCl: Nineteen (19) daily doses; 20 mg (1 x 20 mg tablet) administered QD on Days 4 to 6, 40 mg (2 x 20 mg tablets) administered QD on Days 7 to 19, 20 mg (1 x 20 mg tablet) administered QD on Day 20, and 10 mg (1 x 10 mg tablet) administered QD on Days 21 and 22; Lot: ZR1493 (10 mg tablets); Lot: ZR1510 (20 mg tablets)</p>
<p>Duration of treatment: 22 day study; 20 days of study drug administration (Day 1, then Days 4 through 22)</p>
<p>Reference therapy, dose and mode of administration, batch number: not applicable to this study</p>
<p>Criteria for evaluation:</p> <p>Pharmacokinetics: The following PK parameters were estimated for lofexidine: maximum plasma drug concentration (C_{max}), time to reach maximum plasma drug concentration (T_{max}), observed terminal elimination rate constant (λ_z), apparent terminal elimination half-life (T_{1/2}), area under the plasma drug concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{last} [AUC_{0-t}]), area under the plasma drug concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), the percentage of AUC_{inf} based on extrapolation (AUC_{Extrap} [%]), the last quantifiable plasma drug concentration (C_{last}), time of the last quantifiable plasma drug concentration (T_{last}), and apparent total body clearance after oral administration (CL/F).</p> <p>Safety: Safety was assessed by recording adverse events (AEs), measuring vital signs (blood pressure and pulse rate) and weight, performing clinical laboratory tests (coagulation, chemistry, hematology, and urinalysis), recording 12-lead safety and Holter ECGs, performing physical examinations, and collecting Columbia Suicide Severity Rating Scale (C-SSRS) assessments.</p>

Statistical methods:

Disposition, Demographics, and Exposure: Two analysis data sets were defined: the PK analysis data set included all subjects with sufficient PK data to estimate at least C_{max} or AUC_{last} for lofexidine, alone and in combination with paroxetine (i.e., the PK Population), and the safety analysis set included all subjects who received at least 1 dose of study drug (i.e., the Safety Population). Subject disposition is summarized by the number and percentage of subjects who completed or discontinued. Protocol deviations were categorized and are provided in a data listing. Demographic and baseline characteristics are summarized for the Safety Population.

Pharmacokinetic Analysis: Concentration-time data of lofexidine were used in the PK analysis. Pharmacokinetic results of lofexidine are summarized by treatment (lofexidine alone or lofexidine + paroxetine) using descriptive statistics including arithmetic mean, standard deviation (SD), minimum, median, maximum, and coefficient of variation.

Comparison of the log-transformed PK parameters C_{max} , AUC_{inf} , and AUC_{last} for lofexidine across treatments was performed using an analysis of variance model and the 2 one-sided t-tests procedure. Specifically, lofexidine C_{max} , AUC_{inf} , or AUC_{last} was compared for Day 13 (lofexidine + paroxetine) vs. Day 1 (lofexidine alone). The ratios of the geometric means (lofexidine + paroxetine vs. lofexidine alone) and 90% CI were calculated.

Safety Analysis: The AE summary includes only treatment-emergent adverse events (TEAEs). The Medical Dictionary for Regulatory Activities (version 18.0) was used to classify all AEs with respect to system organ class and preferred term. Summary tables are provided for all TEAEs by system organ class and preferred term for all study phases and each treatment phase (i.e., lofexidine alone/washout [Days 1-3]; paroxetine alone [Days 4-12]; and lofexidine + paroxetine [Days 13-22]). Additionally, TEAEs are presented by relationship to study drug and by maximum severity.

For clinical laboratory tests, vital sign measurements, body weight, and 12-lead safety ECGs, descriptive statistics were used to summarize the observed results at screening, Baseline, and post-treatment time points. Clinically significant abnormalities are listed, and clinically significant vital sign results are summarized by time point. The C-SSRS was administered at screening, Day 7, Day 13, end-of-study (discharge), and within 14-28 days after discharge. The responses for suicidal ideation are summarized by time point. The safety analysis included analysis of centrally read Holter ECGs; these data are reported in a separate Cardiac Safety Report.

Demographic Results:

A total of 24 subjects participated and all completed the study. All 24 subjects were included in the Safety Population and PK Population.

Half of the subjects were male (50.0%). The majority were Black or African American (58.3%) and were not Hispanic or Latino (66.7%). The mean age was 40.6 years, and the ages ranged from 29 to 59 years. Most subjects had never smoked (95.8%), and no subject was smoking at the time of the study. The mean height was 167.17 cm (range of 145.5 to 183.5 cm), and the mean weight was 76.21 kg (range of 49.0 to 104.8 kg). The mean BMI was 27.07 kg/m² and ranged from 19.5 to 32.4 kg/m². All 24 subjects received the protocol-specified doses of lofexidine and paroxetine.

Pharmacokinetic Results:

Overall, mean lofexidine concentrations were slightly greater after co-administration of lofexidine + paroxetine compared to lofexidine alone, but mean plasma lofexidine concentrations at each sampling time for the two treatment conditions were typically within one standard deviation. The time to maximum lofexidine plasma exposure (C_{max}) was similar on Day 1 (lofexidine alone) and Day 13 (lofexidine + paroxetine), ranging from 2.80 to 3.02 hours, respectively. Mean lofexidine C_{max} , AUC_{last} , and AUC_{inf} values were slightly greater after co-administration of lofexidine + paroxetine (Day 13) compared to that after administration of lofexidine alone (Day 1). Mean T_{last} and $T_{1/2}$ values were

similar for Day 1 (lofexidine alone) and Day 13 (lofexidine + paroxetine). Mean CL/F values were slightly smaller after co-administration of lofexidine + paroxetine (Day 13) compared to that after administration of lofexidine alone (Day 1).

The co-administration of lofexidine + paroxetine resulted in an increase in overall maximum and total lofexidine exposure compared to that after lofexidine alone. The presence of paroxetine increased lofexidine C_{max} , AUC_{last} , and AUC_{inf} by approximately 11%, 30%, and 28%, respectively. An increase in lofexidine exposure in the presence of a strong CYP2D6 inhibitor (paroxetine) was expected; however, the increase was not as large as anticipated. Analysis of venous blood samples was performed to confirm that the concentrations of paroxetine were in the expected range. All but 1 subject had paroxetine concentrations in the expected range. The samples were re-assayed and the values were confirmed. Most subjects were normal CYP2D6 metabolizers (79.2%), and only 2 subjects (8.3%) were rapid metabolizers. The reason that a less than expected increase in lofexidine exposure was seen when co-administered with a strong CYP2D6 inhibitor is not known. However, the similar distribution of interaction magnitude from a strong CYP2D6 inhibitor across metabolizer status suggests that CYP2D6 is not a prominent clearance pathway for lofexidine and that co-administration of CYP2D6 inhibitors with lofexidine should have minimal effect on lofexidine clearance.

Safety Results:

The most common TEAEs were hypotension (83.3%), somnolence (50.0%), orthostatic hypotension (20.8%), and dizziness (16.7%). The pattern and incidence of lofexidine-related TEAEs was similar to all TEAEs reported. All TEAEs reported were considered by the Investigator to be either mild or moderate in severity; no TEAEs were considered to be severe.

Across treatment phases, 83.3% of subjects experienced a TEAE during the lofexidine alone phase, 25.0% had a TEAE during the paroxetine alone phase, and 83.3% had a TEAE during the lofexidine + paroxetine phase. During the lofexidine alone treatment phase, the most common TEAEs were hypotension (62.5%), somnolence (20.8%), orthostatic hypotension (12.5%), dizziness (12.5%), and bradycardia (12.5%). During the lofexidine + paroxetine treatment phase, hypotension (75.0%) and somnolence (29.2%) were observed most commonly. The TEAEs occurring during the lofexidine alone treatment phase were consistent with known effects of lofexidine. The TEAEs reported during the lofexidine + paroxetine treatment phase showed no unexpected pattern; however, a slight increase in hypotension was reported as compared to the lofexidine alone phase.

Decreases in mean seated and standing blood pressure were seen at 3.5 and 7.5 hours postdose in both the lofexidine alone treatment phase and the lofexidine + paroxetine treatment phase, but the effects were slightly more prominent in the lofexidine + paroxetine treatment phase. When assessed using pre-determined criteria, clinically significant decreases in systolic blood pressure were slightly more common in the lofexidine + paroxetine phase than the lofexidine alone phase. Fewer clinically significant decreases in diastolic blood pressure were noted than systolic blood pressure. The occurrence of orthostatic hypotension according to the various categorical definitions and the inability to stand for orthostatic assessments was comparable during the lofexidine alone phase and the lofexidine + paroxetine phase.

Decreases in pulse were also observed in both treatment phases, with the mean decreases being slightly more prominent in the lofexidine alone phase. Clinically significant decreases in pulse were infrequent and observed only on Day 1.

The results of Holter monitor recordings of ECG data showed no adverse cardiac safety signal when lofexidine and paroxetine were administered concomitantly in this study.

Clinically relevant findings were not observed in results from clinical laboratory tests, physical examinations, body weight, 12-lead safety ECGs, or concomitant medications.

Conclusions:

The following conclusions are based on the results of this study:

- The presence of paroxetine at steady state increased single-dose lofexidine PK parameters of C_{max} , AUC_{last} , and AUC_{inf} by approximately 11%, 30%, and 28%, respectively.
- Lofexidine was, in general, well tolerated in this study. No deaths, SAEs, or discontinuations due to AEs occurred.
- Hypotension was the most common AE and the incidence was slightly greater when lofexidine was co-administered with paroxetine. However, this is an expected effect of alpha 2 agonists.
- No unexpected safety concerns were observed when lofexidine and paroxetine were administered concomitantly.

Date of the report: 22 March 2017

4.4.10 Study LX1-1011: QT study

LX1-1011 Clinical Study Report

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: An Open-Label, Single-Dose, Pilot Study to Determine the Maximum Tolerated Dose, Pharmacokinetics, and QTc Effects of Lofexidine in Healthy Men and Women		
Principal Investigator: Mark T. Leibowitz, MD		
Study center(s): CEDRA Clinical Research, LLC, 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217		
Publications (reference): None		
Studied period (weeks): 1 Date first subject enrolled: 09 December 2009 Date last subject completed: 17 December 2009	Phase of development: I	
Objectives: <ul style="list-style-type: none"> To assess the safety and tolerability of a single dose of lofexidine HCl 2.0 mg, and a single dose of lofexidine HCl 3.0 mg (or 1.6 mg) in healthy adult subjects To assess the ECG effects (specifically QTc) of a single dose of lofexidine HCl 2.0 mg, and a single dose of lofexidine HCl 3.0 mg (or 1.6 mg) in healthy adult subjects To assess the pharmacokinetics (PK) of a single dose of lofexidine HCl 2.0 mg, and a single dose of lofexidine HCl 3.0 mg (or 1.6 mg) in healthy adult subjects 		
Methodology: This was an open-label pilot study that evaluated the safety and tolerability, QTc effects, and PK of lofexidine in 12 healthy volunteers. Two study periods were planned, with a single dose of lofexidine HCl administered in each period. Each study drug administration was separated by a washout interval of at least 7 days. In Study Period 1, each subject received a single-dose of lofexidine HCl 2.0 mg (10 x 0.2 mg tablets). In Study Period 2, each subject received a single-dose of lofexidine HCl 1.6 mg (8 x 0.2 mg tablets). For Study Period 2, the protocol stated 2 dose level options (1.6 mg or 3.0 mg lofexidine HCl). The dose chosen was dependent on the adverse events (AEs) reported during Study Period 1. The protocol stipulated that if more than 50% of subjects tolerated lofexidine HCl 2.0 mg in Study Period 1, then the dose chosen for Study Period 2 was to be 3.0 mg, but if more than 50% of subjects were unable to tolerate the dose in Study Period 1 and discontinued the study, then the dose chosen for Study Period 2 was to be 1.6 mg. While no subjects discontinued the study during Study Period 1, significant treatment-emergent AEs did occur, such as somnolence, dry mouth, dizziness, nausea, hypotension, orthostatic hypotension, and vasovagal syncope. These events are known side effects of lofexidine. Based on the safety data observed in Study Period 1, the Principal Investigator and Sponsor determined that the number and nature of the AEs was such that further dose escalation was not advisable. The lower dose option (1.6 mg) was selected for Period 2.		

LX1-1011 Clinical Study Report

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride	Volume: Page:	
Name of Active Ingredient: Lofexidine hydrochloride		
<p>Subjects were admitted to the research facility 36 hours before dose administration for Study Period 1 and remained in the research facility until completion of the 24-hour procedures for Study Period 1. For Study Period 2, subjects were required to check in to the research facility at an appropriate time to ensure a minimum 10-hour fast before consumption of the light meal beginning approximately 30 minutes before the scheduled dose administration.</p> <p>With each administration of lofexidine HCl, venous blood samples were collected for lofexidine PK analysis. Blood samples were collected before dosing, and 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 16, and 22 hours after each dose administration. The predose blood sample was collected within 30 minutes before each dose administration. Electrocardiograms were recorded via Holter recorder at baseline (prior to the first dose of lofexidine HCl in Study Period 1) and at 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 16, and 22 hours postdose in each study period.</p>		
<p>Number of subjects (planned and analyzed): Planned: 12; Enrolled: 12; Analyzed: 12</p>		
<p>Diagnosis and main criteria for inclusion: Healthy males or females between the ages of 18 to 55 years with a body mass index between 18 and 30 kg/m², and a minimum weight of 50 kg (110 lbs) were eligible to participate in the study. Subjects were also required to meet all of the following criteria:</p> <ul style="list-style-type: none"> • If female, subject must have agreed to use an acceptable form of birth control (see Section 9.3.1) from screening until 14 days after completion of the study. • Voluntarily consented to participate in this study and provided written informed consent before the start of any study-specific procedures. • Willing and able to remain in the study unit for the entire duration of each confinement period. • Vital signs measured seated after 3 minutes of rest within the following ranges: <ul style="list-style-type: none"> – heart rate: 40 to 90 bpm – systolic blood pressure: 100 to 140 mmHg – diastolic blood pressure: 50 to 90 mmHg – oral temperature: within normal range of 35.6 to 37.7°C 		
<p>Test product, dose and mode of administration, batch number: Lofexidine HCl 0.2 mg tablets were used for each single-dose administration as follows:</p> <ul style="list-style-type: none"> • Study Period 1: lofexidine HCl 2.0 mg (10 x 0.2 mg tablets) • Study Period 2: lofexidine HCl 1.6 mg (8 x 0.2 mg tablets) <p>Each dose was orally administered along with 240 mL of room temperature water after consumption of a light meal beginning approximately 30 minutes before dose administration. No food was allowed until 4 hours postdose; water was allowed ad libitum. The dose administrations were separated by at least a 7-day washout interval.</p> <p>The lot number for lofexidine HCl was 2271V.</p>		

