CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215320Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

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Application Number(s)	215320
Priority or Standard	Standard
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Division/Office	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)/ Office of Neuroscience (ON)/Office of New Drugs (OND)/Center for Drug Evaluation and Research (CDER)
Reviewer Name(s)	Tanya Brescia-Oddo, MD
Review Completion Date	See electronic stamp
Established/Proper Name	Acetaminophen 1000 mg/Ibuprofen (as sodium dihydrate) 300 mg in 100 mL
(Proposed) Trade Name	Combogesic IV
Applicant	AFT Pharmaceuticals
Dosage Form(s)	Injection
Applicant Proposed Dosing Regimen(s)	Acetaminophen 1000 mg /Ibuprofen 300 mg every 6 hours as needed
Applicant Proposed Indication(s)/Population(s)	relief of mild to moderate pain, and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	None

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
ROCF	rescue observation carried forward
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

AFT Pharmaceuticals Ltd. has developed Combogesic IV (acetaminophen 1000 mg/ibuprofen 300 mg in 100 ml solution) injection solution for intravenous infusion. The proposed indication for Combogesic IV is relief of mild to moderate pain, and for management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary. The recommended dosage and administration of Combogesic IV for adults is acetaminophen 1000 mg/ibuprofen 300 mg administered as a 15-minute infusion every 6 hours, as necessary. The maximum total daily dose of Combogesic IV of 4000 mg acetaminophen and 1200 mg ibuprofen in 24 hours should not be exceeded.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant's pivotal efficacy study, AFT-MXIV-07, provided substantial evidence that Combogesic IV is effective for its intended use. The primary endpoint for Study AFT-MXIV-07 was the Time-Adjusted Summed Pain Intensity Difference from baseline over 48 hours (SPID48). The Applicant incorrectly calculated the SPID48 using VAS scores from baseline to the first pre-rescue (inclusive) instead of from baseline to 48 hours. In order to account for the applicable efficacy assessments over the 48-hour period and half-life of the permitted rescue medications, sensitivity analyses were conducted using ROCF (rescue observation carried forward) 4 hours and ROCF 2 hours. The results from these sensitivity analyses support the conclusion that Combogesic IV is superior to the other treatment arms.

1.3. Benefit-Risk Assessment

The reader is referred to the following page.

Benefit-Risk Integrated Assessment

Acute pain is a serious clinical condition which when inadequately treated, may result in increased morbidity, prolonged hospital stays, and decreased patient satisfaction. Additionally, uncontrolled acute pain increases the risk of developing chronic pain.

AFT Pharmaceuticals Ltd. has developed Combogesic IV (acetaminophen 1000 mg/ibuprofen 300 mg in 100 ml solution) Injection Solution for intravenous infusion. The proposed indications for Combogesic IV are relief of mild to moderate pain and for management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary. The Applicant has submitted a 505(b)(2) New Drug Application (NDA) on August 31, 2021, relying in part on the Agency's previous findings of safety and efficacy of the Listed Drugs, Ultracet tablets (acetaminophen 325 mg/tramadol hydrochloride 37.5 mg; NDA 21123), and Motrin (ibuprofen) tablet (NDA 017463). The application will receive a Complete Response due to nonclinical deficiencies including inadequate data from leachable studies to permit a substantive toxicological risk assessment.

Combogesic IV is a fixed-dose combination product formulated with two active ingredients, acetaminophen and ibuprofen, both of which are widely used for a variety of painful conditions, have a well-characterized safety profile, and are formulated for multiple routes of administration including an intravenous route. The dosage and administration of Combogesic IV does not exceed that of approved intravenous products, Ofirmev (acetaminophen injection) and Caldolor (ibuprofen injection), for the management of pain. The recommended dosage and administration of Combogesic IV for adults is acetaminophen 1000 mg/ibuprofen 300 mg administered as a 15-minute infusion every 6 hours, as necessary. The maximum total daily dose of Combogesic IV of 4000 mg acetaminophen and 1200 mg ibuprofen in 24 hours should not be exceeded.

The Applicant conducted two Phase 3 clinical studies, AFT-MXIV-07 and AFT-MXIV-11, to support the safety and efficacy of the NDA. The pivotal study of Combogesic IV, AFT-MXIV-07, was a Phase 3, placebo-controlled, prospective, randomized, double-blind, parallel-design trial comparing the analgesic efficacy and safety of Combogesic IV with acetaminophen alone, ibuprofen alone and placebo, after bunionectomy surgery. Patients received study treatments as 15-minute infusions every 6 hours for 48 hours (total 8 doses). The primary efficacy endpoint, time-adjusted Sum of Pain Intensity Differences over 48 hours (SPID48), demonstrated statistically significant pain relief compared to monotherapies of acetaminophen, ibuprofen, or placebo. Additionally, Study AFT-MXIV-11, was a Phase 3, open-label, single-arm, multiple-dose, multicenter exposure study to determine the incidence of treatment-emergent adverse events in patients with prolonged exposure following orthopedic, plastic, or general surgery. Of 232 patients, fifty patients completed five days of treatment (total 20 doses) of Combogesic IV. Overall, no unique safety signals were observed in patients treated with Combogesic IV, and no overlapping toxicities were observed compared to the individual components.

Furthermore, the Applicant conducted three pharmacokinetic studies, AFT-MXIV-01, AFTMXIV-06, and AFT-MXIV-12, and one in vitro drug interaction study. For the former, the Applicant evaluated the pharmacokinetics of Combogesic IV and established the scientific bridge to the Listed Drugs, Ultracet tablet (acetaminophen 325 mg and tramadol HCl 37.5 mg) (NDA 21123) and Motrin (ibuprofen) tablet (NDA 017463).

The Applicant provided a safety update of Maxigesic IV including an updated Periodic Safety Update Report (PSUR) detailing the worldwide post-marketing safety surveillance for this product. Maxigesic IV, owned by the Applicant, is identical to Combogesic IV, however, it is marketed abroad. The PSUR covered a reporting period of approximately 17 months (from June 21, 2020, to November 30, 2021). Between 2019 and 2020, Maxigesic IV (paracetamol 1000 mg/ibuprofen 300 mg/100 mL intravenous infusion) was approved and marketed in Australia, New Zealand, United Arab Emirates, Germany, and Austria. Maxigesic IV and its other product names have since received marketing registration approval in numerous European Union and non-European Union countries. No new safety signals or risks were identified during the reporting period.

I recommend a regulatory action of Complete Response due to nonclinical deficiencies including inadequate data from leachable studies to permit substantive toxicological risk assessment. In order to resolve this deficiency, the nonclinical review team requests that the Applicant submit a revised toxicological risk assessment for all leachable compounds detected above the 5 mcg/day threshold.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute pain is commonly associated with tissue injury, inflammation, surgical procedures, childbirth, or a brief disease process • Post-surgical pain is a major form of acute pain • Clinical symptoms of acute pain often include increased heart rate, blood pressure, and respiratory rate, shallow respirations, agitation or restlessness, facial grimacing, or splinting • Symptoms can last hours, days, or weeks	Effective postsurgical analgesia is an essential component in the care of the surgical patient Inadequate acute pain control can result in increased morbidity, prolonged hospitalization time, and decreased patient satisfaction

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Current treatments for acute postoperative pain include opioids, acetaminophen (APAP), and NSAIDs	A multimodal strategy including drug-drug combinations of marketed drug products with well-characterized safety profiles may be useful compared to administering the individual drugs as monotherapy

Benefit	• The Phase 3 clinical efficacy study (AFT-MXIX-07) won the primary endpoint of SPID48
	  ○ Combogesic IV provides superior analgesia compared to the same doses of ibuprofen or acetaminophen as monotherapy
	• Clinically meaningful benefit to patients
	  ○ Convenience of two intravenous analgesic drugs in one infusion allowing for improved post-operative pain control and less drug infusion time
		Demonstrated efficacy of primary endpoint through several sensitivity analyses
		
		Clinically meaningful benefit to patients in the form of improved post-operative analgesia and convenience

Risk and Risk Management	• Ofirmev (IV acetaminophen) has been approved since 2010 • Caldolor (IV ibuprofen) has been approved since 2009 • No drug-drug interactions between acetaminophen and ibuprofen • No overlapping toxicities observed in clinical studies (liver transaminases) • No SAEs attributed to Combogesic IV • Infusion site pain occurred at a higher rate in the Combogesic IV treatment arm; severity mostly mild • Incidence of common AEs was comparable or improved compared to monotherapies and/or placebo	Size of the safety database was adequate to characterize the safety profile as agreed on in the pre-NDA meeting The overall safety experience is consistent with that of the monotherapies, acetaminophen and ibuprofen, when administered over a short duration of time (5 days or less) No serious safety signals were observed in the safety population

1.4. Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Acute pain is one of the most common symptoms for which patients seek medical attention. It is generally self-limited and serves as a protective mechanism designed to prevent tissue injury.

Acute pain is commonly associated with tissue injury, inflammation, a surgical procedure, childbirth, or a brief disease process, and typically is less than three months in duration.