LX1-1011 Clinical Study Report

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Duration of treatment: 8-day study; 2 days of study drug administration separated by a washout interval of at least 7 days		
Duration of participation: 36 days (screening through discharge)		
Reference therapy, dose and mode of administration, batch number: None		
Criteria for evaluation: <p>Pharmacodynamics: To evaluate QTc effects, subjects had baseline ECGs recorded via Holter recorder for 24 hours before the first dose in a time-matched manner to the planned postdose ECGs for use in the change from baseline statistical analysis and determination of the individual-based heart rate-corrected QT (QTcI) interval. Selected Holter ECG recordings were extracted under resting conditions over 5-minute time spans at approximately 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 16, and 22 hours postdose in each study period.</p> <p>Pharmacokinetics: The following PK parameters were estimated from plasma lofexidine concentration data and actual plasma sampling times: maximum observed plasma concentration (C_{max}), observed time to reach maximum plasma concentration (T_{max}), area under the plasma concentration-time curve (AUC) from time zero to infinite time (AUC_{inf}), percentage of AUC_{inf} obtained by extrapolation (AUC_{Extrap}), AUC from time zero to the time of the last quantifiable concentration (AUC_{last}), last quantifiable plasma concentration (C_{last}), observed time to reach the last quantifiable plasma concentration (T_{last}), first-order terminal-phase rate constant obtained from the slope of the concentration-time terminal phase (λ_z), and apparent terminal elimination half-life, obtained as $\ln(2)/\lambda_z$ ($T_{1/2}$).</p> <p>Safety: Safety was assessed by recording AEs, measuring vital signs (blood pressure and pulse rate) and clinical laboratory tests (coagulation, chemistry, hematology, and urinalysis), recording 12-lead safety and Holter ECGs, and performing physical examinations.</p>		
Statistical Methods: <p>Sample Size Determination: The sample size was not based on statistical considerations. The number of subjects planned for enrollment (n=12) was considered sufficient to achieve the study objectives.</p> <p>Study Analysis Sets: The pharmacodynamics (PD) analysis set was defined as all Holter ECGs collected at the specified sample extraction times from all subjects who were dosed. The PK analysis set was defined as all subjects who received at least one dose of lofexidine HCl and had an evaluable plasma lofexidine concentration-time profile. The safety data set was defined as all subjects who received at least one dose of lofexidine HCl.</p> <p>Pharmacodynamic Analysis: Primary PD endpoint was time-matched change from baseline in the QTcI interval as collected by Holter recorder. Secondary PD endpoints were change from baseline in the Fridericia's corrected QT (QTcF) and Bazett's corrected QT (QTcB) intervals as collected by Holter recorder; time-matched change from baseline in heart rate, PR interval, QRS interval, uncorrected QT interval, blood pressure (systolic and diastolic), and morphology changes on the T wave on the ECG; and correlation of the QTc effects with lofexidine parent molecule concentrations. Categorical analyses included absolute QTc interval prolongation (>450, >480, and >500 msec); increase from baseline in QTc interval (>30 and >60 msec); absolute QRS interval >110 msec and increase from baseline >25%;</p>		

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Lofexidine hydrochloride	Volume: Page:	
Name of Active Ingredient: Lofexidine hydrochloride		
<p>and absolute PR interval >200 msec and increase from baseline >25%. Descriptive statistics were provided by dose level (Study Period 1, 2.0 mg; and Study Period 2, 1.6 mg) and time point for each QTc interval, PR interval, QRS interval, and heart rate and for change from baseline to each time point by dose level. Mean changes from the time-matched baseline were also presented graphically.</p> <p>Pharmacokinetic Analysis: Plasma lofexidine concentration-time results were processed according to standard noncompartmental analytical procedures. Dose-normalized C_{max} and AUC values were used to assess dose proportionality. Descriptive statistics were used to summarize plasma lofexidine concentrations and resultant PK parameters across study subjects by dose level (Study Period 1, 2.0 mg; and Study Period 2, 1.6 mg).</p> <p>Safety Analysis: No formal statistical testing was performed on safety data. The incidence (number and percent) of treatment-emergent adverse events (TEAEs) was summarized by dose level. All safety data, including TEAEs, clinical laboratory tests, vital signs, 12-lead safety ECGs, and physical exams, were presented in by-subject data listings.</p>		
<p>SUMMARY – CONCLUSIONS</p> <p>Twelve subjects were enrolled in the study and all 12 subjects completed both study periods. All 12 subjects were included in the PD, PK, and safety analysis sets.</p> <p>Of the protocol deviations that occurred, none were considered to have an impact on the study results and conclusions.</p> <p>The subject population was comprised of 7 females and 5 males. Mean age of the subject population was 34 years (range 20 to 50 years) and 7 subjects were white and 5 subjects were black. Body mass index, height, and weight ranged from 22.0 to 27.5 kg/m², 156.0 to 183.5 cm, and 60.4 to 91.7 kg, respectively.</p> <p>All 12 subjects received the protocol-specified dose of lofexidine HCl (2.0 mg) during Study Period 1. All 12 subjects continued into Study Period 2 after a washout interval and received the protocol-specified dose of lofexidine HCl (1.6 mg) during Study Period 2.</p> <p>PHARMACODYNAMIC RESULTS:</p> <p>Primary Endpoint: For time-matched change from baseline in the QTcI interval, mean increases from baseline for both lofexidine HCl doses (2.0 and 1.6 mg) were at or above approximately 8 msec (range 7.9 to 22.3 msec) between 3 and 7 hours postdose, the time of peak plasma lofexidine concentrations.</p> <p>Secondary Endpoints: For the change from baseline in the QTcF interval, mean increases from baseline for both lofexidine HCl doses (2.0 and 1.6 mg) were at or above approximately 12 msec (range 11.9 to 23.1 msec) between 3 and 7 hours postdose, the time of peak plasma lofexidine concentrations.</p> <p>For the QTcB interval, a large spike occurred at 4 hours postdose for both the 2.0 mg and 1.6 mg doses, whereas at only 1 other time point was the change from baseline above 0 msec. Heart rates also spiked at 4 hours postdose. Since the QTcB interval is known to over-correct at high heart rates and under-correct at low heart rates, the heart rate changes might explain the spike in the ΔQTcB interval at 4 hours postdose and the lack of an increase at all other time points. The increase in heart rate at 4 hours postdose may have been related to subjects having orthostatic vital signs taken at that time; only the 4 hour collection time for orthostatic vital signs coincided with an ECG extraction interval.</p>		

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Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Lofexidine hydrochloride	Volume: Page:	
Name of Active Ingredient: Lofexidine hydrochloride		

With respect to heart rate, change from baseline spiked at 4 hours postdose to nearly the baseline value, while being at or below -10 bpm (range -9.8 to -22.1 bpm) from baseline at all other time points between 2 and 12 hours postdose.

Mean PR intervals increased from 1 to 12 hours postdose after both doses of lofexidine HCl. From hours 3 to 7 all but one mean increase from baseline was 9 msec or greater (range 6.8 to 14.5 msec).

Mean QRS intervals changed only minimally over the course of the study.

Categorical Analyses of QT Interval: One to 3 subjects had at least one QTcI, QTcF, or QTcB interval >450 msec and no QTcF or QTcB interval exceeded 480 msec. One subject had a QTcI interval >480 msec after both doses. No subject had a QTc interval that exceeded 500 msec. Similarly, 1 to 3 subjects had increases in QTc >30 msec at all time points compared to baseline except for 4 hours postdose where up to 50% of subjects experienced this degree of increase. No subject had an increase from baseline that exceeded 60 msec.

Because the data collected documented an effect of lofexidine on cardiac conduction manifested as an at least 5 to 10 msec mean prolongation of the QTcI and QTcF at clinically achievable concentrations, and because a formal thorough QT study would not be expected to contradict that result with a significantly lesser prolongation, US WorldMeds submitted a request for a waiver with respect to conducting a thorough QT study with lofexidine; the FDA granted the waiver on 01 April 2011 (Appendix 16.10.1).

PHARMACOKINETIC RESULTS:

After single-dose administration of 2.0 mg or 1.6 mg of lofexidine HCl, lofexidine reached the systemic circulation quickly for both doses, with a broad concentration maximum from 2 to 7 hours postdose. Mean postdose concentrations for the 2.0 mg dose were higher than those for the 1.6 mg dose from 3 hours onward. Lofexidine terminal half-life was approximately 12 hours, similar for both doses, and consistent with observations from previous lofexidine studies. Mean C_{max} values were 2.49 ng/mL for the 1.6 mg dose and 2.97 ng/mL for the 2.0 mg dose. Lofexidine exhibited dose proportional PK, with an AUC_{inf} of approximately 80% for the 1.6 mg dose relative to the 2.0 mg dose (54.4 ng•h/mL and 71.5 ng•h/mL, respectively).

SAFETY RESULTS:

All 12 subjects experienced at least 1 TEAE in each study period. No SAEs or deaths occurred during the course of the study and no subjects discontinued from the study because of a TEAE.

A total of 88 TEAEs were reported for the 12 subjects over the course of the entire study, including Study Periods 1 and 2 combined. The most commonly reported TEAEs were somnolence (n=20; 10 in Study Period 1 and 10 in Study Period 2), dry mouth (n=13; 8 in Study Period 1 and 5 in Study Period 2), dizziness/intermittent dizziness (n=12; 7 in Study Period 1 and 5 in Study Period 2), hypotension/intermittent hypotension/orthostatic hypotension (n=11; 4 in Study Period 1 and 7 in Study Period 2), and nausea/intermittent nausea (n=9; 7 in Study Period 1 and 2 in Study Period 2).

The majority of the TEAEs were considered probably related to study drug (78 of 88; 89%); and 9 of 88 (10%) TEAEs were considered possibly related to study drug. One TEAE (headache, mild in nature) was considered unrelated to study drug.

LX1-1011 Clinical Study Report

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride	Volume: Page:	
Name of Active Ingredient: Lofexidine hydrochloride		
<p>Thirty of the TEAEs were mild, 52 were moderate, and 6 were severe. The severe TEAEs included vasovagal syncope (n=3), somnolence (n=2), and dizziness (n=1), and all of these severe events were considered probably related to study drug. No TEAEs were related to abnormal laboratory evaluations. Seven subjects had 11 clinically significant episodes of hypotension, intermittent hypotension, and/or orthostatic hypotension reported as TEAEs during the course of this study. All of these episodes were judged to be probably related to study drug by the Investigator, were mild to moderate in severity, and required oral fluids only. None required intravenous fluids or concomitant medications, and all episodes resolved.</p> <p>Two subjects experienced 3 episodes of vasovagal syncope during the course of the study. All 3 episodes were severe but resolved quickly (within 1 to 3 minutes). The episodes were judged to be probably related to study drug by the Investigator.</p> <p>Clinically relevant findings were not observed in the results from the 12-lead safety ECGs, clinical laboratory evaluations, or physical exams.</p> <p>The safety results of this study suggested that the frequency of AEs in healthy volunteers was greater than in opioid withdrawing subjects. US WorldMeds, therefore, asked the FDA if future Phase 1 studies evaluating PK in healthy volunteers or special populations could use single, subtherapeutic doses of 0.2 mg or 0.4 mg. The FDA agreed with the use of a lower dose for future Phase 1 PK studies in healthy volunteers on 02 September 2010 under certain conditions (Appendix 16.10.2).</p>		
<p>CONCLUSION:</p> <p>The following conclusions are based on the results of this study:</p> <ul style="list-style-type: none"> • The potential for lofexidine to cause QTc prolongation on the order of approximately 8 to 23 msec was established at concentrations approaching (although still somewhat lower than) steady-state levels typically observed at the maximum lofexidine HCl clinical dose (approximately 5 ng/mL at 0.8 mg 4 times a day). • No subject had a QT interval prolongation reported as a TEAE. • The lofexidine PK profile exhibited in this study was dose proportional and consistent with the profile characterized in other clinical studies conducted with lofexidine. • No unexpected safety concerns due to lofexidine were observed and no deaths, SAEs, or discontinuations due to AEs occurred. 		
<p>Date of the report: 20 October 2016</p>		

4.4.11 Study LX1-1013: Lofexidine metabolite

US WorldMeds, LLC
Clinical Study Report Synopsis USWM-LX1-1013

209229

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride	Volume:	
Name of Active Ingredient: Lofexidine hydrochloride	Page:	
Title of Study: A Phase 1 Study to Evaluate the Relative Exposures of Lofexidine and its Major Metabolites in Subjects Seeking Buprenorphine Dose Reduction		
Principal Investigator: Debra J. Kelsh, MD		
Study center(s): Vince & Associates Clinical Research, Inc., Overland Park, Kansas		
Publications (reference): None to date		
Studied period (months): 1.5 Date first subject enrolled: 14 June 2016 Date last subject completed: 01 August 2016		Phase of development: I
<p>Objectives:</p> <p>Primary:</p> <ul style="list-style-type: none"> Assess the steady-state exposures of lofexidine and its 3 major metabolites (N-[2-aminoethyl-2-[2,6-dichlorophenoxy] propanamide [LADP], 2-[2,6-dichlorophenoxy] propionic acid [LDPA], and 2,6-dichlorophenol [2,6-DCP]) achieved with administration of lofexidine HCl (2.4 mg per day or 3.2 mg per day) to subjects tapering from buprenorphine maintenance treatment. <p>Secondary:</p> <ul style="list-style-type: none"> Assess elimination of lofexidine HCl and its 3 major metabolites from subjects tapering from buprenorphine maintenance treatment. Assess safety and tolerability of lofexidine HCl treatment in subjects tapering from buprenorphine maintenance treatment. Assess efficacy of lofexidine HCl treatment in subjects tapering from buprenorphine maintenance treatment. 		
<p>Methodology: This was a single center, open-label, inpatient study in male or female subjects who were seeking at least a 4-mg per day reduction of their buprenorphine maintenance dose. Enrolled subjects were required to be on a daily dose of between 8 and 24 mg of buprenorphine for at least 30 days. Once enrolled, subjects received lofexidine HCl as follows: Days 1 through 3, 0.6 mg 4 times daily (QID) (2.4 mg daily); Days 4 through 6, 0.8 mg QID (3.2 mg daily); and Day 7, 0.8 mg at 8 AM. Subjects took their scheduled lofexidine doses at approximately 8 AM, 1 PM, 6 PM and 11 PM, consistent with clinic logistics, unless any of the dose-hold criteria were met. Subjects reduced their current buprenorphine dose by at least 4 mg on Day 1. Further reductions of buprenorphine after Day 1 were allowed. Reductions were arranged between the Principal Investigator and the subject's treating physician. Subjects remained in the clinic from Day -1 through discharge on Day 8. On Day 8, subjects were trained on the use of a portable blood pressure device and recorded morning vital signs</p>		

measurements into a diary for 7 days following Day 8. Site personnel called subjects each day after discharge before noon to record the subject's morning vital sign measurements. Subjects returned to the clinic on Days 15 to 17 to return the device and vital signs diary.

Lofexidine doses were permitted to be scheduled at the convenience of the clinic, but the relative spacing accomplished with the 8 AM, 1 PM, 6 PM and 11 PM schedule was to be maintained (± 0.5 hours). In addition to recording the amount of the lofexidine doses administered, the actual dosing times and blood collection times associated with the nominal 8 AM dose schedule were recorded. In the event a subject was not dosed within the time window as a result of hypotensive and/or bradycardic symptoms, it was not considered a protocol deviation; however, source documents noted the reason for dose acceleration or dose delay. Subjects took their scheduled buprenorphine dose either at 8 AM daily or, if preferred, the dose was split and taken at 8 AM and 6 PM.

Lofexidine and lofexidine metabolite exposures were assessed by assaying concentrations in plasma samples collected at select times during the course of treatment. Daily blood samples (venous and fingerstick) were collected before and 3 hours after the 1 PM lofexidine dose on Days 1 through Day 6. In addition, a predose sample and multiple serial postdose samples were collected with the 8 AM dose on Day 7.

If subjects had evidence of ongoing withdrawal at the time of discharge, the Investigator had the discretion to continue inpatient monitoring and/or the use of medications (as needed) for up to 72 hours to ensure stabilization or reduction in withdrawal symptoms.

Number of subjects (planned and analyzed):

Planned: Approximately 10 subjects were planned to ensure that 8 completed the study through the Day 8 blood samples; Enrolled: 10; Analyzed: 10

Diagnosis and main criteria for inclusion: Males or females between the ages of 18-64 years with current opioid dependence who were maintained on a buprenorphine dose of 8-24 mg per day and were seeking reduction of their buprenorphine dose by at least 4 mg per day were evaluated for study eligibility. Other inclusion criteria included:

- Was able to verbalize understanding of the consent form, was able to provide written informed consent, and verbalized willingness to complete study procedures.
- Urine toxicology screen positive for buprenorphine at Screening.
- Agreed to collection of whole blood samples for genotyping of cytochrome P450 (CYP) 2D6 metabolizer status.
- If female and of childbearing potential, subject must have been using birth control for at least 30 days and must have agreed to use one of the following methods of birth control for at least 30 days after the last dose of study drug:
 - Oral contraceptives
 - Patch
 - Barrier (diaphragm, sponge, or condom) plus spermicidal preparations
 - Intrauterine contraceptive system
 - Levonorgestrel implant
 - Medroxyprogesterone acetate contraceptive injection
 - Complete abstinence from sexual intercourse
 - Hormonal vaginal contraceptive ring; or surgical sterilization or partner sterile
- If male, must have agreed to use one of the birth control methods listed above throughout the entire study period and for 90 days after the last dose of study drug. Male subjects were instructed not to donate sperm for 90 days after the last dose of study drug.

<p>Test product, dose and mode of administration, batch number: Lofexidine hydrochloride (HCl) 0.2 mg tablets administered orally as follows:</p> <ul style="list-style-type: none">• Days 1 through 3: 3 tablets (0.6 mg) QID for a total of 2.4 mg daily• Days 4 through 6: 4 tablets (0.8 mg) QID for a total of 3.2 mg daily• Day 7: 4 tablets (0.8 mg) as a single dose on Day 7 <p>Lot: 33405-5588</p>
<p>Duration of treatment: 38-day study, 7 days of study drug administration</p>
<p>Reference therapy, dose and mode of administration, batch number: not applicable to this study</p>
<p>Criteria for evaluation:</p> <p>Pharmacokinetics: The following PK parameters were estimated for the lofexidine, LADP, LDPA, and 2,6-DCP: maximum plasma concentration (C_{max}), time of maximum plasma concentration (T_{max}), observed terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($T_{1/2}$), area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{last}), area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), the percentage of AUC_{inf} in plasma based on extrapolation (AUC_{Extrap} [%]), the last quantifiable plasma concentration (C_{last}), time to the last quantifiable plasma concentration (T_{last}), metabolite-to-parent ratio (R_{mp}) for predose and postdose concentrations, R_{mp} for AUC_{last}, and R_{mp} for AUC_{inf}.</p> <p>Efficacy: Efficacy of lofexidine was assessed using the Modified Clinical Global Impression (MCGI) scales (rated by both subject and observer) and the Visual Analog Scale for Efficacy (VAS-E).</p> <p>Safety: Safety was assessed by reported adverse events (AEs), vital signs, physical examination, continuous electrocardiogram (ECG) recordings (via Holter monitors), urine drug screening, concomitant medications, and the Columbia Suicide Severity Rating Scale (C-SSRS).</p>
<p>Statistical methods:</p> <p><u>Datasets, Disposition, Demographics, and Exposure:</u> Two analysis data sets were defined: the PK Population which included all subjects with at least one quantifiable concentration of lofexidine or one of its metabolites, and the Safety Population which included all subjects who received at least one dose of the study medication lofexidine. The PK analyses were conducted on the PK population with the following additional constraints for specific analyses:</p> <ul style="list-style-type: none">• Only subjects who received a dose at 8 AM on each study day were included in the analysis for R_{mp} for Days 1 through 6.• Only subjects who received a dose both at 11 PM on Day 6 and 8 AM on Day 7 were included in the analysis for R_{mp} on Day 7.• Only subjects who received a dose at 8 AM on each study day were included in the analysis for fingerstick-to-venous ratios for Days 1 through 6.• Only subjects who received a dose both at 11 PM on Day 6 and 8 AM on Day 7 were included in the analysis for fingerstick-to-venous ratios on Day 7. <p>The safety and efficacy analyses were conducted on the Safety Population.</p> <p>For each population, subject disposition is summarized by the number and percentage of subjects who completed or discontinued. Protocol deviations were categorized and are provided in a data listing. Demographic and baseline characteristics were summarized for the Safety Population. For exposure, the number of lofexidine doses were summarized by day and buprenorphine daily dose and dose reductions were summarized by day.</p> <p>Pharmacokinetic Analysis: Concentration-time data of lofexidine, LADP, LDPA, and 2,6-DCP were</p>

used in the PK analysis. Pharmacokinetic results of lofexidine, LADP, LDPA, and 2,6-DCP were summarized using descriptive statistics including arithmetic mean, standard deviation, minimum, median, maximum, and coefficient of variation; in addition, the geometric mean was reported for C_{max} and AUCs. If one or more CYP2D6 poor metabolizers was identified by genotyping, descriptive statistics were planned to be reported with and without the poor metabolizer(s) included. The metabolite-to-parent ratios (corrected using molecular weight to report the molar ratio) were tabulated for each subject of the PK Population, for each sample collection time on each of the treatment days.

Efficacy Analysis: MCGI and VAS-E scores were summarized descriptively.

Safety Analysis: The AE summary includes only treatment-emergent adverse events (TEAEs). The Medical Dictionary for Regulatory Activities (version 18.0) was used to classify all AEs with respect to system organ class and preferred term. Summary tables are provided for all TEAEs for all study phases and each treatment phase (in-clinic phase [Days 1-6], washout day [Day 7], and study discontinuation phase [Days 8-15]). Additionally, TEAEs are presented by relationship to study drug and by maximum severity. Clinically significant changes in physical examinations were reported as TEAEs. Descriptive statistics were used to summarize the vital sign assessments. The number of subjects with dose holds and number of subjects with potentially clinically significant vital signs were summarized descriptively. The safety analysis included pairing centrally-read Holter ECGs with the PK samples; these data are reported in a separate Cardiac Safety Report.

Demographic Results:

A total of 10 subjects participated and all 10 subjects were included in the Safety Population and PK Population. Nine subjects completed the study; one subject discontinued prematurely due to mild somnolence on Day 3.

The majority of subjects were male (60.0%) and not Hispanic or Latino (90.0%), and all were white. The mean age was 34.4 years, and the ages ranged from 20 to 49 years. Mean body mass index was 29.37 kg/m² (range of 19.2 to 47.6 kg/m²). The majority of subjects (80.0%) were current smokers at the time of the study.

Pharmacokinetic Results:

The study demonstrated concordance between fingerstick and venous collection methods across all time points. The highest mean lofexidine plasma concentrations were observed at 3 hours after the 8 AM dose on Day 7 from both fingerstick and venous samples (4.52 ng/mL and 4.67 ng/mL, respectively). Fingerstick-to-venous ratios were at or close to 1 for all collection times, ranging from 0.8772 to 1.0720.

The most abundant metabolite of lofexidine in plasma was LDPA, followed by LADP, then 2,6-DCP on Days 1 through 6 as well as Day 7. On Days 1 through 6, mean metabolite-to-parent plasma concentration ratios ranged from 0.1384 to 0.2649 for LDPA, from 0.0789 to 0.1142 for LADP, and from 0.0188 to 0.2100 for 2,6-DCP. Mean metabolite-to-parent ratios at steady-state were approximately 0.25 for LDPA and approximately 0.10 for both LADP and 2,6-DCP.

Mean metabolite-to-parent ratios on Day 7 were highest for LDPA, followed by LADP, then 2,6-DCP. The metabolite-to-parent ratio for LDPA increased as washout progressed because of the longer $T_{1/2}$ for LDPA. AUC_{inf} , $T_{1/2}$, and λ_z were not estimable for 2,6-DCP. Mean $T_{1/2}$ (\pm SD) values for lofexidine, LADP, and LDPA were 15.46 \pm 2.24 hours, 17.62 \pm 3.13 hours, and 42.71 \pm 12.03 hours, respectively.

Efficacy Results: Mean MCGI scores for severity of opiate withdrawal symptoms and side effects rated by the subject and mean MCGI scores for severity of illness and side effects rated by the observer were low indicating low symptoms of withdrawal throughout the assessment period. The sample size for VAS-E was too low to allow interpretation.

Safety Results: During the in-clinic phase (Days 1 through 6), the most common TEAEs were somnolence (90.0%), dry mouth (50.0%), headache (40.0%), and constipation (40.0%). The most common treatment-related TEAEs in this time period were somnolence (90.0%), dry mouth (50.0%),

headache (30.0%), hypotension (30.0%), and bradycardia (30.0%). These TEAEs are generally consistent with the known effects of lofexidine.

Most TEAEs were considered mild with a few rated as moderate. No SAEs were reported during the study. One subject had a TEAE leading to discontinuation (mild somnolence).

Mean systolic blood pressure, diastolic blood pressure, and heart rate tended to decrease at each post-Baseline time point (Days 1 through 7) when compared to Baseline. Changes from Baseline in standing blood pressure measurements tended to be more pronounced than those observed for seated measurements. Three subjects (30.0%) had a TEAE of bradycardia and 4 subjects (40.0%) had a TEAE of hypotension.

No clinically meaningful findings were observed in the analysis of concomitant medications or C-SSRS results.

No clinically relevant or concerning ECG effects were observed.

Conclusion:

The following conclusions are based on the results of this study:

- The most abundant metabolite of lofexidine in plasma was LDPA, followed by LADP, then 2,6-DCP. Lofexidine plasma concentrations were greater than any of the 3 metabolites throughout the course of treatment. Mean metabolite-to-parent ratios at steady-state were approximately 0.25 for LDPA and approximately 0.10 for both LADP and 2,6-DCP.
- Mean $T_{1/2}$ values for lofexidine, LADP, and LDPA were 15.46 hours, 17.62 hours, and 42.71 hours, respectively. The elimination $T_{1/2}$ for 2,6-DCP could not be calculated. Metabolite-to-parent ratios for LADP and LDPA reached their steady-state levels within 3 of their respective elimination half-lives during QID dosing.
- Mean lofexidine plasma concentrations were similar after fingerstick and venous collection across all study days and time points.
- Lofexidine was generally well tolerated when administered concomitantly with buprenorphine in subjects undergoing a reduction in buprenorphine dose.
- Subject and observer ratings for severity of opiate withdrawal symptoms and side effects of treatment were low, indicating subjects did not experience significant withdrawal symptoms associated with a 4 mg reduction in buprenorphine dose while receiving concomitant lofexidine; however the lack of a control group in study limits the interpretability of the results.

Date of the report: 16 May 2017

4.4.12 Pivotal Phase 3 Studies (3002 and 3003-1)

USWM-LX1-3002 Clinical Study Report Synopsis

2. SYNOPSIS

Name of Sponsor/Company: USWorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: A Phase III, Randomized, Multi-Center, Double Blind, Placebo Controlled Study of Safety and Efficacy of Lofexidine for Relief of Symptoms in Subjects Undergoing Inpatient Opiate Detoxification		
Principal Investigator: 15 Principal Investigators		
Study center(s): 15 medical centers (3 Veterans Affairs [VA] and 12 non-VA centers) in the United States		
Publications (reference): None.		
Studied period (years): Date first subject enrolled: June 16, 2006 Date last subject completed: October 26, 2007	Phase of development: 3	
<p>Objectives:</p> <p>The primary objective was to investigate the efficacy of lofexidine hydrochloride (HCl) in reducing withdrawal symptoms in subjects undergoing opioid detoxification as assessed by: (1) Day 3 Short Opiate Withdrawal Scale (SOWS-Gossop) score during the treatment phase and (2) time to dropout during the treatment phase.</p> <p>Secondary objectives included determining: (1) efficacy of lofexidine in the reduction of withdrawal symptoms in subjects undergoing opioid detoxification, using a variety of assessment scales, (2) efficacy of lofexidine in the reduction of the need for any concomitant medication to alleviate opiate withdrawal symptoms, (3) efficacy of lofexidine in increasing the number of completers during the treatment phase, and (4) safety of lofexidine in the study population.</p>		

Methodology: This was an inpatient, randomized, multicenter, double-blind, placebo-controlled, multiple-dose, parallel-group study. There were 3 major phases: Phase I (Screening), Phase II (Days 1 through 5, lofexidine/placebo treatment), and Phase III (Days 6 and 7, placebo treatment; Day 8, discharge).

Phase I Screening	Phase II Study Medication Administration (a)	Phase III Posttreatment	
Days -7 to -1	Days 1-5	Days 6-7	Day 8
No Treatment	Lofexidine Hydrochloride	Placebo	Discharge
	0.8 mg QID	QID oral	
	3.2 mg/day oral		
	Placebo	Placebo	Discharge
	QID oral	QID oral	No Treatment

(a) Subjects received 4 tablets of study medication for each dose: lofexidine HCl 0.8 mg (4 x 0.2 mg lofexidine tablets); placebo (4 placebo tablets).

Baseline safety and efficacy assessments were performed on Days -7 to -1. Subjects were randomized to receive either lofexidine or placebo on Day 1; lofexidine subjects received 0.8 mg 4 times a day (QID) on Days 1 through 5. Treatment efficacy and safety assessments were performed on Days 1 through 8. All subjects received placebo on Days 6 and 7, during which time efficacy and safety assessments continued to be performed. Study discharge was on Day 8.

Number of patients (planned and analyzed): Screened: 448; Planned: 264 (132/group); Randomized: 264 (134 Lofexidine + 130 Placebo)

Analyzed for Efficacy:

Intent to Treat (ITT): randomized to treatment
264 (134 Lofexidine + 130 Placebo)

Evaluable: ITT subjects who received at least one dose of study medication and completed the post-medication SOWS-Gossop on Day 1.

259 (133 Lofexidine + 126 Placebo)

Completer: ITT subjects who received at least one dose of study medication on Day 5 and completed the SOWS-Gossop assessment on Day 5.