Acute pain that is moderate to severe in intensity constitutes a serious condition for which there is an urgent need for safe and effective treatments. Pain is a serious clinical condition that is associated with morbidity that can have substantial impact on day-to-day functioning. If untreated, pain may have a negative impact on sleep, physical function, and quality of life. Inadequate acute pain management can increase risk for chronic pain, especially in the post-surgical setting.

Furthermore, treatment of acute pain should be secondary to treatment of the medical condition causing pain. Analgesics should be given only as needed and at the minimum effective dosage to improve the benefit/risk ratio of the drug.

2.2. Analysis of Current Treatment Options

While multiple drug classes are available for treatment of pain, FDA-approved parenteral medications for management of acute pain include acetaminophen, NSAIDs, and opioids. The local anesthetic drug class, particularly lidocaine, has been known to be used off-label parenterally for control of acute pain.

Ofirmev, IV acetaminophen, was approved in 2010 and has potential for hepatic injury, including severe hepatotoxicity if administered in doses higher than recommended.

Caldolor, IV ibuprofen, was approved in 2009 and in addition to potential for hepatotoxicity and nephrotoxicity, it also has boxed warnings related to risk of cardiovascular events, gastrointestinal bleeding and ulceration.

Other IV NSAIDs approved for management of acute pain include diclofenac and ketorolac, approved in 2014 and 1989, respectively.

Parenteral opioids are indicated to treat moderate to severe acute pain and have well-known, serious adverse events such as respiratory depression and risk of misuse, abuse, and addiction.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Combogesic IV is not currently marketed in the U.S; however, the Division is reviewing the resubmission for Combogesic tablets (acetaminophen 325 mg/ibuprofen 97.5 mg) under NDA 209471 as of June 13, 2022. Both Combogesic IV and Combogesic tablets were developed by AFT Pharmaceuticals.

For NDA 209471, AFT-MX-6 was the pivotal Phase 3 study that established efficacy. AFT-MX-6 was a randomized, double-blind, placebo-controlled, parallel-group, full factorial study that evaluated the analgesic effect of Combogesic tablets in an acute dental pain population. Moreover, the safety database for NDA 209471 was adequate to support the safety of acetaminophen and ibuprofen when used in combination as Combogesic tablets. Despite clinical support for efficacy and safety, the Applicant has twice received a Complete Response due to CMC deficiencies.

Importantly, Combogesic IV is a drug-drug combination product containing acetaminophen 1000 mg and ibuprofen 300 mg in 100 ml solution as an Injection solution for intravenous infusion. Both acetaminophen and ibuprofen have been marketed as IV formulations of Ofirmev and Caldolor, respectively. Ofirmev was approved in 2010 and Caldolor was approved in 2009. The safety profile of both Ofirmev and Caldolor is well-characterized through over a decade of widespread marketing experience. The acetaminophen component in Combogesic IV has the same recommended dosage, maximum single dose, minimum dosing interval and maximum daily dose as Ofirmev. The ibuprofen component in Combogesic IV has a lower single dose, 300 mg, and a lower total daily dose of 1200 mg as compared to Caldolor IV with a total daily dose of 3200 mg.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following are highlights of the regulatory activities that occurred during the development of Combogesic IV.

In November 2014, a Pre-IND interaction (Written Responses Only; IND 124213) occurred with the Sponsor. The Division agreed that the proposed design of one clinical efficacy study appeared to meet the FDA's requirements for one adequate and well-controlled, full-factorial study in patients with acute post-operative pain. The study must show that the combination drug product is superior to the components.

The Sponsor proceeded from Phase 1 to Phase 3 without requesting an End-of-Phase 2 meeting. No additional input was requested from the Division. The protocol for Study AFT-MXIV-07 was submitted in September 2016.

In January 2018, a Pre-NDA meeting was held. The following points were agreed on between the Division and Applicant.

- The Division recommended adding the indication of moderate-to-severe pain, consistent with the approved labeling for IV formulations of the individual components, acetaminophen and ibuprofen; remove proposed indication of (b) (4)
- The Sponsor agreed to (b) (4)
- The Division recommended pooling safety data across patients with single-dose

exposures (Studies 01, 06, and 12) and then patients with multiple-dose exposures (Studies 07 and 11)

- Safety data from studies of the Combogesic oral formulation are not directly supportive of the IV formulation due to PK; data from Combogesic tablets may be submitted and cross-referenced if the relevance is clearly stated
- Required safety data: exposure of at least 300 patients with multiple-dose exposures and at least 50 of those patients exposed for at least 5 days (required because of higher Cmax and more rapid rise in concentrations with the IV formulation compared to the oral formulations of RLDs)
- Conduct a bridging study for Combogesic IV to rely on the Agency's previous findings for Ultracet and ibuprofen; must use the absolute PK for comparison

Additionally, at the pre-NDA meeting, the sponsor noted their decision to not to refer to Ofirmev and Caldolor as listed drugs for commercial reasons, and proposed Ultracet and Motrin as the listed drug products.

3.3. Foreign Regulatory Actions and Marketing History

While Combogesic IV has been developed for the U.S. market, it is identical to Maxigesic IV[1], paracetamol 1000 mg/ibuprofen 300 mg in 100 mL solution for intravenous infusion, developed for foreign markets.

The Applicant provided a safety update of Maxigesic IV including an updated Periodic Safety Update Report (PSUR) detailing the worldwide post-marketing safety surveillance for this product. The PSUR covered a reporting period of approximately 17 months (from June 21, 2020, to November 30, 2021). Between 2019 and 2020, Maxigesic IV (paracetamol 1000 mg/ibuprofen 300 mg/100 mL intravenous infusion) was approved and marketed in Australia, New Zealand, United Arab Emirates, Germany, and Austria. Maxigesic IV and its other product names have since received marketing registration approval in numerous European Union and non-European Union countries. No new safety signals or risks were identified during the reporting period. No safety-related actions were taken during the reporting period.

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

4.1. Office of Scientific Investigations (OSI)

The review team determined that an OSI audit was not necessary and therefore, was not requested. The clinical efficacy study for this Application, AFT-MXIV-07, was conducted by Investigator Stephen E. Daniels, DO. In 2017, the Office of Scientific Investigations (OSI)

[1] (b) (4)
Throughout this review, "Maxigesic" and "Combogesic" are used interchangeably as they are identical drug products.

conducted an inspection of the clinical site of Dr. Stephen E. Daniels under NDA 209471 for Combogesic oral tablets. The final classification of this inspection was NAI. Due to this classification, the site will not be re-inspected for Combogesic IV. For further details, refer to the Clinical Inspection Summary by Dr. Damon Green in DARRTS on October 20, 2017.

4.2. Product Quality

Chemistry, Manufacturing, and controls (CMC) recommends approval of this drug product based on review by drug substance, drug product, process/facilities and microbiology. Additionally, the drug product used in the clinical drug development program is the same as the 'to be marketed' product.

4.3. Clinical Microbiology

The proposed product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

4.4. Nonclinical Pharmacology/Toxicology

The proposed product is recommended for a Complete Response due to the Applicant not providing adequate data from the leachable studies to permit a substantive toxicological risk assessment. In order to resolve the deficiency, the Applicant must submit a revised toxicological risk assessment for all leachable compounds detected above the 5 mcg/day threshold.

See Dr. Carlic Huynh's review for additional detail.

4.5. Clinical Pharmacology

The NDA is approvable from the Clinical Pharmacology perspective.

See Dr. Wei Qui's review for additional detail. The following is excerpted from Dr. Qui's review:

> No PK drug interaction between intravenous acetaminophen and intravenous ibuprofen were found in Combogesic IV. Acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf for Combogesic IV (1000 mg acetaminophen and 300 mg ibuprofen) were bioequivalent to 1000 mg intravenous acetaminophen and intravenous 300 mg ibuprofen given alone, respectively. Acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf were shown to be dose proportional between Combogesic IV full dose and Combogesic IV half dose.

Additionally, the Combogesic IV product used in the clinical pharmacology and clinical studies are the final commercial product.

The following is excerpted from Dr. Qui's review:

The clinical pharmacology program consisted of pharmacokinetic Studies AFT-MXIV-01, AFTMXIV-06, and AFT-MXIV-12, and an in vitro drug interaction study. The Applicant conducted clinical pharmacology studies to evaluate the pharmacokinetics of Combogesic IV and establish the scientific bridge to the identified listed drug products, Ultracet tablet (acetaminophen 325 mg and tramadol HCl 37.5 mg) (NDA 21123) and Motrin (ibuprofen) tablet (NDA 017463). Because NDA 017463 product, Motrin tablet, was withdrawn not for reasons of safety or efficacy, a generic product Dr. Reddy's IBU tablet (ANDA 75682) to NDA 017463 was used as the comparator in the comparative bioavailability study (Study AFT-MXIV-12) to establish the scientific bridge to the listed drug product, Motrin.

- Study AFT-MXIV-01 compared the proposed Combogesic IV with FDC 500/150 tablets, Combogesic IV half dose, acetaminophen IV, and ibuprofen IV to evaluate comparative bioavailability to FDC 500/150 tablets, dose proportionality between Combogesic IV half dose and full dose, and PK drug interaction between intravenous acetaminophen and intravenous ibuprofen.