117 (72 Lofexidine + 45 Placebo)

Analyzed for Safety:

Randomized to study medication:

264 (134 Lofexidine + 130 Placebo)

<p>Diagnosis and main criteria for inclusion: Male and female opioid-dependent subjects (opioid use in 21 out of previous 30 days) at least 18 years of age were enrolled. Subjects also had to have a score of ≥ 2 on the Objective Opiate Withdrawal Scale (OOWS-Handelsman) immediately before study admission. Pregnant or lactating women, and subjects with significant pancreatic, liver, gastrointestinal, renal, neurological, psychiatric, or cardiac disorders were excluded</p>
<p>Test product, dose and mode of administration, batch number:</p> <p>Lofexidine hydrochloride 0.2 mg tablets (batch numbers 0474R and 1119S); placebo tablets (batch numbers 0475R and 50006).</p> <p>Lofexidine: Oral administration of 0.8 mg (4 x 0.2 mg lofexidine tablets) QID on Days 1-5, followed by placebo (4 tablets) QID on Days 6-7.</p> <p>Placebo: Oral administration of 4 placebo tablets QID on Days 1-7.</p>
<p>Duration of treatment: 7 days, including 5 consecutive days of lofexidine treatment</p>
<p>Reference therapy, dose and mode of administration, batch number: Placebo tablets, to match lofexidine, administered orally as 4 placebo tablets QID on Days 1 through 7.</p> <p>Batch numbers: 0475R and 50006</p>
<p>Criteria for evaluation:</p> <p>Efficacy</p> <p>Primary: SOWS-Gossop scores on Day 3 of treatment for the Evaluable population using a prescribed multiple imputation technique to provide estimates for missing data.</p> <p>Co-Primary: Time-to-dropout for 5-day treatment phase.</p> <p>Secondary:</p> <ul style="list-style-type: none"> • Detoxification area under the withdrawal symptom-time curves (AUCs); • Daily mean scores for SOWS Gossop, OOWS-Handelsman, Visual Analog Scale for Efficacy of Medication in Alleviation of Withdrawal Sickness (VAS-E), and Modified Clinical Global Impressions (MCGI) (Subject and Rater); • Proportion of subjects completing detoxification; • Concomitant medication use to alleviate opioid withdrawal symptoms; • Opioid rescue medication use; and • Withdrawal-related adverse events (AEs). <p>Safety: Adverse events (AEs), vital signs, clinical laboratory tests, 12-lead electrocardiograms (ECGs), and physical examinations.</p>
<p>Statistical methods:</p> <p>The primary outcome measure of the SOWS-Gossop score on Day 3 was carried out using the Evaluable population and a prescribed Multiple Imputation Technique to estimate missing data. The Day 3 SOWS Gossop mean scores were compared between the lofexidine and placebo groups using an analysis of covariance (ANCOVA) model adjusted for baseline SOWS-Gossop scores and using the pre-randomization opioid dependence severity based on SCID (Structured Clinical Interview Axis I) as a covariate. For the second co-primary outcome measure (time-to-dropout), a log rank test was used to compare the risk-adjusted dropout rates between the treatment groups. Statistical analyses of the secondary outcome measures were carried out using ANCOVA, a t-test, Chi-square test, or Fisher's exact test, as appropriate, as detailed in the Statistical Analysis Plan (SAP; see Section</p>

16.1.9). Several repeated measures analyses were also done to assess the impact of missing observations on the study results (see SAP in Section 16.1.9).

Fisher's exact test was used to compare the treatment groups with respect to the proportion of subjects with each type of AE: all AEs, withdrawal-related AEs, non-withdrawal-related AEs, treatment-related AEs, mild/moderate/severe AEs, mild/moderate/severe withdrawal-related AEs, and mild/moderate/severe non-withdrawal-related AEs.

ECG variables (QTc, PR, and QRS interval) were analyzed using an ANCOVA model adjusted for respective baseline readings to compare the respective responses between treatment groups over the active treatment phase on the study. Mean changes from baseline in vital signs data were analyzed using t-tests. For clinical laboratory tests, a paired t-test was used to compare end of study to baseline within each treatment group. A two sample t test was used to compare treatment groups with respect to change from baseline.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The 2 treatment groups were comparable at Baseline regarding demographic characteristics and Baseline values for SOWS-Gossop, OOWS-Handelsman, and MCGI: Severity of Illness.

- For the primary assessment (mean Day 3 SOWS-Gossop score), lofexidine demonstrated significantly superior efficacy over placebo, with the mean score being about 2.4 points lower relative to the placebo group ($p=0.0212$). Various analyses, which assessed the impact of missing SOWS-Gossop observations on the results, yielded significantly favorable results for lofexidine over placebo.
- For the co-primary outcome measure (time-to-dropout), significantly fewer subjects in the lofexidine group were early terminators and subjects who dropped out early stayed longer in the trial if they were taking lofexidine ($p=0.0034$). Additionally, the proportion of subjects who completed the 5 day active treatment period was statistically significantly greater for the lofexidine group relative to the placebo group ($p=0.0087$).
- Lofexidine was significantly superior to placebo in terms of detoxification area under the withdrawal symptoms-time curves (AUC) over the 5 day active treatment phase for both the ITT and Completer populations ($p=0.0260$ and $p=0.0188$, respectively). Over the entire 8-day study period, the lofexidine group had a significantly lower mean AUC compared to the placebo group for the Completer population ($p=0.0306$).
- Daily mean SOWS-Gossop, OOWS-Handelsman, VAS E, MCGI: Severity of Illness [Subject and Rater]) also showed similar positive effects of lofexidine over placebo. SOWS-Gossop, OOWS-Handelsman, and VAS E data consistently favored lofexidine over placebo throughout the study. MCGI: Severity of Illness (Subject and Rater), mean scores consistently favored lofexidine over placebo throughout the study. With respect to MCGI: Side Effects Index (Subject and Rater), mean scores were higher for the lofexidine group relative to the placebo group throughout the study.
- As anticipated, placebo-treated subjects experienced opioid withdrawal symptoms, whereas lofexidine-treated subjects experienced some side effects of the medication plus some, though reduced, withdrawal symptoms. The average number of withdrawal-related AEs was less in the lofexidine group relative to the placebo group during the 5-day treatment period, with differences between treatment groups being statistically significant on Days 2 and 3 ($p<0.01$).
- More placebo-treated subjects than lofexidine-treated subjects used concomitant medications to alleviate opioid withdrawal, and the average number of concomitant medications used by placebo-treated subjects was significantly higher ($p<0.05$) relative to lofexidine-treated subjects

on all treatment days except Day 4. Very few subjects required opioid rescue medication during the study (2 lofexidine-treated subjects and 3 placebo-treated subjects).

SAFETY RESULTS:

Due to opioid withdrawal symptoms, AEs were reported for 97.0% of lofexidine-treated subjects and 93.8% of placebo-treated subjects, with no significant group difference ($p=0.2496$). Those AEs significantly higher ($p<0.01$) in the lofexidine group versus the placebo group were: hypotension (25.4% vs. 0.8%); dizziness (22.4% vs. 6.9%); dry mouth (14.2% vs. 1.5%); and bradycardia (9.7% vs. 1.5%). Those AEs marginally higher ($0.01<p<0.10$) in the lofexidine group versus the placebo group were: pain in extremity (9.0% vs. 1.5%); sedation (8.2% vs. 1.5%); stomach discomfort (5.2% vs. 0.8%); malaise (3.7% vs. 0.0%); and sinus bradycardia (3.7% vs. 0.0%).

Withdrawal-related AEs were reported for 85.1% of lofexidine-treated subjects and 87.7% of placebo-treated subjects, with no significant group difference ($p=0.5928$).

Hypotension (9.7% vs. 0.0%) was the only withdrawal-related AE statistically significantly higher ($p<0.01$) in the lofexidine group versus the placebo group. Those withdrawal-related AEs marginally higher ($0.01<p<0.10$) in the lofexidine group versus the placebo group were: pain in extremity (8.2% vs. 1.5%) and malaise (3.7% vs. 0.0%).

Non-withdrawal-related AEs were reported for 59.7% of lofexidine-treated subjects and 43.1% of placebo-treated subjects, with a significant group difference ($p=0.0096$). There were 3 non-withdrawal-related AEs for which the incidence was statistically significantly higher ($p<0.01$) in the lofexidine group compared to the placebo group: dizziness (19.4% vs. 5.4%); hypotension (17.2% vs. 0.8%); and dry mouth (9.0% vs. 0.0%). Those non-withdrawal-related AEs marginally higher ($0.01<p<0.10$) in the lofexidine group versus the placebo group were: bradycardia (8.2% vs. 1.5%); sedation (7.5% vs. 1.5%); somnolence (6.7% vs. 1.5%); anxiety (3.7% vs. 0.0%); and orthostatic hypotension (3.7% vs. 0.0%).

Eight lofexidine-treated subjects and 8 placebo-treated subjects experienced serious AEs (SAEs). There were no deaths and none of the SAEs were life threatening. Nine of the 16 events were severe opioid withdrawal, requiring a day of additional hospitalization for stabilization; these were the only SAEs requiring any medical treatment. All SAEs reported during the study resolved rapidly and were without sequelae.

Because of lofexidine's mechanism as an alpha 2-adrenergic agonist, cardiovascular effects were closely monitored in this study. There was no evidence of QTc prolongation from the analyses of safety ECGs. The data did show statistically significant differences in mean PR and QRS intervals between the treatment groups, with both intervals more prolonged in lofexidine-treated versus placebo-treated subjects. The differences, however, were very small and the mean values for these intervals were well below a level indicating pathology. Examination of individual subject data indicated that neither PR nor QRS interval prolongation appear to be a clinically significant problem with lofexidine treatment.

Lofexidine caused systolic and diastolic hypotension and bradycardia, with a significant difference from placebo on most treatment days, and with some rebound on Days 6 and 7 after lofexidine discontinuation. AE reports of hypotension and bradycardia were generally mild to moderate in severity and did not require therapeutic intervention. One lofexidine-treated subject (b) (6) was discontinued from the study due to hypotension. In addition, 4 SAEs in lofexidine-treated subjects were characterized as hypotension and bradycardia, although the reasons for study discontinuation

were missed doses (in 3 cases) and subject request in one case. A large majority (if not all) of withheld doses in this study were very likely due to hypotension and/or bradycardia. In most cases, subjects continued on treatment when their vital signs recovered.

A significantly greater number of subjects met criteria for “potentially clinically significant” changes (decreases) in vital signs for lofexidine versus placebo in all 3 vital sign parameters. By these criteria, systolic blood pressure decreased in 76 (56.7%) vs. 2 (1.5%) subjects, diastolic blood pressure decreased in 43 (32.1%) vs. 6 (4.6%) subjects, and pulse decreased in 33 (24.6%) vs. 6 (4.6%) subjects treated with lofexidine vs. placebo, respectively. Aside from the few cases described above, however, these subjects did not require intervention (other than positional, e.g., lying down) and were not discontinued from the study.

In fact, persistent symptomatic hypotension (leading to more than 2 missed doses in a day or more than 4 missed doses during the study), symptomatic bradycardia, and required medical intervention were protocol-specified requirements for study discontinuation.

Although blood pressure and pulse decreases sometimes led to one or more missed doses and often met pre-set increased tracking criteria for “potentially clinically significant changes” in lofexidine-treated subjects, the mean daily values for systolic blood pressure, diastolic blood pressure, and heart rates in the treatment group were well within clinically acceptable ranges, subjects did not require medical intervention, and the Principal Investigators in this trial did not consider the cardiovascular side effects of lofexidine a significant clinical problem.

No clinically significant changes in clinical laboratory values were noted in either treatment group.

CONCLUSIONS:

For the primary outcome measure (mean Day 3 SOWS Gossop score), lofexidine at a dose of 3.2 mg/day demonstrated significantly superior efficacy over placebo ($p=0.0212$).

For the co-primary outcome measure (time-to-dropout), significantly fewer subjects in the lofexidine group were early terminators and subjects who dropped out early stayed longer in the trial if they were taking lofexidine ($p=0.0034$). Additionally, the proportion of subjects who completed the 5-day treatment period was statistically significantly greater for the lofexidine group relative to the placebo group ($p=0.0087$).

Lofexidine was significantly superior to placebo in terms of detoxification area under the withdrawal symptoms-time curves (AUC) over the 5-day active treatment phase for both the ITT and Completer populations ($p=0.0260$ and $p=0.0188$, respectively). Over the entire 8-day study period, the lofexidine group had a significantly lower mean AUC compared to the placebo group for the Completer population ($p=0.0306$).

SOWS-Gossop, OOWS-Handelsman, and VAS-E data consistently favored lofexidine over placebo throughout the study, including the various analyses that assessed the impact of missing observations on the study results.

MCGI: Severity of Illness (Subject and Rater) mean scores consistently favored lofexidine over placebo throughout the study, and the various analyses that assessed the impact of missing observations trended in favor of lofexidine over placebo.

MCGI: Side Effects Index (Subject and Rater) mean scores were higher for the lofexidine group relative to the placebo group throughout the study. This was expected given that

lofexidine-treated subjects were experiencing some side effects of the drug as well as some withdrawal signs/symptoms, whereas placebo-treated subjects were experiencing only withdrawal signs/symptoms.

More placebo-treated subjects than lofexidine-treated subjects used concomitant medications to alleviate opioid withdrawal, and the average number of concomitant medications used by placebo-treated subjects was significantly higher relative to lofexidine-treated subjects on all treatment days except Day 4.

The average number of withdrawal-related AEs was less in the lofexidine group relative to the placebo group during the 5-day treatment period, with differences between treatment groups being statistically significant on Days 2 and 3.

The adverse event profile observed with lofexidine was not unexpected. The most commonly occurring AEs likely related to lofexidine were hypotension, bradycardia, dizziness, sedation, and dry mouth, known side effects of the treatment.

There were no deaths or life-threatening SAEs. All SAEs resolved rapidly and were without sequelae.

There was no evidence of QTc prolongation from analysis of safety ECGs and there were no clinically significant changes in other ECG intervals.

Lofexidine caused systolic and diastolic hypotension and bradycardia, which were generally assessed as mild or moderate in severity by the site Investigator and did not require therapeutic intervention.

Decrease in blood pressure and pulse led to some missed doses, but most subjects continued in the study.

There were no clinically significant changes in clinical chemistry, hematology, and urinalysis.

Lofexidine at a dose of 3.2 mg/day (0.8 mg QID) was safe and generally well tolerated, with some occurrence of mild to moderate hypotension and bradycardia.

Date of the report: March 14, 2010

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy, Safety, and Dose-Response Study of Lofexidine in the treatment of Opioid Withdrawal (Days 1 to 7) Followed by Open-Label, Variable-Dose Lofexidine Treatment (Days 8 to 14)		
Investigators: Information on investigators is provided in Section 16.1.4 of the report.		
Study center(s): 18 study sites in the United States		
Publications (reference): None.		
Studied period (years): Date first subject screened: 17 June 2013 Date last subject completed: 24 December 2014	Phase of development: 3	
Objectives: The primary objective was to investigate the efficacy, safety, and dose-response of lofexidine (2.4 mg/day or 3.2 mg/day) in reducing withdrawal signs and symptoms and facilitating completion of withdrawal/extending treatment retention in subjects undergoing withdrawal from short-acting opioids in a double-blind inpatient setting (Days 1 to 7) followed by an open-label inpatient/outpatient setting (Days 8 to 14).		
Methodology: This Phase 3, multicenter study was completed in two parts. Part 1 of the study (Days 1 to 7) used an inpatient, randomized, double-blind, placebo-controlled design. Subjects were randomized to receive lofexidine HCl 2.4 mg/day, lofexidine HCl 3.2 mg/day, or placebo. Part 2 (Days 8 to 14) used an open-label, variable-dose design to capture longer-term exposure in subjects requiring lofexidine treatment beyond Day 7. Subjects who completed Part 1 were eligible to participate in the open-label phase (Days 8 to 14), during which subjects received variable-dose lofexidine HCl treatment (not to exceed 3.2 mg/day). Each subject's Part 1 randomized treatment assignment remained blinded during the open-label phase.		
Number of subjects (planned and analyzed): Planned: 600; Intent-to-treat Population: 603; Modified Intent-to-treat Population: 602; Safety Population: 602; Per Protocol Population: 589		
Diagnosis and main criteria for inclusion: Subjects at least 18 years of age, who were dependent on short-acting opioids and seeking treatment for withdrawal.		
Test product, dose and mode of administration, batch number: <ul style="list-style-type: none"> • Lofexidine HCl 2.4 mg/day (administered as 3 × 0.2 mg tablets and 1 placebo tablet QID) • Lofexidine HCl 3.2 mg/day (administered as 4 × 0.2 mg tablets QID) Lot Numbers: 24004-3561		
Duration of treatment: Part 1, 7 days; Part 2, 7 days		

Reference therapy, dose and mode of administration, batch number:

- Matching placebo (administered as 4 × placebo tablets QID)

Lot Numbers:77661AO

CRITERIA FOR EVALUATION:

Efficacy:

Part 1, Days 1-7: Efficacy assessments were performed daily at estimated time of maximum plasma concentration (i.e. 3.5 hours after the first dose): Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop), Objective Opiate Withdrawal Scale of Handelsman (OOWS-Handelsman) Modified Clinical Global Impression Scale (MCGI) (Subject and Rater), Visual Analog Scale-Efficacy (VAS-E), Clinical Opiate Withdrawal Scale (COWS), concomitant medication use, and completion of detoxification as assessed by the investigator (at completion of inpatient treatment on Day 7 only or, if applicable, early termination during Days 1-7).

Part 2, Day 8-14: Efficacy assessments were performed daily before dosing: SOWS-Gossop, OOWS-Handelsman, MCGI (Subject and Rater), VAS-E, COWS, concomitant medication use, and completion of detoxification as assessed by the investigator.

Pharmacokinetics:

Fingerstick blood samples for assessment of lofexidine plasma concentrations were collected during Part 1.

Safety:

Safety assessments included adverse events (AEs), vital signs, 12-lead electrocardiogram (ECGs), clinical laboratory evaluations, physical examinations, and the Columbia Suicide Severity Rating Scale (C-SSRS).

STATISTICAL METHODS:

Subject populations:

The intent-to-treat (ITT) population included all randomized subjects, with subjects analyzed by randomized treatment; the modified intent-to-treat (mITT) population included all ITT subjects who received at least 1 dose of study medication, with subjects analyzed by randomized treatment; the per protocol (PP) population included all mITT subjects who satisfied the inclusion/exclusion criteria, received the treatment to which they were randomized, and had no major protocol deviation during the double-blind phase. The safety population included all subjects who received at least 1 dose of study medication, with subjects analyzed according to the treatment received.

The PK population included all subjects who had at least 1 post-baseline lofexidine concentration assay result (subjects randomized to placebo were not included).

The ECG population included all subjects who were dosed and had centrally interpreted ECGs.

Efficacy:

The primary endpoint was defined as the difference between the overall LS means from a pattern mixture model based on log-transformed SOWS-Gossop scores from Days 1 through 7 (mITT population). Data sets imputed using multiple imputations from a pattern-mixture model were analyzed using a mixed-model repeated measures (MMRM) model that included fixed effects for treatment group, baseline log-transformed SOWS-Gossop score, sex, study day (Days 1 to 7), and treatment group-by-day interaction. Sensitivity analyses included analysis of log-transformed SOWS-Gossop score from Day 1 to Day 7 using an MMRM model; and the “tipping point” δ was determined at which the conclusions changed from being statistically significant to not statistically significant, at the $\alpha = 5\%$ level using a 2-sided test in favor of lofexidine.

The secondary endpoint, completion status, was defined as the proportion of completers in each treatment arm (mITT population) and was analyzed using a logistic regression model that included fixed effects for treatment group, sex, and site (mITT population). Each lofexidine treatment group was compared with the placebo group. A sensitivity analysis was performed on this endpoint using the ITT population.

Pharmacokinetics:

Lofexidine plasma concentration data were analyzed descriptively for dose proportionality, effects of intrinsic factors, and relationship between potentially clinically significant (PCS) vital signs and selected adverse events.

Safety:

Safety measures in the lofexidine HCl 2.4 mg/day and 3.2 mg/day treatment groups were compared descriptively. Treatment-emergent adverse events (TEAEs) were summarized by treatment. The incidence of TEAEs was summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, overall and by severity and relationship to treatment. The number and percentage of subjects with serious AEs and the number of subjects who discontinued from the study due to AEs were tabulated by study treatment. TEAEs were also summarized as opioid withdrawal related (OWR) and non-opioid withdrawal related (NOWR). Laboratory evaluations and vital signs were summarized descriptively.

Twelve-lead ECGs were analyzed by a central laboratory. The primary focus was change in QTc Fridericia (QTcF) from time-matched predose (screening) value and change of QTcF as a function of lofexidine concentration. Also analyzed were change in QTcB, heart rate (HR), PR, and QRS, and ECG morphologies not seen on any ECG during Baseline.

SUMMARY – CONCLUSIONS

The ITT, mITT, PP, and overall safety populations included 17 study sites and 602 (mITT, overall safety) or 603 (ITT) subjects.

(b) (4)
 (b) (4)
 (b) (4) The PK population

included 468 subjects and the ECG population included 681 subjects.

Efficacy results:

Primary efficacy analysis:

The LS means for the overall log-transformed SOWS-Gossop scores were statistically significantly lower in the lofexidine HCl 2.4 mg/day and lofexidine HCl 3.2 mg/day groups (indicating greater relief from withdrawal symptoms) compared with the placebo group (2.4 mg/day group, p=0.0166; 3.2 mg/day group, p=0.0033) (Synopsis Table 1).

Synopsis Table 1. Pattern Mixture Model on SOWS-Gossop Score from Days 1 to 7 Inclusive, Double Blind Phase, mITT Population

Day/Treatment	Overall Geometric Mean ^a	LS Mean ^b	Difference vs Placebo	Two-sided 95% CI for Mean Difference	P-value
Placebo	5.23	1.83			
Lofexidine HCl 2.4 mg/day	4.07	1.62	-0.21	(-0.37, -0.04)	0.0166
Lofexidine HCl 3.2 mg/day	3.80	1.57	-0.26	(-0.44, -0.09)	0.0033

CI = confidence interval; LS = least squares; mITT = modified intent-to-treat.

^a The geometric mean SOWS-Gossop score on each study day is the back-transformed LS mean estimate based on log-transformed data.

^b Least squares means from a pattern mixture model using an unstructured covariance model and degrees of freedom (df) associated with the error term computed using the Kenward-Rogers method. The log transformation is log (SOWS-Gossop score + 1). P-values are from inference on the log scale.

The same analysis using the PP population and other sensitivity analyses were supportive.

Secondary efficacy analysis:

The percentage of subjects who completed the double-blind phase of the study (i.e., received at least 1 dose of study medication on Day 7 and completed the 3.5-hour post-dose SOWS-Gossop assessment on Day 7) was statistically significantly larger in both active treatment groups versus the placebo group for the mITT population (Synopsis Table 2). The percentages of subjects achieving completion were 27.8%, 41.5%, and 39.6% in the placebo, lofexidine HCl 2.4 mg/day (p=0.0067), and lofexidine HCl 3.2 mg/day (p=0.0191) groups, respectively.

Synopsis Table 2. Completion Status, mITT Population

Parameter	Statistic	Placebo (N = 151)	Lofexidine HCl	
			2.4 mg/day (N = 222)	3.2 mg/day (N = 222)
Completed double-blind phase ^a	n (%)	42 (27.8%)	95 (41.5%)	88 (39.6%)
Pair-wise comparison versus placebo ^b	OR (95% CI) p-value	--	1.85 (1.18, 2.88) 0.0067	1.71 (1.09, 2.67) 0.0191

^a Subject received at least 1 dose of study medication on Day 7 and completed the 3.5-hour postdose SOWS Gossop assessment on Day 7.

^b From logistic regression model with factors for treatment and sex.
Source: Table 14.2.2.1

Results were similar in for the same analysis using the ITT population.

Pharmacokinetic results:

Comparison of mean plasma lofexidine concentrations in the lofexidine HCl 2.4 mg/day and 3.2 mg/day treatment groups demonstrated dose proportionality. At all sample collection time points, the ratios of the mean concentrations were generally close to 0.75, which is the theoretical ratio expected from the 2 doses. This dose proportionality held despite the possibility that dose holds occurred in many subjects at some time during the course of treatment, indicating that the dose holds and missed doses occurred with similar frequencies in both treatment groups. There were between-group trends suggestive of lower body weight and lower body surface area being associated with higher lofexidine plasma concentrations. On average, females had higher plasma concentrations than males, which is consistent with the difference in mean body weight between male and female subjects. Analyses of the relationship of lofexidine plasma concentrations to the occurrence of key AEs and PCS vital signs were unable to identify strong trends that support a quantitative exposure-response relationship. However, the inability to identify any convincing exposure-response relationships is likely to be a result of study design-related difficulties in knowing the lofexidine exposure near the time of the response being evaluated. The inability to identify a relationship cannot be interpreted as meaning that such relationships do not exist for lofexidine.

Safety results:

No unexpected safety concerns were observed over the 7-day double-blind phase, nor with continued open-label treatment with lofexidine for up to an additional 7 days.

During the double-blind phase of the study, TEAEs overall were reported in approximately 95% of subjects in the lofexidine group and approximately 89% of subjects in the placebo group. The most common TEAEs in the lofexidine treatment groups were insomnia, orthostatic hypotension, hypotension, and bradycardia. The most common TEAEs in the placebo group were insomnia, pain, diarrhea, and myalgia. AEs considered treatment-related occurred more often in the groups who received lofexidine HCl (2.4 mg/day 72.1%; 3.2 mg/day, 76.1%) than in the placebo group (33.8%). OWR TEAEs were

reported more frequently in the placebo group (84.8%) than in the lofexidine HCl 2.4 mg/day (79.0%) and lofexidine HCl 3.2 mg/day (79.7%) groups; and NOWR TEAEs were reported more frequently in the lofexidine HCl groups (2.4 mg/day, 76.9%; 3.2 mg/day, 79.3%) than in the placebo group (40.4%). The percentage of subjects experiencing TEAEs that led to study discontinuation was higher in the placebo group (29.1%) than either the lofexidine HCl 2.4 mg/day group (18.8%) or the lofexidine HCl 3.2 mg/day group (24.8%). Of the TEAEs leading to discontinuation, TEAEs generally accepted as symptoms of opiate withdrawal were more prevalent in the placebo group and NOWR TEAEs were more prevalent in the lofexidine groups.

Over the course of the entire study, there was 1 death, which was due to accidental multiple drug intoxication 3 days after completing 7 days of lofexidine treatment. The fatal event was definitely not related to study medication according to the Investigator and the Sponsor. A total of 7 subjects (1.2%) experienced serious AEs: 2 subjects (1.3%) in the placebo group, 0 in the lofexidine HCl 2.4 mg/day group, and 5 (2.3%) in the lofexidine HCl 3.2 mg/day group. In the 3.2 mg/day group, the SAEs were the death due to multiple drug intoxication noted above, 2 events of syncope (both considered related to study medication), 1 event of suicidal ideation (not related to study medication) and 1 event of overdose involving multiple drugs of abuse (not related to study medication).

During the double-blind phase, mean changes from baseline in clinical laboratory findings were unremarkable. Five subjects in the lofexidine HCl groups (2.4 mg/day, 2 subjects; 3.2 mg/day, 3 subjects) had elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values reported as adverse events. None of the events were considered serious or severe, and none led to discontinuation from the study.

During the double-blind phase, mean values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) decreased from screening in lofexidine-treated subjects and generally increased from screening in placebo-treated subjects. The mean decreases in SBP in lofexidine-treated subjects ranged from 2 to 17 mmHg below screening and consistently occurred 3.5 hours after the first daily dose; SBP decreases were generally greater upon standing. Mean SBP and DBP measurements were observed to be consistently 2-5 mmHg lower in the lofexidine HCl 3.2 mg/day group compared with the lofexidine HCl 2.4 mg/day group. The incidence of orthostatic hypotension was greater in lofexidine-treated subjects than placebo-treated subjects and greater in the lofexidine HCl 3.2 mg/day group compared with 3.2 mg/day group. The proportion of subjects experiencing orthostatic BP changes remained stable or decreased for all treatment groups as the study progressed. Mean sitting HR decreased in lofexidine-treated subjects (maximal mean decrease approximately -6 bpm) and increased in placebo-treated subjects; standing HRs increased in both treatment groups. In general, mean HR changes were clinically unremarkable. Mean orthostatic change in HR increased in both the lofexidine and placebo groups; lofexidine treatment did not appear to blunt the compensatory orthostatic HR increase.

None of the findings for AEs, laboratory evaluations, or vital signs in the open-label phase of the study changed any of the observations drawn from the double-blind phase nor revealed any new observations of note.

As assessed by the C-SSRS, a lower percentage of subjects in the lofexidine HCl 3.2 mg/day group (6.8%) reported suicidality (suicidal ideation or behavior) over the course of the study (Baseline through Day 14) compared with subjects in the placebo (10.6%) and lofexidine HCl 2.4 mg/day (10.5%) groups.

Based on the central laboratory analysis of ECGs during the double-blind phase, mean QTcF increased on Day 1 in the lofexidine treatment groups and then decreased for the duration of the double-blind period. Maximum QTcF mean increases were 7.3 msec and 9.3 msec in the 2.4 mg/day and 3.2 mg/day lofexidine HCl groups, respectively. Mean change in QTcF of >30 to ≤60 msec from baseline occurred in 5.0%, 15.9% and 17.0% of subjects in the placebo, lofexidine 2.4 and 3.2 mg/day groups, respectively. QTcF changes >60 msec from baseline were observed for one subject in the placebo group and 1 subject in the lofexidine HCl 3.2 mg/day group. One subject in the placebo group was observed to have QTcF values >500 msec. In the open-label phase, mean values of QTcF were between 403.8 and 404.7 msec,

mean changes of QTcF were within ± 10 msec, and no subjects had a QTcF interval >450 msec. Two subjects had QTcF values of change >30 to ≤ 60 msec.