- Study AFT-MXIV-06 compared Combogesic IV with Ofirmev (IV acetaminophen), Caldolor (IV ibuprofen), and Combogesic tablets (acetaminophen 325 mg/ibuprofen 97.5 mg, aka FDC 325/97.5 or Maxigesic 325 tablets, review pending under NDA 209471 as of June 13, 2022.

- Study AFT-MXIV-12 established the scientific bridge to the listed drug product, Motrin. Pharmacokinetic comparisons were made between the proposed Combogesic IV and listed drug Ultracet (acetaminophen 325 mg + tramadol HCl 37.5 mg per tablet, 2 tablets for a full dose) (NDA 21123) and IBU tablet (ibuprofen 800 mg per tablet, 1 tablet for a full dose) (ANDA 75682), a generic product to the listed drug Motrin.

4.6. Devices and Companion Diagnostic Issues

Not applicable to this Application.

4.7. Consumer Study Reviews

Not applicable to this Application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The reader is referred to the following page.

Table 1 Clinical Study Inventory

Protocol #	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
AFT-MXIV-07	Randomized, Double-blind, Placebo-controlled, multiple-dose, parallel-group, full factorial	Combogesic IV APAP1000 Ibuprofen300 Placebo Q6 hours for 48 hours	1^{o} SPID48 2^{o} SPID 6/12/24 VAS PID Time to/total rescue	48 hours / 5 to 9 days after surgery	276	Bunionectomy	2 sites in United States
Studies to Support Safety							
AFT-MXIV-11	open-label , single-arm	Combogesic IV Q6 hours for 48 hours and extension phase of 50 subjects Q6 hours for 5 days (total 20 doses)	1^{o} incidence of TEAEs 2^{o} Time course of TEAEs / TRAE / TEAEs of interest / Changes in VS, labs / Global	48 hours and extension phase of 50 subjects for 5 days; follow-up 7 days post-discharge	233	Orthopedic, general or plastic surgery	4 sites (2 in United States and 2 in New Zealand)
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
AFT-MXIV-01	Single-dose, open-label, randomized, five-way crossover, BA/BE PK	Maxigesic IV IV paracetamol IV ibuprofen Maxigesic tabs	PK sampling		29	Healthy adults	
AFT-MXIV-06	single-dose, open-label, randomized, four-way crossover, BA/BE PK	Maxigesic IV Ofirmev Caldolor Maxigesic 325 tabs	PK sampling		30	Healthy adults	
AFT-MXIV-12	Single-dose, open-label, randomized, three-way crossover, BA/BE PK	Maxigesic IV Ultracet IBU	PK sampling		30	Healthy adults	

5.2. Review Strategy

The Applicant conducted two clinical studies to support the NDA: AFT-MXIV-07, a Phase 3 pivotal efficacy study, and AFT-MXIV-11, an exposure and safety study.

AFT-MXIV-07 compared the analgesic efficacy and safety of Combogesic IV with acetaminophen alone, ibuprofen alone, and placebo, after bunionectomy surgery. This study will be discussed under the review of efficacy and safety. The review team statisticians, Drs. Kate Meaker and Jing Han performed a reanalysis of the Applicant's primary analysis, confirmed the Applicant's sensitivity analyses and performed supplementary analyses for AFT-MXIV-07. The analyses of the results from the review team's statisticians will be presented with commentary by this primary reviewer.

AFT-MXIV-11 was an exposure and safety study conducted to determine the incidence of treatment-emergent adverse events, in addition to changes in vital signs and clinical laboratory values in patients exposed to Combogesic IV for ≥ 48 hours. AFT-MXIV-11 was an open-label, single-arm study in patients undergoing orthopedic, general or plastic surgery. This study will be discussed under the review of safety.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study of Bunionectomy Pain, AFT-MXIV-07

6.1.1. Study Design

Overview and Objective

Study AFT-MXIV-07 is a full factorial study of 48 hours in duration with the purpose of studying the component contribution of the combination product, containing acetaminophen 1000 mg and ibuprofen 300 mg, to analgesic effects and safety in patients with acute post-operative pain after bunionectomy.

Trial Design

Study AFT-MXIV-07 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of a full factorial design to compare the combination of acetaminophen 1000 mg and ibuprofen 300 mg to each active ingredient and placebo in patients with acute post-operative pain after bunionectomy. The study took place at two clinical sites in the United States.

The primary efficacy objective was to determine the efficacy of Combogesic IV, acetaminophen IV, ibuprofen IV versus placebo IV for the treatment of acute postoperative pain after

bunionectomy as measured by the summed pain intensity difference (SPID) (calculated as a time-weighted average) over 0 to 48 hours (SPID-48) after Time 0.

The safety objective was to determine the incidence of treatment-emergent adverse events (AEs) and changes in vital sign measurements.

The sample size was 275 participants with 75 participants each in Combogesic IV, acetaminophen IV, and ibuprofen IV, and 50 participants in the placebo arm.

Treatments were administered every 6 hours for 48 hours in duration and infused over a period of 15 minutes for a total of 8 doses. The dose for each treatment arm was as follows: 1) Combogesic IV 1000 mg/300 mg, 2) acetaminophen IV 1000 mg, and 3) ibuprofen IV 300 mg.

Participants received 48 hours of treatment with a total confinement period of 72 hours. The post-treatment follow-up visit took place within 5-9 days after surgery.

The primary rescue analgesia was oxycodone 5 or 10 mg by mouth every 4-6 hours as needed for pain before and after the anesthetic infusion is discontinued. If adequate pain relief is not achieved with oxycodone, morphine sulfate intravenous of 2-4 mg was permitted every 4 hours, as needed for pain.

Administration of study drug began once the participant's eligibility had been confirmed by a pain intensity rating of ≥ 40 mm on a 100-mm Visual Analogue Scale (VAS) during the 9-hour qualification period after discontinuation of the post-surgical anesthetic block.

The key inclusion criteria included the following: 1) Male or female, ≥ 18 and ≤ 65 years of age; 2) Classified as P1 to P2 in the American Society of Anesthesiologists (ASA) Physical Status Classification System; 3) Has undergone distal, primary, unilateral, first metatarsal bunionectomy (with osteotomy and internal fixation) with no additional collateral bony procedures; 4) Experiences a pain intensity rating of ≥ 40 mm on a 100-mm Visual Analogue Scale (VAS) during the 9-hour qualification period after discontinuation of the post-surgical anesthetic block

They key exclusion criteria included the following: 1) Any ongoing condition (other than bunionectomy) that could generate pain sufficient to confound study results such as gout or severe OA; 2) patient history of peptic or gastric ulcers or GI bleeding; 3) Receiving anticoagulants (e.g. heparin or warfarin); 4) Received course of systemic corticosteroids (oral or parenteral) within 3 months before screening (inhaled nasal or regional topical is acceptable); 5) patient history of chronic use of NSAIDS, opioids, or glucocorticoids within 6 months before study drug administration (Aspirin ≤ 325 mg allowed for cardiovascular prophylaxis if on stable dose for ≥ 30 days before Screening); 6) Treated with agents that could affect the analgesic response (clonidine, tizanidine, neuroleptics) within 2 weeks before dosing with study drug 7) Significant renal (creatinine ≥ 1.5x ULN) or hepatic disease (AST/ALT ≥ 3x ULN).

Table 2 Schedule of Assessments for AFT-MXIV-07

Measurements/Treatments	Screening Period (Days -28 to 0)	Day 0 (Day of Surgery)	Day 1-2 (post-surgery qualification and 48- hours study period) and Day 3 (discharge)	Follow –Up Visit (Day 7 ±2 Days)
Informed Consent	✓			
Inclusion/Exclusion Criteria	✓	✓		
Demographic Data	✓			
Complete Medical History	✓			
Physical Examination	✓	✓		
X ray (Foot 2 views)[1]	✓			
Concomitant Medications	✓	✓	✓	✓
Urine Pregnancy Test (females only)	✓	✓		
Urinalysis	✓			
Biochemistry & Haematology	✓			
Vital Signs	✓	✓	✓[5]	
Urine Drug Screening Test	✓			
Alcohol Breathalyzer Test		✓		
Surgery		✓		
Randomisation[2]			✓	
Study Drug Administration[3]			✓	
Pain Intensity Assessment			✓	
Pain Relief Assessment			✓	
Time to perceptible and meaningful pain relief			✓	
Global Evaluation of Study Drug [4]			✓	
Rescue medication and timing			✓	
AE Monitoring	✓	✓	✓	✓

[1] Radiographs taken within 6 months before Screening will be acceptable.
[2] Randomisation will occur within the 9 hour period after discontinuation of the anesthetic block which is approximately at 3AM on Day 1, when the pain intensity rating is ≥ 40 mm on the VAS.
[3] The first dose of the study drug will be administered once the participant is randomised and continues 6 hourly for up to 48 hours
[4] Done either at early termination or upon completion of the treatment period, prior to discharge from study centre.
[5] Vital signs will be evaluated at Time 0 and following first dose infusion on Day 1, then each morning prior to the intravenous infusion and at discharge, early termination

Source: Applicant's submission of Protocol AFT-MXIV-07 (September 14, 2016)

Additionally, as the full study is conducted within the trial clinics, it is anticipated that there will be very few individuals who do not complete the full 48 hour efficacy assessments even if some withdraw from study medication. For pain intensity and relief measures, any subjects who withdraw from the study early e.g., due to lack of efficacy, an AE or intolerance to study drug, but have post withdrawal assessments, all their scheduled assessments after the time of withdrawal will be included in the ITT population for the primary efficacy endpoint analysis. The data from those who withdraw consent to participate in the study and therefore provide incomplete efficacy data will be imputed using a multiple imputation process.

Study Endpoints

Primary efficacy endpoint was the time-weighted average of the summed pain intensity difference up to 48 hours, SPID-48.

The planned secondary efficacy endpoints included the following:

- Pain intensity difference (PID) at each scheduled assessment time point after Time 0

- Pain intensity score at each scheduled time point
- SPID over 0 to 6 hours (SPID-6), over 0 to 12 hours (SPID-12), and over 0 to 24 hours(SPID-24)
- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) using the two-stopwatch method)
- Peak pain relief
- Time to peak pain relief
- Time to first perceptible pain relief
- Time to meaningful pain relief
- Proportion of subjects using rescue medication
- Time to first use of rescue medication (duration of analgesia)
- Total use of rescue analgesia over 0 to 24 hours and over 0 to 48 hours

The safety endpoints are the incidence of treatment-emergent adverse events (AEs) and changes in vital sign measurements.

Pain Intensity Assessment:

Pain intensity assessment was obtained by a subject's mark on a 100 mm visual analogue scale (VAS) with 0 = No pain and 100 = Worst pain imaginable, and was used to calculate the following efficacy assessment endpoints:

- Summed Pain intensity differences (SPID) (calculated as a time-weighted average) over 0 to 48 hours (SPID-48) after time 0
- Pain intensity difference (PID) at each scheduled time point after Time 0
- Pain intensity score at each scheduled time point
- SPID over 0-4 hours (SPID-4), over 0-8 hours (SPID-8), and over 0-24 hours (SPID-24) after Time 0

Pain intensity assessment on the VAS was recorded in the inpatient subject diary at scheduled time points during the 6-hour period after Time 0 (5, 10, 15, 30 and 45 minutes, then 1, 1.5, 2, 3, 4, 5 and 6 hours) and then immediately before taking each dose of the study drug and 2 hours after each dosing while awake. If additional analgesia was required, Pain intensity assessment on the VAS was recorded immediately before taking each dose of the rescue medication (pre-rescue VAS assessment).

In the event of rescue medication, the time-adjusted SPID up to the administration of rescue medication was calculated.

Statistical Analysis Plan

Refer to the statistical review by Dr. Jing Han for detail on the Statistical Analysis Plan (SAP).

There were no issues with the SAP that affected the ability to interpret the efficacy results.

The Applicant's primary population for the efficacy analysis was the Intent-To-Treat (ITT) population, consisting of all subjects who received at least one dose of study drug.

As per the Statistical Analysis Plan (SAP), an analysis of covariance (ANCOVA) model with baseline pain intensity as the covariate was initially tested. As the baseline VAS score did not have a significant effect in the initial model and there was no correlation between the SPID48 and baseline pain for any of the treatment groups, the covariate was dropped from the final analysis.

Table 3 Protocol Amendments, Study AFT-MXIV-07

Protocol version	Date	Reason for Change	Summary of Changes
Original protocol	2/24/2016		
Amendment 1	6/7/2017	Statistical methods of handling missing data have been amended according to US FDA comments during the IND application review	Section 9.5 Missing Data ---------- The following text has been included in the protocol: "all their scheduled assessments after the time of withdrawal will be included in the ITT population for the primary efficacy endpoint analysis. The data from those who withdraw consent to participant in the study and therefore provide incomplete efficacy data will be imputed as detailed below." "For participants who withdraw from all study procedures (e.g. following an AE) and therefore provide no additional efficacy data beyond the point of withdrawal the relevant efficacy data will be imputed using a multiple imputation process. The imputation model will include the baseline measures age, gender and the baseline efficacy measure additionally the post randomisation measures of the appropriate efficacy outcome, randomised group and the interaction between the post-randomisation efficacy outcome and randomised group."
Amendment 2	10/26/2016	To correct some inconsistency throughout the protocol	Day 5-9 follow up will be a phone call instead of a site visit. Text has been amended in the following sections: Protocol Synopsis-Duration of Treatment, Section 3.1, Section 3.2, Section 4.2, Section 7.1-Table 1: Schedule of Assessment, Section 7.1.4 and Section 7.1.5. Pain Intensity Assessment and Pain Relief Assessment at the end of 48 hours period. Text has been amended in the following sections: Section 6.1.1, Section 6.1.2 and Section 7.1.4

			All the females need to undergo a urine pregnancy test during the screening and on the day of surgery prior to surgery. Text has been amended in the following section: Section 4.2 Inclusion Criteria #6
Amendment 3	1/4/2017	Correction to exclusion criterion #17	Page 20, Exclusion Criterion #17, the requirement of including test of lactate dehydrogenase was incorrect. It has been removed in the protocol amendment 03 and shall read as below: "Has a significant renal or hepatic disease, as indicated by clinical laboratory assessment (results ≥ 3 times the upper limit of normal [ULN] for any liver function test, including aspartate aminotransferase [AST], alanine aminotransferase [ALT], or creatinine ≥ 1.5 times the ULN)."

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided an attestation in study protocol AFT-MXIV-07 that states, "This study will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements."

Financial Disclosure

The financial disclosure form signed by the Applicant certified that no financial arrangement with the listed clinical investigators as below, had been made whereby study outcomes affected compensation as defined in 21CFR 54.2(a). The Applicant certified that each listed investigator was required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b); the listed investigators did not disclose any such interests. Lastly, the Applicant certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The clinical investigators on the list for Study AFT-MXIV-07 included Dr. Stephen Daniels and Dr. Ira Gottlieb.

Patient Disposition

The primary and secondary efficacy endpoints of this study were evaluated using the intent to treat (ITT) population (276 subjects), defined as those participants who have been randomized and taken at least one dose of study medication. Two-hundred and seventy-one subjects completed the study.

The per protocol population (PP) consisted of all ITT subjects who remained in the study for at least 48 hours of treatment (completed the 48-hour treatment period) and who did not incur a major protocol violation that would challenge the validity of their data. Eighteen subjects were excluded from the PP population (early withdrawal, partial dosing of study drug or consumption

of prohibited concomitant medication). Analysis was not conducted on the PP population as it accounted for more than 90% of the ITT population.

Protocol Violations/Deviations

There were no reported protocol violations for Study AFT-MXIV-07.

There were 84 protocol deviations. There were instances of major protocol deviations of prohibited concomitant medications in 12 subjects: 3 in placebo, 4 in ibuprofen IV, 2 in acetaminophen IV, and 3 in Combogesic IV. Eighteen subjects were administered a rescue analgesic with a pre-rescue VAS < 40 mm: 8 in Combogesic IV, 4 in ibuprofen IV, 3 in placebo, and 3 in IV acetaminophen.

None of the above protocol deviations have led to any exclusion of participants from the primary efficacy endpoint, the analysis being done on the ITT population.

Table of Demographic Characteristics

For Study AFT-MXIV-07, a total of 413 patients were screened and 276 subjects were randomized and included in the ITT population. There were 5 discontinuations during the treatment period. For baseline characteristics, 81.5% were female gender, 62% were white race, and the mean age and weight were 42.4 years and 76.9 kg, respectively.