CONCLUSION:

- Lofexidine effectively mitigated symptoms associated with acute opioid withdrawal and facilitated the completion of an abstinence treatment (“detoxification”) program following abrupt discontinuation of opioids compared with placebo. Lofexidine HCl 3.2 mg/day was associated with a greater reduction in opioid withdrawal symptoms compared with lofexidine HCl 2.4 mg/day.
- Lofexidine was associated with an expected higher incidence of hypotension and bradycardia-related adverse effects compared with placebo. The incidence of these events was higher with lofexidine HCl 3.2 mg/day compared with lofexidine HCl 2.4 mg/day.

Date of the report: 31 May 2017

4.4.13 Pilot Studies (LX0-1001, LX1-1001, and LX1-2001)

USWM-LX0-1001 Clinical Study Report Synopsis

2.

Name of Sponsor/Company: USWorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: Plasma Concentrations Following an Intravenous Dose of Lofexidine—A Pilot Dose-Ranging Study.		
Principal Investigator: Wayne E. Spencer, MD		
Study center(s): Heart of America Research Institute (now Lee Research Institute), Shawnee, KS 66218		
Publications (reference): None		
Studied period (years): Date first patient enrolled: 07 January 2009 Date last patient completed: 15 January 2009	Phase of development: 1	
Objectives: The primary objective of this phase I clinical trial was to assess plasma concentrations during and following a single intravenous (IV) infusion of lofexidine HCl 200 µg. The secondary objective was to assess the tolerability of a single IV infusion of lofexidine HCl 200 µg.		

<p>Methodology: This was a single center, non-randomized, open-label, single dose, pilot dose-ranging study.</p> <p>A screening visit was held within 14 days prior to entering the clinical research center (CRC) on Day 1. During the screening visit the investigator performed a physical examination, medical history and medication history. In addition, the following were obtained:</p> <ul style="list-style-type: none"> • Height (cm) and weight (Kg) • Vital signs (blood pressure and 30 second pulse rate); • 12-lead ECG; • Clinical laboratories (hematology, clinical chemistry, urinalysis, Hepatitis A, B, and C, and HIV testing); and • Urine drug screening for all major drugs of abuse. <p>For the dosing period, the subjects entered the CRC in the morning prior to dosing (Day 1). At that time or just prior to the initiation of the study drug infusion, the following tests were performed:</p> <ul style="list-style-type: none"> • Vital signs (blood pressure and 30 second pulse rate) on admission • 12-lead ECG. <p>Prior to dosing on Day 1, all vital signs, ECG, and clinical laboratories were reviewed by the investigator and found to be within the normal ranges. Values outside of normal ranges were acceptable if they were deemed to be not clinically significant by the investigator. Urine drug screening results were all found to be negative.</p> <p>On Day 1, the subjects received a single lofexidine HCl dose of 200 µg IV over 200 minutes. Blood samples for lofexidine concentrations were obtained at time 0 (just prior to the dose) and at 90 and 200 minutes, and at 4.5, 6 and 10 hours after the start of the infusion. After the 10-hour blood sample was obtained, the subjects were discharged from the CRC if they were hemodynamically stable and without clinically significant adverse events.</p> <p>Vital signs were obtained prior to the dose of study medication and at 15, 30, 60, 120 and 200 minutes and at 4.5, 6 and 10 hours after the initiation of the infusion. ECGs were obtained prior to the initiation of the infusion and at 200±10 minutes and 10 hours ±10 minutes after the start of the infusion.</p>
<p>Number of patients (planned and analyzed): Planned: 2 subjects, Enrolled: 2 subjects, Analyzed: 2 subjects.</p>
<p>Diagnosis and main criteria for inclusion: Healthy male volunteers between 18 to 45 years of age, inclusive, with a BMI of 19 to 29 kg/m², inclusive and were willing and able to provide written informed consent.</p>
<p>Test product, dose and mode of administration, batch number: Lofexidine solution for IV infusion, 250 µg/250 mL. All solutions were given intravenously over 200 minutes at a rate of 1 µg/minute. The IV solutions were compounded by (b) (4) for US WorldMeds. The expiration date of the solutions was February 7, 2009. Lot number: 08012009@36.</p>
<p>Duration of treatment: Lofexidine was administered intravenously over 200 minutes on one day.</p>

Reference therapy, dose and mode of administration, batch number: None.						
Criteria for evaluation: Pharmacokinetic: The pharmacokinetic profile following the single intravenous dose of 200 µg. Safety: Adverse events, vital signs and 12-lead ECGs in any subject that received at least some of the IV dose of study medication.						
Statistical methods: No statistics were performed. Pharmacokinetics: Non-compartmental pharmacokinetic parameters were calculated.						
PHARMACOKINETIC RESULTS: The plasma concentrations of lofexidine are in the following table. <p style="text-align: center;">Plasma Concentrations (pg/mL)</p>						
Subject No.	Time (hr) Post Initiation of Study Drug Infusion					
	0	1.5	3.33	4.5	6	10
(b) (6)	0	169	378	332	280	203
	0	158	356	419	362	315
Mean Concentrations	0	163.5	367	375.5	321	259
Due to the small sample size and the short sampling period, confidence in the accuracy of derived pharmacokinetic parameters from this study is limited. The objective of the study was to determine if an intravenous dose of lofexidine HCl 200 µg infused over 200 minutes would provide measurable plasma concentrations of lofexidine. The tested dose produced serum concentrations similar to those reported following a single oral dose of 400 µg. Therefore, this IV dose of lofexidine may be used in the absolute bioavailability trial.						
SAFETY RESULTS: Lofexidine infusion resulted in blood pressure decreases from baseline in both subjects. The blood pressure in Subject (b) (6) dropped to 108/68 mmHg, a decrease from baseline of 15/12 mmHg at 3.3 hours, the time the IV infusion ended and this subject's plasma concentration was maximum. For Subject (b) (6) blood pressure dropped to 78/58 mmHg, a decrease from baseline of 36/29 mmHg at 1.2 hours after completion of the infusion and at the time of maximum plasma concentration for this subject. Subject (b) (6) did not experience any AEs at this time. There was little to no compensatory change in heart rate associated with the blood pressure changes. One subject (Subject (b) (6)) had complaints of feeling faint, nausea and one episode of vomiting which occurred at approximately the time of stopping the infusion. These adverse events were moderate in intensity, possibly study drug-related and resolved within a few minutes with no medical treatment. Overall, lofexidine was generally well-tolerated.						
CONCLUSION: Plasma concentrations of lofexidine HCl 200 µg intravenously infused over 200 minutes resulted in measurable plasma concentrations up to 6.7 hours after the infusion was stopped, the last time point sampled. C _{max} values were similar to those following a single oral dose of 400 µg. There were decreases in blood pressure with little to no change in heart rate. One subject had adverse events considered to be drug related and these events resolved within minutes without medical therapy. This dose and mode of administration of lofexidine was safe and well-tolerated						
Date of the report: 20 June 2009.						

2. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine hydrochloride		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: A Randomized, Two-Way Crossover, Single-Dose, Open-Label Study to Evaluate the Bioavailability of a Tablet Formulation of Lofexidine HCL (0.2 mg) (Britlofex™, (b) (4)) in 4 Fasted Healthy Normal Male Volunteers (Protocol 96275)		
Principal Investigator: William Poggemeier, MD Investigators:		
Study center(s): Gateway Medical Research, Inc., 116 N. Main, St Charles, MO 63301		
Publications (reference): Al-Ghananeem AM. Pharmacokinetics of Lofexidine Hydrochloride in Healthy Volunteers. <i>Journal of Pharmaceutical Sciences</i> 2009 98(1):319-326.		
Studied period (years): Date first patient enrolled: ~ 15 Oct 1996 Date last patient completed: ~ 30 OCT 1996	Phase of development: 1	
Objectives: Primary: The primary objective of this study was to evaluate the single dose pharmacokinetics of a tablet formulation of lofexidine HCl in 4 normal adult males under fasting conditions.		
Methodology: Study LX1-1001 was a randomized, single-dose, open-label, two-way crossover study. Four (4) healthy male volunteers randomly received two separate lofexidine administrations under fasting conditions during two study periods. Each subject received one drug per study period. Periods were separated by a washout period of at least 7 days. Drug administration of "A" consisted of an oral lofexidine HCl 1.2 mg dose (6 tablets containing 0.2 mg lofexidine HCl), taken on study day 1 of either Period I or Period II. Drug administration of "B" consisted of an oral lofexidine HCl 2.0 mg dose (10 tablets of 0.2 mg lofexidine HCl), taken on the alternate Period. Each lofexidine dose was taken following a 10-hour overnight fast. In each study period, blood samples were obtained prior to dosing (hour 0), and postdose at hours 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24 and 30 hours, respectively. A total of 12 blood samples were collected per subject during each study period. Blood samples were assayed for plasma lofexidine concentrations using a validated method, and pharmacokinetic parameters were identified or calculated for plasma lofexidine concentrations over each 30-hour period for each subject. Assay standards exhibited precision and accuracy of 7.2% or better at all tested concentrations between 50 and 10000 pg/mL, and QC samples were within acceptability ranges.		
Number of patients (planned and analyzed): Planned: 4 subjects, Analyzed: 4 subjects		

<p>Diagnosis and main criteria for inclusion: Healthy male volunteers, 18 to 45 years of age, inclusive, and within $\pm 15\%$ of ideal weight for height and frame.</p>
<p>Test product, dose and mode of administration, batch number: Lofexidine HCl was administered orally as a single dose at 1.2 mg (six 0.2 mg tablets) or at 2.0 mg (ten 0.2 mg tablets). Batch number: Unknown</p>
<p>Duration of treatment: Subjects were maintained in a controlled environment for a 10-hour period preceding each study day and were confined for the 30-hour period following each dose. At least a 7-day wash out period separated the two dosing periods. Subjects were in a controlled environment for a total of 4 nights.</p>
<p>Reference therapy, dose and mode of administration, batch number: None.</p>
<p>Criteria for evaluation: Pharmacokinetics: The pharmacokinetic (PK) analyses included the following parameters:</p> <ul style="list-style-type: none"> • Maximum observed lofexidine concentration (C_{max}) • Time from dosing to reach maximum concentration (T_{max}) • Area under the concentration-time curve for 30 hours from dosing (AUC_{0-t}) • Elimination rate constant (K_e) • Area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) • Elimination half-life ($T_{1/2}$) <p>Safety: Adverse events</p>
<p>Statistical methods: This was a single-dose, two-way crossover study with a sample size of 4 subjects. Due to the sparsity of data, no statistical analyses of the pharmacokinetic parameters were conducted. Descriptive statistical summaries, including means, medians, standard errors (SE), minimum and maximum values were calculated using PROC UNIVARIATE from SAS, version 6.09 for VAX Open-VMS environment. Plots of the concentration-time curves (original and semi-log scale) for each subject were generated using PROC GPLOT in SAS.</p>
<p>SUMMARY – CONCLUSIONS</p> <p>PHARMACOKINETICS RESULTS: Plasma lofexidine concentrations were below assay quantification limits for all predose samples and for all 0.5 hour samples except for Subject (b) (6) receiving the 2.0 mg lofexidine HCl dose. Lofexidine was quantifiable in all other plasma samples. Dose proportionality was supported by the 1.59-fold increase in plasma lofexidine C_{max} (see table below) which was comparable to the 1.67 fold increase in lofexidine dosage from 1.2 mg to 2.0 mg. All subjects reached T_{max} between 2 and 4 hours, except for subject (b) (6) who reached T_{max} at 6 hours after dosing with 2.0 mg. Area under the curve (both AUC_{0-t} and $AUC_{0-\infty}$) demonstrated dose proportionality with a 1.67 fold increase in AUC_{0-t} and a 1.72 fold increase in $AUC_{0-\infty}$ for the 1.67-fold dose increase.</p>

Mean Lofexidine Pharmacokinetic Parameter Results		
Parameter	Lofexidine HCl 1.2 mg	Lofexidine HCl 2.0 mg
C _{max} (pg/mL)	1755.65	2795.18
T _{max} (hours)	3.0	3.25
AUC _{0-∞} (ng/L/h)	31652	54321
Ke (1/hour)	0.063	0.065
T _{1/2} (hours)	11.16	11.44

Ke and T_{1/2} were comparable between dose levels. There was no apparent dose-dependency in T_{max}, Ke or T_{1/2}, suggesting that change in dose does not affect the absorption or elimination rates of lofexidine HCl.

CONCLUSION: The single-dose data from the 4 adult male volunteers indicate that plasma lofexidine concentrations were dose proportional over the 1.2 to 2.0 mg lofexidine HCl dose range.

Date of the report: 9 January 1997

1. SYNOPSIS

Name of Sponsor/Company: US WorldMeds, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Lofexidine		
Name of Active Ingredient: Lofexidine hydrochloride		
Title of Study: An Open Label Safety Evaluation of Lofexidine for the Treatment For Opiate Withdrawal		
Investigators: Elmer Yu, MD; Walter Ling, MD; David Gudeman, MD		
Study center(s): Philadelphia and Los Angeles Veterans Administration (VA) Medical Centers		
Publications (reference): None		
Studied period (years): Date first subject enrolled: July 1996 Date last subject completed: April 1998	Phase of development: 2	
<p>Objectives: The main objective of these 3 related studies (Initial Study, Pilot 1, and Pilot 2) was to evaluate the safety/tolerability of lofexidine, an α_2 adrenergic agonist, in opiate-dependent subjects at lofexidine HCl doses of 1.6, 2.4, and 4.0 mg/day (Initial Study) and 3.2 mg/day (Pilot 1 and Pilot 2). Pilot 2 had additional objectives: to obtain additional safety/tolerability (and efficacy) data in relation to the lofexidine dose (3.2 mg/day) likely to be subjected to further study in the US; to determine the extent to which the efficacy of lofexidine could be demonstrated in a study involving a minimal initial period of baseline treatment with morphine; and to examine a number of different means of assessing the severity of opiate withdrawal.</p>		
<p>Methodology: The investigational plan was developed and initiated by a prior Sponsor and the National Institute on Drug Abuse (NIDA). The first study (Initial Study) was initiated in 1996 as a multicenter investigation of the safety and tolerability of oral lofexidine HCl 1.6 mg/day, 2.4 mg/day and 4.0 mg/day in sequential, ascending-dose cohorts of opiate-dependent subjects undergoing acute opiate withdrawal at the Los Angeles and Philadelphia Veterans Administration (VA) Medical Centers. A total of 54 subjects were to be enrolled to achieve 5, 15, and 5 completing subjects for lofexidine doses 1.6 mg/day, 2.4 mg/day and 4.0 mg/day, respectively. After completion of the Initial Study, 2 additional studies (Pilot 1 and Pilot 2) were initiated at the Philadelphia VA Medical Center to assess the safety and tolerability of lofexidine 3.2 mg/day, using 2 different daily dosing schedules of 0.8 mg 4 times daily (QID) (Pilot 1) and 1.6 mg twice daily (BID) (Pilot 2). The studies in total were completed by 1998. All 3 studies included a morphine sulfate subcutaneous injection run-in period (1 to 8 days depending on the study). In the Initial Study, subjects received the full lofexidine dose for 7 days, followed by a 3-day lofexidine dose taper. In Pilot 1 and Pilot 2, subjects received lofexidine for 5 days with no lofexidine taper period. All 3 studies had a 2-day posttreatment observation period.</p>		