Table 4 Demographic Information – ITT population , Study AFT-MXIV-07

	Maxigesic® N=75	Ibuprofen N=76	Acetaminophen N=75	Placebo N=50	Total N=276
Age (Years)					
N	75	76	75	50	276
Mean (SD)	42.3 (11.6)	43.3 (12.3)	41.9 (12.5)	41.7 (12.7)	42.4 (12.2)
Median	41.0	44.5	41.0	38.5	43.0
Min; Max	21 ; 65	18; 63	19; 65	20; 65	18; 65
Sex					
Male	13 (17.3%)	11 (14.5%)	17 (22.7%)	10 (20.0%)	51 (18.5%)
Female	62 (82.7%)	65 (85.5%)	58 (77.3%)	40 (80.0%)	225 (81.5%)
Race					
White	48 (64.0%)	39 (51.3%)	55 (73.3%)	29 (58.0%)	171 (62.0%)
Black or African American	23 (30.7%)	32 (42.1%)	17 (22.7%)	20 (40.0%)	92 (33.3%)
Asian	3 (4.0%)	3 (3.9%)	2 (2.7%)	1 (2.0%)	9 (3.3%)
Multiple	1 (1.3%)	2 (2.6%)	1 (1.3%)	0 (0.0%)	4 (1.4%)
Ethnicity					
Hispanic or Latino	18 (24.0%)	15 (19.7%)	18 (24.0%)	7 (14.0%)	58 (21.0%)
Not Hispanic or Latino	56 (74.7%)	60 (78.9%)	56 (74.7%)	41 (82.0%)	213 (77.2%)
Not Stated	0 (0.0%)	1 (1.3%)	1 (1.3%)	2 (4.0%)	4 (1.4%)
Unknown	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)

Height (cm)					
N	75	76	75	50	276
Mean (SD)	166.3 (8.4)	166.3 (10.0)	166.8 (8.9)	166.7 (7.9)	166.5 (8.9)
Median	165.1	164.5	165.1	166.8	165.1
Min; Max	152.4; 193.0	151.0; 199.0	149.9; 191.0	152.4; 182.9	149.9; 199.0
Weight (kg)					
N	75	76	75	50	276
Mean (SD)	79.2 (15.5)	75.6 (17.0)	74.2 (15.6)	79.5 (15.5)	76.9 (16.0)
Median	76.2	73.3	74.0	75.2	75.0
Min; Max	54.0 ; 124.3	52.0; 131.0	46.0; 112.9	52.2; 111.0	46.0; 131.0
BMI (kg/m^2)					
N	75	76	75	50	276
Mean (SD)	28.5 (4.6)	27.2 (5.1)	26.6 (5.3)	28.5 (4.8)	27.7 (5.0)
Median	28.5	26.7	26.0	27.7	27.1
Min; Max	18.7 ; 38.8	18.0 ; 39.8	17.1 ; 40.0	20.8 ; 39.3	17.1 ; 40.0

Source: Applicant's submission; Clinical Study Report Version 3 Table 11, page 68
Maxigesic and Combogesic are used interchangeably as they are identical drug products. For additional detail, refer to the footnote on page 17 of this review.

Reviewer's comment:
There were no large differences between treatment groups for male and female sex; however, significantly more female participants were enrolled than male participants, 81.5% vs. 18.5%, respectively, which is attributed to the bunionectomy pain model used in Study AFT-MXIV-07. Moreover, the baseline characteristics were comparable across the four treatment groups.

Table 5 Baseline Pain Level – ITT Population, Study AFT-MXIV-07

	Maxigesic® N=75	Ibuprofen N=76	Acetaminophen N=75	Placebo N=50	Total N=276
VAS (mm)					
N	75	76	75	50	276
Mean (SD)	69.3 (15.8)	68.9 (14.4)	66.2 (14.2)	68.1 (15.8)	68.1 (15.0)
Median	68.0	67.5	65.0	67.5	67.0
Min ; Max	41 ; 100	40 ; 100	41 ; 100	42 ; 100	40 ; 100

Source: Applicant's submission; Clinical Study Report Version 3, Table 14, page 70

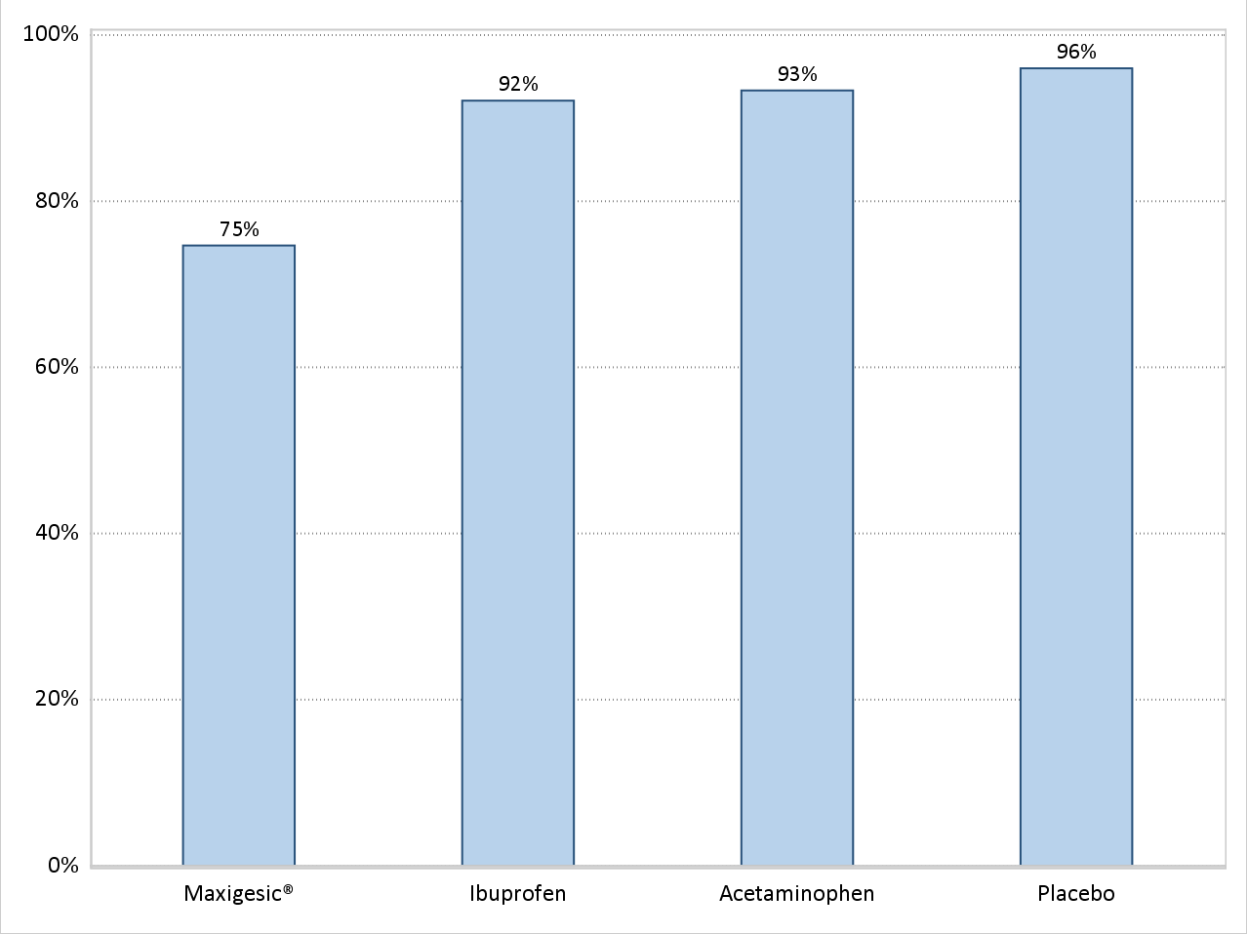
Reviewer's comment: When subjects requested pain medication, they were asked to rate their pain intensity using the 100 mm VAS (Visual Analogue Scale) assessment (0-100). During the 9-hour qualification period after discontinuation of the anesthetic block, subjects who experienced a pain intensity rating of ≥ 40 mm on the VAS were eligible to be enrolled into the study. Notably, the baseline pain levels (median VAS) of the ITT population were comparable across the four treatment groups and were on the higher side of "moderate" pain.

Treatment Compliance, and Rescue Medication Use

Treatment compliance:
In total, 276 participants were randomized. Three subjects discontinued in the first 24 hours; 1 subject each in the ibuprofen and acetaminophen groups, and in the first 24 hours, the volume of one dose for one patient in the placebo group was not recorded. There were no obvious differences in compliance among the four groups. Refer to Section 8.3.3 for discontinuations due to adverse events.

Rescue Medication Data:
The Applicant reported the number of patients and proportions taking rescue during the entire evaluation period of 48 hours. Median time to rescue was reported for the subset rescued in 48 hours.

Figure 1 Requirement of Rescue Medication – ITT Population, Study AFT-MXIV-07



Source: Applicant's submission; Clinical Study Report Version 3, Figure 22, page 116

Table 6 Requirement of Rescue Medication – ITT Population, Study AFT-MXIV-07

	Maxigesic® N=75	Ibuprofen N=76	Acetaminophen N=75	Placebo N=50	Total N=276
Using Rescue Medication	56 (74.7%)	70 (92.1%)	70 (93.3%)	48 (96.0%)	244 (88.4%)
Odds Ratio Estimate[1]	-	4.13	5.49	9.03	
95% Confidence Interval	-	1.52 ; 11.20	1.89 ; 15.96	1.97 ; 41.47	
p-value	-	0.005	0.002	0.005	

[1] Logistic regression model: rescue = treatment + baseline pain

Source: Applicant's submission; Clinical Study Report Version 3, Table 31, page 117

Table 7 Time to First Use of Rescue Medication – ITT Population, Study AFT-MXIV-07

	Maxigesic® N=75	Ibuprofen N=76	Acetaminophen N=75	Placebo N=50
Time to First Use of Rescue Medication (hours)				
Subjects Analyzed	75	76	75	50
Achieved	56 (74.7%)	70 (92.1%)	70 (93.3%)	48 (96.0%)
Censored	19 (25.3%)	6 (7.9%)	5 (6.7%)	2 (4.0%)
Mean (SE)	12.98 (1.87)	3.09 (0.35)	5.62 (0.83)	2.92 (0.53)
Median Estimate	3.32	1.68	2.08	1.18
95% Confidence Interval	2.53 ; 4.92	1.38 ; 2.20	1.62 ; 3.00	1.12 ; 2.12
p-value vs. Maxigesic®	-	<0.001	0.006	<0.001

Source: Applicant's submission; Clinical Study Report Version 3, Table 36, page 123

Reviewer's comment:
Statistically significant differences were demonstrated between treatment groups regarding the use of rescue medication and time to first use of rescue medication.

Efficacy Results – Primary Endpoint

The primary endpoint for Study AFT-MXIV-07 was the Time-Adjusted Summed Pain Intensity Difference from baseline over 48 hours (SPID48). The Applicant analyzed the SPID48 on the Intention-To-Treat (ITT) population using an analysis of covariance (ANCOVA) model including treatment effect as the fixed factor and baseline pain intensity as the covariate according to the agreed upon protocol.

The Statistics review team noted that the Applicant's initial analysis of the primary results were not valid because they calculated the primary endpoint, (SPID48), using all Visual Analog Scale (VAS) pain intensity scores until the first pre-rescue VAS score (inclusive). Therefore, the Applicant effectively calculated the primary endpoint from baseline to first pre-rescue instead of from baseline to 48 hours. Subsequently, the Applicant conducted a sensitivity analysis using rescue observation carried forward (ROCF) 4 hours which utilized the efficacy assessments over 48 hours, and which also corresponded to the half-life of the permitted rescue medications,

oxycodone and IV morphine sulfate. The statistical review team also requested a reanalysis using ROCF 2 hours.

The following is an excerpt from Dr. Jing Han's statistical review:

> The results from both ROCF 4 hours and ROCF 2 hours analyses support the conclusion that Combogesic® IV is superior to the other three arms (P<0.001). The results from sensitivity analyses, supplementary analyses and subgroup analyses by gender, age and race are also consistent with the primary finding.
>
> From the statistical team's point of view, efficacy of the combination for this indication was established.

The following Table shows the statistical review team's reanalysis of the Applicant's primary analysis results which was subsequently included in the Clinical Study Report.

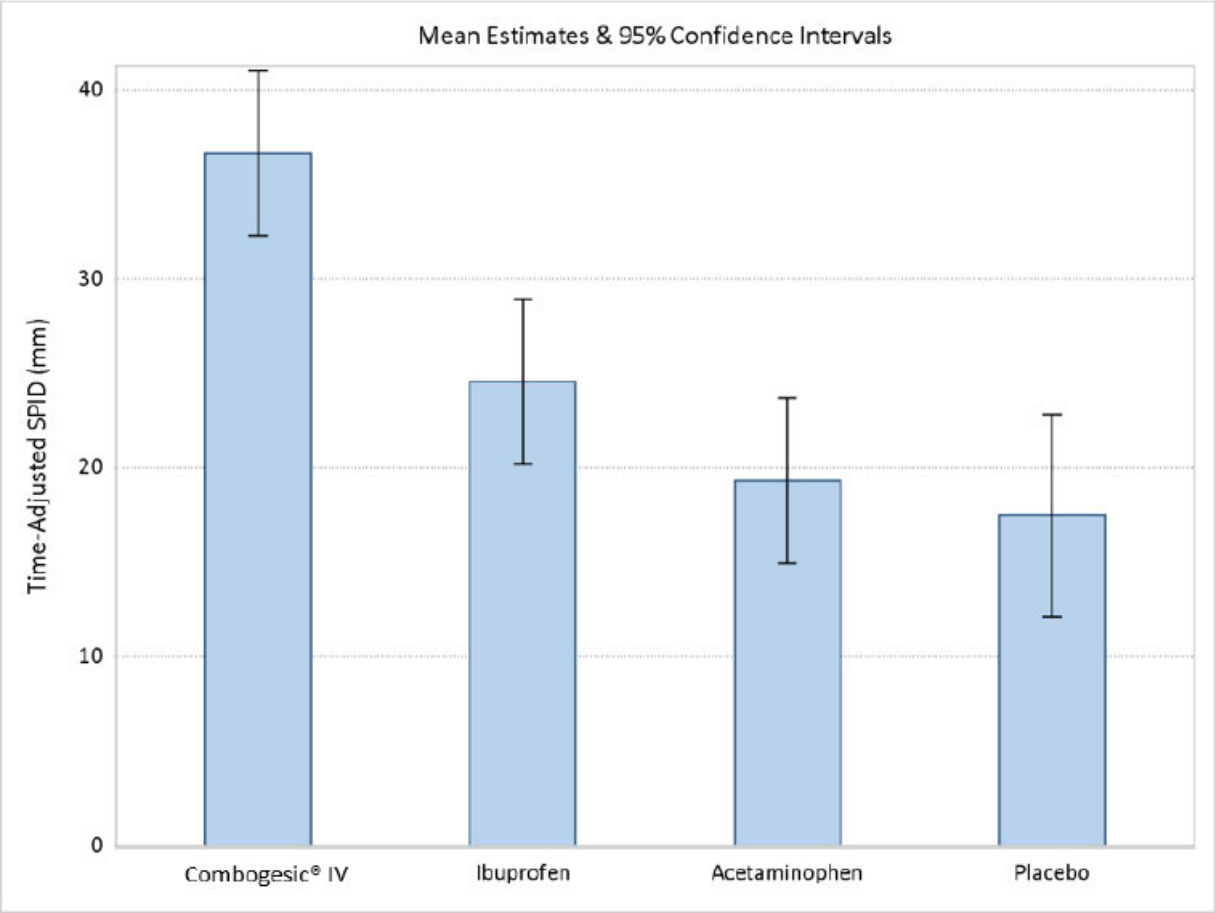
Table 8 Time-adjusted SPID48 with each Pre-Rescue VAS score carried forward up to 2 hours, Study AFT-MXIV-07

	Maxigesic® N=75	Ibuprofen N=76	Acetaminophen N=75	Placebo N=50
N	75	76	75	50
Mean (SE)	37.26 (2.56)	24.99 (2.68)	18.32 (2.00)	17.47 (2.59)
Median	41.14	23.93	16.88	20.09
Min ; Max	-23.21 ; 78.58	-21.09 ; 81.17	-30.03 ; 69.84	-16.91 ; 57.80
Mean Estimate (SE)	36.68 (2.22)	24.57 (2.21)	19.32 (2.22)	17.49 (2.72)
95% Confidence Interval	32.31 ; 41.05	20.23 ; 28.91	14.94 ; 23.70	12.14 ; 22.84
Difference Estimate (SE)	-	12.11 (3.13)	17.36 (3.15)	19.19 (3.51)
95% Confidence Interval	-	5.95 ; 18.27	11.17 ; 23.56	12.28 ; 26.10
p-value	-	<0.001	<0.001	<0.001

Model TASPID = Treatment + Baseline Pain

Source: Applicant's submission (Clinical Study Report; Version 5, page 78)

Figure 2 Mean Estimates & 95% Confidence Intervals for SPID48, Study AFT-MXIV-07



Source: Applicant's submission (Clinical Study Report; Version 5, page 79)

The analysis of the primary efficacy endpoint was also presented by gender, age, and race. Refer to the section titled, Additional Analyses Conducted on the Individual Trial, for these results.

Data Quality and Integrity

An OSI audit was not requested for reasons summarized in Section 4.1.

A Data Fitness assessment was performed in collaboration with the Office of Computational Science (OCS). The data integrity and submission quality were adequate for this review.

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoints were analyzed using all participants in the ITT population that had the appropriate assessment of an endpoint or an estimate. There was no correction for multiple comparisons for the analyses of the secondary endpoints.

Exploratory endpoints are presented below in 'Additional Analyses Conducted on the Individual Trial.'

Dose/Dose Response

Dose response was not studied in this trial.

Durability of Response

The time to the first request for rescue medication was increased for Combogesic IV compared with ibuprofen, acetaminophen, or placebo (median time, 3.32 hours for Combogesic IV, 1.68 hours for ibuprofen IV, 2.08 hours for acetaminophen IV, and 1.18 hours for placebo). However, this secondary endpoint comparison did not have an adjustment for multiplicity.

Persistence of Effect

Persistence of effect over time after treatment is stopped could not be evaluated since efficacy data was not collected beyond the 48-hour treatment period.

Additional Analyses Conducted on the Individual Trial

The following subgroup analyses are exploratory, were performed by the Applicant and then confirmed by the Statistical review team. The text, Table 9, and Figure 11, were reproduced from Dr. Jing Han's primary review.

> The main objective of the exploratory subgroup analysis is to assess consistency across subgroups with respect to the primary analysis results. Because of the exploratory purpose of the subgroup analyses, the p-values are not presented here. The estimated treatment effect in the primary endpoint SPID48 with ROCF 2 hours is consistent across gender, age, and race subgroups. There were no important differences in the results within these subgroups compared to the overall analysis. The statistical team confirmed the applicant's subgroup analysis in the updated clinical study report version 5. Table 9 summarizes the mean estimates and their 95% CI, and Figure 11 illustrates the mean difference estimates and their 95% CI.