<p>Number of subjects (planned and analyzed): Enrolled: Initial Study, 42 subjects; Pilot 1, 6 subjects; Pilot 2, 6 subjects Analyzed: Initial Study, 34 subjects; Pilot 1, 6 subjects; Pilot 2, 6 subjects</p>
<p>Diagnosis and main criteria for inclusion: Adults aged 21 to 59 years, inclusive, who were dependent on heroin, morphine, or hydromorphone according to the Diagnostic and Statistical Manual, fourth edition (DSM IV) criteria, and self-reported use of heroin, morphine, or hydromorphone for at least 21 of past 30 days were recruited.</p>
<p>Test product, dose and mode of administration, batch number: Lofexidine HCl was available in 0.2 mg tablets. In the Initial Study, subjects received lofexidine HCl 1.6 mg/day (0.8 mg BID), 2.4 mg/day (1.2 mg BID or 0.8 mg three times daily [TID]), or 4.0 mg/day (1.0 mg QID). In Pilots 1 and 2, subjects received lofexidine HCl 3.2 mg/day (Pilot 1, 0.8 mg QID; Pilot 2, 1.6 mg BID). Batch number: Unknown</p>
<p>Duration of treatment: For the Initial Study, successfully screened subjects were stabilized on morphine for 8 days, followed by 10 days lofexidine treatment (including a 3-day dose taper). In Pilot 1, subjects were stabilized on morphine for 4 to 7 days, followed by 5 days of lofexidine treatment. In Pilot 2, subjects were stabilized on morphine for 1 day followed by 5 days of lofexidine treatment. All 3 studies had a 2-day posttreatment observation period.</p>
<p>Reference therapy, dose and mode of administration, batch number: None</p>
<p>Criteria for evaluation: Efficacy: Efficacy assessments included the Modified Himmelsbach opiate withdrawal scale (MHOWS), the Subjective Opiate Withdrawal Scale of Handelsman (SOWS-Handelsman), the Objective Opiate Withdrawal Scale (OOWS), a subject-rated visual analog scale that assessed craving for opiates (VAS-C), and the Modified Clinical Global Impression Scale (CGIS). Safety: Safety assessments included vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, oral temperature), ECGs, clinical laboratory tests (hematology and chemistry), and adverse events. Pharmacokinetics: Plasma and urine levels of lofexidine were analyzed.</p>
<p>Statistical methods: Efficacy and safety data were summarized descriptively. Plasma concentration-time data were analyzed using noncompartmental methods.</p>
<p>SUMMARY – CONCLUSIONS EFFICACY RESULTS: Collectively for all 3 studies, MHOWS scores were lower for subjects who received lofexidine 2.4 to 4 mg/day compared with subjects who received lofexidine 1.6 mg/day. Scores were generally similar between the lofexidine 2.4 mg/day, 3.2 mg/day (0.8 mg QID or 1.6 mg BID), and 4.0 mg/day groups. In the Initial Study and Pilot 2, the mean SOWS-Handelsman score showed a rise to a peak on the</p>

second or third day of lofexidine treatment, followed by a progressive fall to low levels thereafter. SOWS-Handelsman data were not reported for Pilot 1.

SAFETY RESULTS:

Collectively for all 3 studies, the most frequently reported adverse events during lofexidine treatment were appetite decreased, rhinorrhea, insomnia, muscle aches, and anxiety. Hypotension (< 90 mmHg) was reported as an adverse event in 14 subjects (25.9%); the frequency of hypotension tended to increase with increasing daily dose of lofexidine HCl (1.6 mg, 0; 2.4 mg, 36.4%; 3.2 mg, 25.0%; 4.0 mg, 100%). There were no deaths, serious adverse events, adverse events resulting in study discontinuation, or other significant adverse events reported during the studies.

Dose-dependent decreases in BP and heart rate were observed. All 3 subjects in the lofexidine 4.0 mg/day dose group experienced sitting systolic BP < 85 mmHg. There was no apparent dose-response between the lofexidine 2.4 mg/day and 3.2 mg/day dose groups. No ECG abnormalities were regarded as clinically significant in any subject at any time.

PHARMACOKINETIC RESULTS:

Lofexidine was measurable in the plasma at 0.5 hours after dosing. Lofexidine appears to accumulate in the plasma by the second day of lofexidine dosing for all doses.

CONCLUSION:

Lofexidine HCl doses of 1.6 mg/day, 2.4 mg/day and 3.2 mg/day were generally well tolerated in subjects experiencing acute opiate withdrawal. Lofexidine 4.0 mg/day was associated with a notably higher incidence of hypotension. The observed safety profiles for lofexidine 2.4 mg/day and 3.2 mg/day were generally similar, supporting further evaluation of lofexidine 3.2 mg/day for efficacy and safety.

Date of the report: 10 April 2017

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04/18/2018



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 209-229/0002
Supplement Number:	NA
Drug Name:	Lofexidine 0.18 mg tablets
Indication(s):	Mitigation of symptoms associated with opioid withdrawal Facilitation of completion of opioid discontinuation treatment
Applicant:	US WorldMeds, LLC
Date(s):	Date of Document: 9/26/2017 Consult received date: 12/22/2017 Completion date: 2/2/2018
Review Priority:	Priority (30 days)
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Wei Liu, Ph.D., Mathematical Statistician, QT-CSS/DBVI/OB/OTS
Concurring Reviewers:	Qianyu Dang, Ph.D., Team Leader, DBVI/OB/OTS Atiar Mohammad Rahman, Ph.D., Acting Division Director, DBVI/OB/OTS
Medical Division:	DAAAP and Controlled Substance Staff
The CSS Team:	Shalini Bansil, M.D., Medical Officer, OD/CSS Martin S. Rusinowitz, M.D., Medical Officer, OD/CSS Silvia Calderon, Ph.D., Senior Pharmacologist, OD/CSS
Project Manager:	Sandra Saltz, OD/CSS
Keywords:	NDA review, clinical studies, Crossover design; Clinical abuse potential study; Self-reported endpoint; Multiple endpoints

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EXECUTIVE SUMMARY

Data of NDA 209229 Study 1020 (USWM-LXI-3001) was submitted by US Worldmeds, Inc. (the sponsor) for FDA approval of Lofexidine 0.18 mg tablets for mitigation of symptoms associated with opioid withdrawal. The Study 1020 is entitled “Evaluation of the efficacy and safety profiles of lofexidine hydrochloride in the treatment of opiate detoxification in opiate-dependent patients.”

Confirmation about drug abuse potential:

This was a randomized, multicenter, double-blind, placebo-controlled, multiple-dose, parallel-group study. There were 3 major phases: Phase I (Days 1-3, morphine stabilization), Phase II (Days 4-8, lofexidine/placebo treatment), and Phase III (Days 9-10, placebo treatment).

A total of 68 subjects were randomized (35 Lofexidine + 33 Placebo). There were 10 completers in the lofexidine group and 5 in the placebo group.

This reviewer identified some issues in the study design, data collection, and analysis. The data showed that the differences between morphine and placebo are negligible, thus the study population is not able to discriminate the known abusable drug morphine from placebo based on analysis of the endpoints for drug abuse evaluation, VAS high (Figure A) and the overall ARCI-MGB sores (Figure B). Therefore, this reviewer concludes that the data were inconclusive about the abuse potential of lofexidine.

Figure A Box Plot of Day-3-Value-Corrected VAS-HIGH (Observed Data)

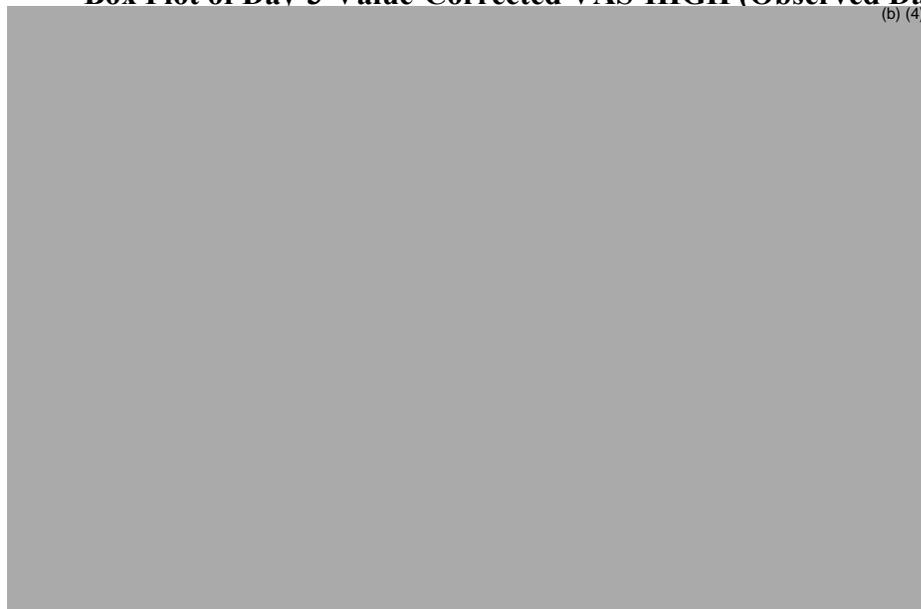


Figure B Box Plot of Day-3-Value-Corrected Overall Score of True Responses to ARCI-MBG (Observed Data)



Statistical considerations that may limit the effect:

- The endpoint VAS high should be the peak value (E_{max}) of a time course of outcomes. For morphine, the time of peak effect (T_{E_{max}}) in VAS high usually occurs about 6 to 20 minutes after drug administration, therefore the collected VAS-high values at 2 hours after medication would be likely smaller than the E_{max} value and the analysis may not provide the designed power.
- The sponsor did not preselect the margins for the hypothesis tests of VAS high and ARCI-MBG, respectively.

Recommendations:

Recommendations for the proposed label are included in the subsection 2.2.3.3.

1 INTRODUCTION

1.1 Overview

1.1.1 Background Information

On 12/22/2017, CSS sent a consult request for statistical review for NDA 209229 Study 1020 (USWM-LX1-3001)/1020-R (referenced IND 047857) submitted by US WorldMeds, LLC (the sponsor) on 9/26/2017. The sponsor seeks an approval of Lofexidine hydrochloride for the proposed indication of Mitigation of symptoms associated with opioid withdrawal Facilitation of completion of opioid discontinuation treatment. The Study 1020 (USWM-LX1-3001)/1020-R is entitled “Evaluation of the efficacy and safety profiles of lofexidine hydrochloride in the treatment of opiate detoxification in opiate-dependent patients.” The Sponsor has performed a descriptive analysis on visual analog scales HIGH (VAS high) and ARCI-MBG between lofexidine and placebo.

Lofexidine hydrochloride (HCl) is a selective alpha-2 adrenergic receptor agonist (α_2 receptor agonist) that is structurally and pharmacologically similar to the unscheduled substance, clonidine, and other α_2 receptor agonists. If approved, lofexidine would be the first non-narcotic medication in the United States (US) indicated for the mitigation of symptoms associated with opioid withdrawal and for the facilitation of completion of opioid discontinuation treatment. Lofexidine’s proposed indicated uses would be complimentary to currently approved treatment options, thereby providing an option for the treatment of the opioid withdrawal syndrome itself and improving a patient’s chances of completing an opioid discontinuation program to achieve an opioid-free state.

1.2 Data Sources

The sponsor submitted this NDA including the study data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown below. The data were submitted in SAS Xport transport format.

Application:	NDA209229
Company	US WorldMeds, LLC
Drug	Lofexidine
CDER EDR link	\\Cdseub1\evsprod\NDA209229\0002\m5\datasets\uswm-lx1-3001\tabulations\legacy
Letter date	September 26, 2017

2 STATISTICAL EVALUATION

2.1 Data and Analysis Quality

None.

2.2 Study 1020

2.2.1 Overview

2.2.1.1 Objectives of the Study

Primary Objective

The primary objective was to compare the efficacy of lofexidine hydrochloride to that of placebo in the treatment of opioid detoxification.

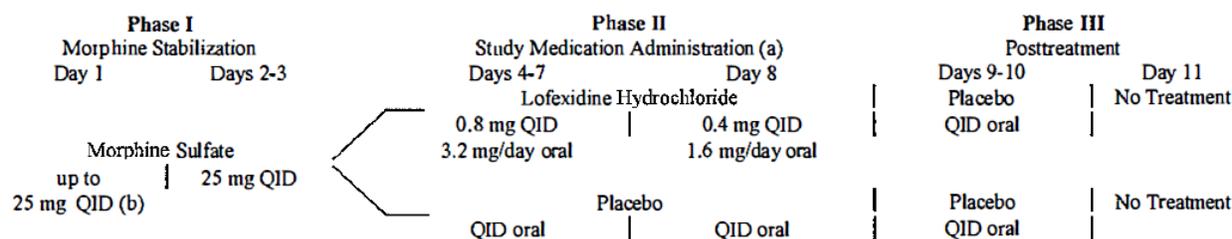
Secondary Objective

The secondary objectives were to assess the safety profile, treatment retention, and pharmacokinetic (PK) profile of lofexidine hydrochloride in the treatment of opioid detoxification in opioid-dependent subjects.

2.2.1.2 Study Design

This was a randomized, multicenter, double-blind, placebo-controlled, multiple-dose, parallel-group study. There were 3 major phases: Phase I (Days 1-3, morphine stabilization), Phase II (Days 4-8, lofexidine/placebo treatment), and Phase III (Days 9-10, placebo treatment) as seen in Figure 1.

Figure 1 Study Schematic



- (a) Subjects received 4 tablets of study medication for each dose: lofexidine 0.8 mg (4 x 0.2 mg lofexidine tablets); lofexidine 0.4 mg (2 x 0.2 mg lofexidine tablets + 2 placebo tablets); placebo (4 placebo tablets).
(b) Maximum subcutaneous dose of 25 mg QID; dose for each subject varied, depending on the time of day the subject enrolled.

Baseline safety and efficacy assessments were performed on Days 1-3. Subjects were randomized to receive either lofexidine or placebo on Day 4; lofexidine subjects received 0.8 mg QID on Days 4-7 and 0.4 mg QID on Day 8.

Treatment efficacy and safety assessments were performed on Days 4-8. All subjects received placebo on Days 9 and 10, during which time efficacy and safety assessments continued to be performed. Study discharge was on Day 11.

Planned sample size: 96 (48/group); Enrolled: 90; Randomized: 68 (35 Lofexidine + 33 Placebo); Analyzed for Efficacy: 68; Analyzed for Safety: 68

2.2.1.3 Abuse Potential Measures

Primary PD endpoint:

Modified Himmelsbach Opiate Withdrawal Scale (MHOWS) on Day 5.