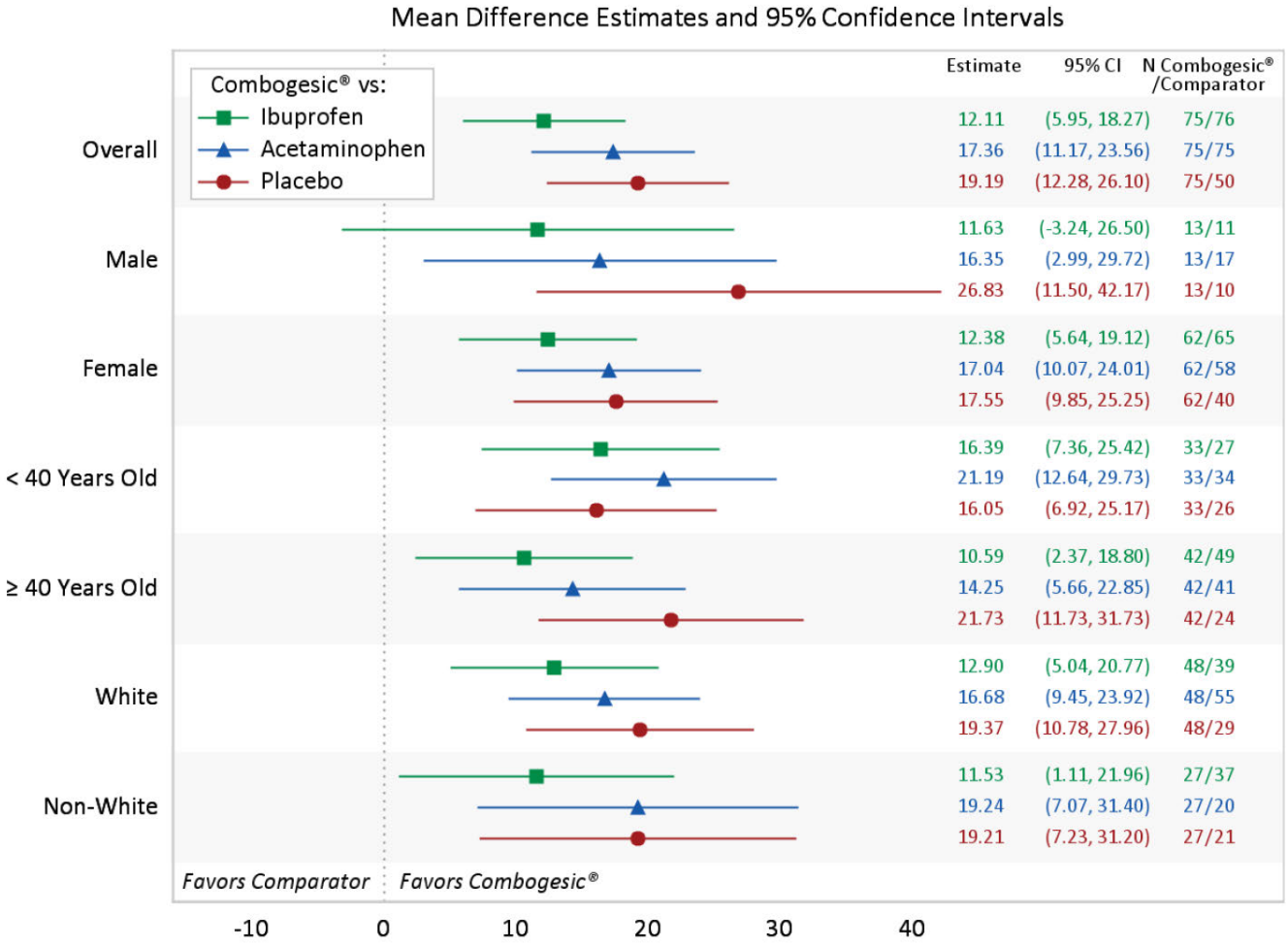
Table 9 Subgroup Analyses by Gender, Age and Race (ITT), Study AFT-MXIV-07

	Maxigesic		Ibuprofen		Acetaminophen		Placebo	
	n	$SPID_{48}$(95% CI)	n	$SPID_{48}$(95% CI)	n	$SPID_{48}$(95% CI)	n	$SPID_{48}$(95% CI)
Gender								
Male	13	34.4 (24.3, 44.4)	11	22.7 (11.8, 33.7)	17	18.0 (9.2, 26.8)	10	7.5 (-4.0, 19.1)
Female	62	37.2 (32.3, 42.0)	65	29.1 (23.0, 35.2)	58	20.1 (15.1, 25.1)	40	19.6 (13.6, 25.6)
Age Group								
<40	33	33.9 (27.9, 40.0)	27	17.5 (10.8, 24.2)	34	12.7 (6.8, 18.7)	26	17.9 (11.0, 24.7)
>=40	42	39.0 (32.9, 45.0)	49	28.4 (22.8, 34.0)	41	24.7 (18.6, 30.8)	24	17.2 (9.2, 25.2)
Race								
White	48	35.8 (30.5, 41.0)	39	22.9 (17.0, 28.7)	55	19.1 (14.1, 24.0)	29	16.4 (9.6, 23.2)
Non-white	27	38.3 (30.4, 46.2)	37	26.8 (20.0, 33.6)	20	19.1 (9.9, 28.3)	21	19.1 (10.1, 28.1)

Source: Clinical Study Report Version 5 (Dated May 20, 2022), Table 47, pages 143-144/188, using ANCOVA model of $TASPID_{48}$ with treatment as the fixed effect and baseline pain as the covariate on the ITT population.

Maxigesic and Combogesic are used interchangeably as they are identical drug products. For additional detail, refer to the footnote on page 17 of this review.
TASPID48 = time-adjusted Summed Pain Intensity Difference from baseline over 48 hours = SPID48

Figure 3 Forest Plots for Subgroup Analyses



Source: Clinical Study Report Version 5 (Dated May 20, 2022), Figure 29, page 144/188, using ANCOVA model of $TASPID_{48}$ with treatment as the fixed effect and baseline pain as the covariate on the ITT population.
TASPID48 = time-adjusted Summed Pain Intensity Difference from baseline over 48 hours = SPID48

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The efficacy of Combogesic IV is supported by a single trial, AFT-MXIV-07. The comprehensive review of AFT-MXIV-07 has been presented in Section 6.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are no additional efficacy considerations for Combogesic IV as it relates to subpopulations. The estimated treatment effect in the primary endpoint (SPID48) with ROCF 2 hours is consistent across subgroups of age, race, and sex. Per the statistical reviewer's conclusions, there were no important differences in the results within these subgroups compared to the overall analysis.

However, with regard to post-market use, it is possible that clinicians may not prescribe Combogesic IV continuously every 6 hours for 48 hours as it was in Studies AFT-MXIV-07 and AFT-MXIV-11. In this clinical scenario, patients who receive Combogesic IV in the post-market setting may not derive the same cumulative benefit in pain intensity differences as those patients studied in clinical trials. Despite that efficacy concern, from a safety standpoint the dosage and administration section of labeling appropriately notes that Combogesic IV infusion should be administered "as necessary" and that the lowest effective dosage for the shortest duration consistent with individual treatment goals should be administered.

7.2.2. Other Relevant Benefits

A relevant benefit to patients and providers will likely be the convenience of a combination of two analgesics with different mechanisms of action to provide post-operative pain relief. With a combination analgesic product, patients will spend less time receiving intravenous infusions and as well as less inconvenience of limited mobility during the infusion period. Less infusion-related time for both patients and bedside nurses is as compared to the labeled infusion times of both Ofirmev (IV acetaminophen) and Caldolor (IV ibuprofen) which are 15 minutes and 30 minutes, respectively.

7.3. Integrated Assessment of Effectiveness

The Applicant has submitted evidence of effectiveness that meets the statutory evidentiary standard. As agreed with the Division in prior interactions, the Applicant submitted one adequate and well-controlled investigation, Study AFT-MXIV-07, in which the results of the analyses support the conclusion that Combogesic IV is superior to the individual components of ibuprofen and acetaminophen as well as placebo. For additional detail on Study AFT-MXIV-07 and the evidence it provides for effectiveness, the reader is referred to Section 6. This evidence supports the Applicant's proposed indication of relief of mild to moderate pain, and for management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary.

The demonstrated efficacy of Combogesic IV has potential to be of clinically meaningful benefit to patients. With Combogesic IV, patients will receive two analgesic drugs within a 15-minute infusion time according to the proposed labeling. Alternatively, if patients received Ofirmev (IV acetaminophen) and Caldolor (IV ibuprofen) the labeled infusion times are 15 minutes and 30 minutes, respectively. Two IV access points would need to be established in order to administer these medications concurrently, which is inconvenient in clinical practice to both patients and practitioners. Therefore, it is likely that in clinical practice, patients would not receive the individual components concurrently. It is also unlikely that patients would receive the individual components back-to-back in a timely manner given the intense demands on the attention of bedside staff in an inpatient setting. Therefore, Combogesic IV offers an advantage of convenience and efficacy over the individual components.