Secondary PD endpoints:

Drop Out Day/Day-by-day dropout rate; Peak :MI-IOWS score observed during Days 4-8 inclusive; number of concomitant medications related to opioid withdrawal, Days 4-8 inclusive; Objective Opiate Withdrawal Scale (OOWS, Handelsman); Short Opiate Withdrawal Scale (SOWS-Gossop); Modified Clinical Global Impressions (MCGI) Rating Scale (Subject and Rater); Subjective Opiate Withdrawal Scale (SOWS, Handelsman); Visual Analog Scale for Efficacy of Medication in Alleviation of Withdrawal Sickness (VAS-E); VAS-High; Addiction Research Center Inventory for Morphine-Benzedrine (ARCI-MBG); and Tobacco Withdrawal.

Sample size estimate

A sample size required to achieve a power of 0.90 (beta = 0.10) with an alpha level of 0.05, assuming an equal number of evaluable subjects in the 2 groups was 82 subjects (41+41). On the (conservative) assumption of approximately 15% loss of "evaluable" subjects due to dropout (before completion of MHOWS on the first day of randomized treatment), this equated to approximately 96 subjects (48+48) starting on randomized treatment. This figure of 96 also satisfied the desire for a sample size that is an exact multiple of 6, thereby facilitating a balanced allocation across 3 sites and 2 randomized treatment groups.

2.2.1.4 Statistical Methodologies used in the Sponsor's Analyses

The following populations are defined by the sponsor for the analysis and reporting of data.

- Intent-to-treat (ITT) Population consisted of all patients who received study drug and provided some post-baseline efficacy values.
- Completer Population included all patients who completed the study (i.e., complete Day 14). The primary efficacy analyses were based on the Completer Population.
- Safety Population included all patients who received any study drug. All safety analyses were based on the Safety Population.

For efficacy variables, descriptive statistics (N, mean, standard deviation, minimum, median, and maximum) were generated for values collected on Days 4 through 10 and for mean changes from Baseline on Days 4 through 10.

For MHOWS, SOWS-Gossop, SOWS-Handelsman, OOWS-Handelsman, VAS-E, and VAS-High, treatment comparisons were performed at each appropriate study visit day on mean changes from Baseline using a 2-way ANOVA model with terms for center, treatment, and treatment*center interaction. Repeated measures analyses were performed on mean changes from Baseline to evaluate treatment differences across time (study visit days).

Statistical analyses were performed on 3 data sets: observed data, Last Observation Carried Forward (LOCF) data, and completed subjects (those who completed study procedures up to Day 8, and took 1 dose of study medication and completed the MHOWS on Day 8). This same analysis was performed on observed tobacco withdrawal symptoms. No formal statistical comparisons between treatment groups were performed on MCGI or ARCI-MBG.

2.2.1.5 Sponsor's Summary and Conclusions of VAS high and ARCI-MBG
The descriptive analysis of VAS high and ARCI-MBG are shown in Tables 1 and 2, respectively.

Table 1 Descriptive Analysis of VAS High (Observed data)

(b) (4)



Source: Table 30A1 in sponsor's uswm-lx1-3001-csr-final-legacy-report.pdf.

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2.2.2.1 VAS High Analysis

The study design for collecting outcomes is shown in Table 3, showing that *the VAS high scores were “Measured once daily, approximately 2 hours after first morning dose of medication.”* It is problematic because the endpoint VAS high should be the peak value (Emax) of a time course of outcomes. For morphine, the TEmax of VAS high usually occurs between 6 to 20 minutes, therefore the collected VAS-high values were lower than Emax and the analysis may not provide the enough power.

Table 3: Data Collection Schedule

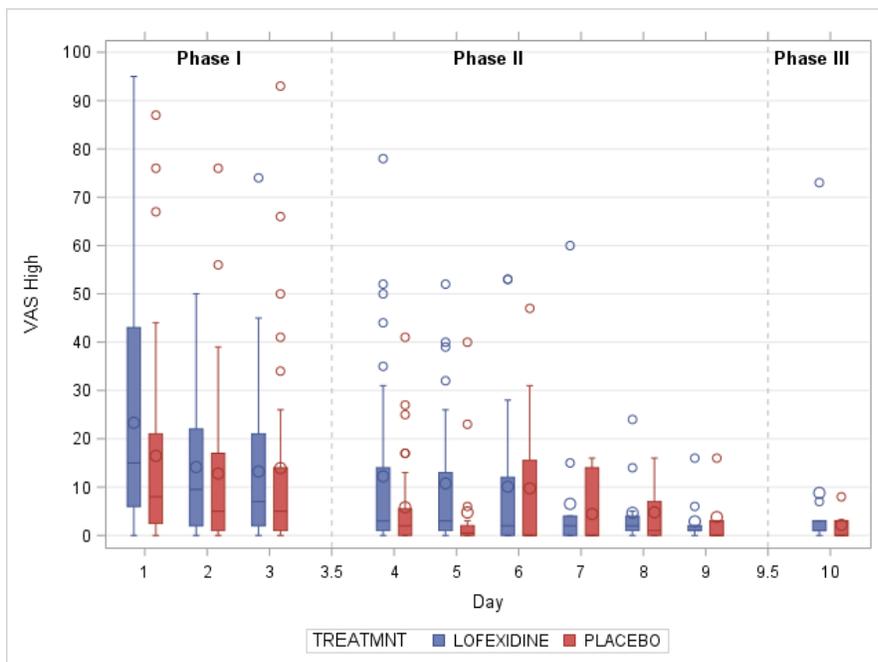
Study Procedure	Phase I Opiate Agonist (Day)			Phase II Study Medication (Day)				Phase III Detox (Day)		Post Tx (Day)	
	1	2	3	4	5	6	7	8	9	10	11
Informed Consent	X										
Opiate Screening	X										
Medical History	X										
Physical Exam	X										X
Weight (1)	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X										
Medication History	X										
Clinical Safety Labs	X										X
Serum Pregnancy Test (females only)	X										
Tuberculosis Skin Test (PPD), RPR, CD4	X										
HIV Screen (optional, separate consent)		X									
Psychiatric Assessment (SCID, Axis I, DSM IV)		X									
Addiction Severity Index (ASI)		X									
Study Medication Administration											
Morphine sc (2)	X	X	X								
Lofexidine or Placebo po QID (3)				X	X	X	X	X			
Placebo po QID (4)									X	X	
Outcome Measures (5)											
Modified Himmelsbach (MHOWS)	X	X	X	X	X	X	X	X	X	X	
Emesis Assessment	X	X	X	X	X	X	X	X	X	X	
Objective Opiate Withdrawal Scale (OOWS Handelsman)			X	X	X	X	X	X	X	X	
Short Opiate Withdrawal Scale (SOWS Gossop)	X	X	X	X	X	X	X	X	X	X	
Subjective Opiate Withdrawal Scale (SOWS Handelsman)	X	X	X	X	X	X	X	X	X	X	
Modified Clinical Global Impressions Scale- Patient and Rater (MCGI)				X	X	X	X	X	X	X	
VAS for Reduction in Withdrawal Sickness	X		X	X		X		X		X	
Abuse Potential Assessments											
Addiction Research Center Inventory (ARCI-MGB)	X	X	X	X	X	X	X	X	X	X	
VAS-High	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (orthostatic)	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram	X					X					X
Adverse Signs and Symptoms	X	X	X	X	X	X	X	X	X	X	X
Tobacco Withdrawal Scale (6)	X	X	X	X	X	X	X	X	X	X	
Urine Toxicology	X				Monday, Wednesday, Friday and As Needed						X
PK Sample Blood Collection (7)				X		X	X	X		X	
Study Discharge											X

(1) Measured at admission and once daily On Days 1-10 between 0630 and 0800, prior to breakfast.
(2) Day 1: maximum dose of 25 mg QID; dose for each patient varied, depending on the time of day the patient enrolled. Days 2-3: 25 mg QID. Administered at 0630, 1100, 1630 and 2200 hr.
(3) Total daily lofexidine dose was 3.2 mg (0.8 mg QID) on Days 4-7 and 1.6 mg (0.4 mg QID) on Day 8. Lofexidine or placebo was administered at 0800, 1300, 1800 and 2300 hr.
(4) Placebo administered to all patients at 0800, 1300, 1800 and 2300 hr.
(5) Measured once daily, approximately 2 hours after first morning dose of medication. On Day 4, additional PM assessments performed for MHOWS and OOWS-Handelsman.
(6) Performed once daily at 1730 hours.
(7) Blood samples were to be collected prior to the morning dose on Days 4, 6, 7 and 8 and serial blood samples were collected for 24 hours on Day 7. Posttreatment sample was collected on Day 10.

Source: Table 3 on page 25 in sponsor's uswm-lx1-3001-csr-final-legacy-report.pdf .

This reviewer plotted the time course of VAS high as shown in Figure 4. Note that, although all subjects in the Phase I took morphine, the two groups at each day denote the values of randomized subjects who would receive either lofexidine or placebo in Phases II and III. The plot shows that VAS high scores in Phases II and III were sometimes similar, while other times lower than those in the corresponding group in Phase I.

Figure 4 Box plot over time for VAS-HIGH (Observed Data)



To find the drug abuse potential of lofexidine, this reviewer first checked whether this study participants can discriminate morphine from placebo based on their responses of VAS high. Per FDA guidance of HAP studies, subjects qualified to enter the treatment phase of drug abuse study should satisfy some Qualification criteria. One of them is that subjects should tell the difference between a positive control and placebo by a predefined threshold. For example, a subject should like the positive control drug 15 points or more than he/she likes the placebo in drug liking VAS score (bipolar scales). This reviewer did a post-hoc validation analysis to see whether this study population can discriminate the known abusable drug morphine from placebo. The pair-wise differences of drug high score between morphine treatment at day 3 and placebo at day 4 is shown in Figure 5 and the descriptive is summarized in Appendix Table 1. The 95% confidence interval (CI) of the mean difference is (0.98, 15.32). The lower bound is less than 1 reveals that the such difference is too small to support that the study population can discriminate the known abusable drug morphine from placebo. Thus, the data failed to support that lofexidine is not abusable since the participants did not produce meaningful differences in VAS high scores between morphine and placebo.

Figure 5 Box Plot of Day-3-Value-Corrected VAS-HIGH (Observed Data)

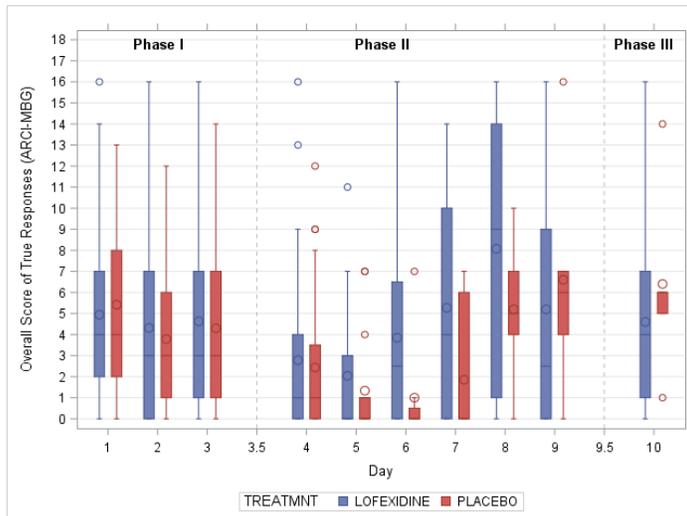


2.2.2.2 ARCI-MGB Analysis

Analyses on the overall ARCI-MGB sores showed similar pattern as VAS high.

The time course of the overall ARCI-MGB sores (shown in Figure 6) shows that comparing to the responses in Phase I the subjects randomized to placebo group had lower mean scores in Phase II Days 4-6 but had similar responses in Days 7-10; similarly, the subjects randomized to the lofexidine group had lower scores in Days 4-5 but the responses were higher in Days 6-10.

Figure 6 Overall Score of True Responses to ATCI-MGB (Observed Data)



The pair-wise difference of morphine treatment at Day 3 and placebo at Day 4 is shown in Figure 7 and the descriptive is summarized in Appendix Table 1. The 95% confidence interval (CI) of the mean difference is (0.77, 3.79). The lower bound is less than 1 reveals that such

difference is too small to support the study population can discriminate the known abusable drug morphine from placebo. The difference of 1 in the overall ARCI-MBG score is equivalent to select only 1 more “FALSE” when answering the 16 Questions and it is not considered clinically meaningful. In conclusion, the data failed to support that lofexidine is not abusable since participants did not produce meaningful differences in overall ARCI-MBG scores between morphine and placebo.

Figure 7 Box Plot of Day-3-Value-Corrected Overall Score of True Responses to ARCI-MBG (Observed Data)



2.2.3 Conclusion

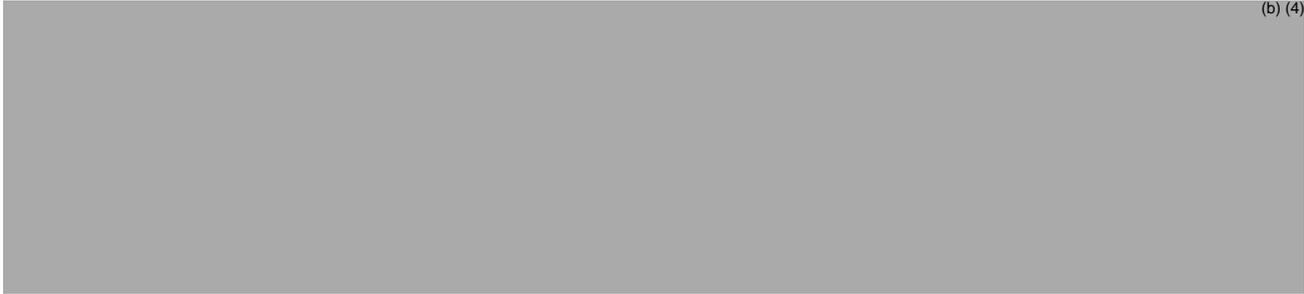
2.2.3.1 Statistical Issues

- The endpoint VAS high should be the peak value (Emax) of a time course of outcomes. For morphine, the TEmax of VAS high usually occurs about 6 to 20 minutes after dosing, therefore the collected VAS-high values at 2 hours after medication would be likely smaller than the Emax value and the analysis may not provide enough power.
- The sponsor did not preselect the margins for the hypothesis tests of VAS high and ARCI-MBG, respectively.

2.2.3.2 Conclusions and Recommendations

The study was not appropriately designed for data collection of the abuse potential endpoint VAS high. The data showed that the study population is not able to discriminate the known abusable drug morphine from placebo in VAS high and the overall ARCI-MBG scores with meaningful differences. Therefore, the data were inconclusive about the abuse potential of lofexidine.

2.2.3.3 Labeling Recommendations



(b) (4)

3 APPENDIX

For the endpoints VAS high and overall ARCI-MBG score, the difference between morphine and placebo for each subject was computed (morphine - placebo) for each endpoint at each Day.

Table 1

endpoint	Day	N	Mean diff	stdErr	LB, 95%CI	UB, 95% CI
VAS High	4	32	8.16	3.52	0.98	15.34
ARCI-MBG	4	32	2.28	0.74	0.77	3.79

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/s/

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