8. Review of Safety

8.1. Safety Review Approach

The clinical safety of Combogesic IV was determined from the following studies:

- AFT-MXIV-07: Phase 3 safety and efficacy study of Combogesic IV in the treatment of acute postoperative pain following bunionectomy surgery
- AFT-MXIV-11: Phase 3 open-label exposure study of Combogesic IV
- AFT-MXIV-01, AFT-MXIV-06, and AFT-MXIV-12: Phase 1 single-dose pharmacokinetic studies

Moreover, during the pre-NDA meeting held between the Agency and Sponsor on July 18, 2018, the Agency agreed that referencing the oral products, Ultracet and Motrin, in support of a 505(b)(2) NDA for Combogesic IV would be acceptable; however, if the exposures of Combogesic IV exceeded that of the individual components of the referenced products (i.e.,

with regard to Cmax) when administered according to approved labeling, additional safety data would be required. In that situation, the Division advised that safety data using Combogesic IV in at least 300 patients with multiple-dose exposures and at least 50 of those patients exposed for at least 5 days would be required.

Because the Applicant referenced Ultracet and Motrin as the listed drugs, and because Cmax of Combogesic IV exceeded that of the individual components of the listed drugs, the Applicant conducted AFT-MXIV-11 to generate the required safety data. AFT-MXIV-11 is an open-label safety and exposure study in which at least 50 patients of a total of 232, were exposed to Combogesic IV for 5 days or more. A primary objective was to elucidate the safety profile of Combogesic IV in patients exposed to Combogesic IV for ≥ 48 hours.

Furthermore, the safety signals of acetaminophen and ibuprofen are well-characterized. Studies AFT-MXIV-07 and AFT-MXIV-11 determined if the incidence of safety signals in Combogesic IV was different compared to that of the individual monotherapies of IV acetaminophen, IV ibuprofen, and to placebo.

8.2 Review of the Safety Database

8.1.1. Overall Exposure

Safety population:
The safety population of 307 patients included patients who were exposed to at least one dose of Combogesic IV in the multiple-dose studies, AFT-MXIV-07 and AFT-MXIV-11. The Phase 1, single-dose studies during which 89 subjects were exposed to Combogesic IV, were excluded from the safety population. Despite this exclusion, the Applicant summarized the adverse events of the Phase 1 single-dose studies for review.

Applicant's pooling strategy:
In the Pre-NDA meeting on July 18, 2018, the Agency advised the Applicant to pool safety data for the Integrated Summary of Safety as follows:

1) single-dose studies (AFT-MXIV-01, AFT-MXIV-06, and AFT-MXIV-12)

2)multiple-dose studies (AFT-MXIV-07 and AFT-MXIV-11)

The Division disagreed with the Sponsor's initial proposal to (b) (4)

(b) (4)

Exposure of Safety Population:
The following Tables show a total of 307 subjects exposed to Combogesic IV with 75 subjects exposed in Study AFT-MXIV-07 and 232 subjects exposed in study AFT-MXIV-11. AFT-MXIV-07 had a treatment period of 48 hours, while AFT-MXIV-11 had a treatment period of 48 hours to 5 days, of which 50 participants were treated for 5 days.

Table 10 Number of subjects in the pooled safety population (intravenous formulation) by study and treatment group

Clinical Study	Combogesic® IV	Ibuprofen	Acetaminophen	Placebo	Total
AFT-MXIV-07	75	76	75	50	276
AFT-MXIV-11	232	-	-	-	232
Total	**307**	**76**	**75**	**50**	**508**

Source: Applicant's submission (Integrated Summary of Safety, page 11)

Table 11 Exposure to the study drugs during AFT-MXIV-07, by number of doses

Number of Doses n (%)	Combogesic® IV N=75	Ibuprofen IV N=76	Acetaminophen IV N=75	Placebo N=50	Total N=276
8	75 (100%)	73 (96.1%)	73 (97.3%)	48 (96%)	269 (97.5%)
7					
6		1 (1.3%)		1 (2%)	2 (0.7%)
5			1 (1.3%)	1 (2%)	2 (0.7%)
4					
2		2 (2.6%)	1 (1.3%)		3 (1.1%)

Source: Applicant's submission (Summary of Clinical Safety, page 12)

Table 12 Exposure to the study drugs during AFT-MXIV-11, by number of doses

Number of Doses n (%)	Combogesic® IV N=232
20	50 (21.6%)
8	169 (72.8%)
7	3 (1.3%)
6	1 (0.4%)
5	1 (0.4%)
4	3 (1.3%)
3	2 (0.9%)
2	1 (0.4%)
1	2 (0.9%)

Source: Applicant's submission (Summary of Clinical Safety, page 12)

Table 13 shows 89 subjects exposed to full-dose Combogesic IV in three Phase 1 studies, AFT-MXIV-01, AFT-MXIV-06, and AFT-MXIV-12. Again, these subjects were not included in the Applicant's safety population.

Table 13 Exposure to study drugs in Phase 1 studies of Combogesic IV

Study	APAP/IBU	IBU	APAP	# subjects
AFT-MXIV-01 (5 period)	1000/300 (*i.v.*)			29
	500/150 (*i.v.*)			30
	500/150 x2 (*p.o*)			30
			1000 (*i.v.*)	29
		300 (*i.v.*)		29
AFT-MXIV-06 (4 period)	1000/300 (*i.v.*)			30
	325/97.5 x 3 (*p.o*)			30
			1000 (*i.v.*)	30
		400 (*i.v.*)		30
AFT-MXIV-12 (3 period)	1000/300 (*i.v.*)			30
			325 x 2 (*p.o*)*	30
		800 (*p.o*)		30

* With tramadol hydrochloride 37.5 mg/tablet

Source: Applicant's submission (Summary of Clinical Safety, page 12)

8.1.2. Relevant characteristics of the safety population:

Refer to Section 6.1.2, Study Results, for additional information on the demographic characteristics of AFT-MXIV-07. There were no large differences between treatment groups for male and female sex; however, significantly more female participants were enrolled than male participants, 81.5% vs. 18.5%, respectively, which is attributed to the bunionectomy pain model used in Study AFT-MXIV-07. Moreover, the baseline characteristics were comparable across the four treatment groups.

Phase 1 studies mainly consisted of healthy, young, white males. The pooled data for the safety population, Studies AFT-MXIV-07 and AFT-MXIV-11, shows no large differences between treatment groups.

Notably, patients aged 75 and over made up 5.2% of the safety database and therefore, were not adequately represented. This demographic included 16 subjects from Study AFT-MXIV-11, the open-label safety and exposure study.

Reviewer's comment: While there were no large differences in treatment groups, the pooled data show imbalances overall in race and sex. Despite these imbalances within the study, but

not between treatment groups, these imbalances are likely reflective of real-world enrollment for these types of pain models and therefore, the safety data still allow for generalizability of the safety findings.

Table 14 Demographic characteristics of participants in studies of Combogesic IV

	AFT-MXIV-01	AFT-MXIV-06	AFT-MXIV-12	AFT-MXIV-07	AFT-MXIV-11
	N=30	*N=30*	*N=30*	*N=276*	*N=232*
Age					
Mean	23.9	24.8	30	42.4	53.4
Min ; Max	19 ; 43	19 ; 44	19 ; 49	18 ; 65	19 ; 87
Race*					
American Indian or Alaska Native	-	-	-	-	3
Asian	-	3	-	9	1
Black or African American	-	1	-	92	91
Multiple	-	1	-	4	3
Native Hawaiian or other Pacific Islander	-	1	-	-	3
White	30	24	30	171	131
Gender					
Female	7	16	-	225	144
Male	23	14	30	51	88

Source: Applicant's submission (Integrated Summary of Safety Report, page 15)

Table 15 Demographic characteristics of participants in the pooled safety population (intravenous formulation)

	Combogesic® IV N=307	Ibuprofen N=76	Acetaminophen N=75	Placebo N=50	Total N=508
Age (Years)					
N	307	76	75	50	508
Mean (SD)	50.7 (15.3)	43.3 (12.3)	41.9 (12.5)	41.7 (12.7)	47.4 (14.8)
Median	52.0	44.5	41.0	38.5	47.5
Min ; Max	19 ; 87	18 ; 63	19 ; 65	20 ; 65	18 ; 87
18-24 Years	12 (3.9%)	7 (9.2%)	6 (8.0%)	3 (6.0%)	28 (5.5%)
25-34 Years	48 (15.6%)	13 (17.1%)	19 (25.3%)	14 (28.0%)	94 (18.5%)
35-44 Years	52 (16.9%)	18 (23.7%)	18 (24.0%)	11 (22.0%)	99 (19.5%)
45-54 Years	53 (17.3%)	20 (26.3%)	17 (22.7%)	11 (22.0%)	101 (19.9%)
55-64 Years	80 (26.1%)	18 (23.7%)	13 (17.3%)	10 (20.0%)	121 (23.8%)
65-74 Years	46 (15.0%)	0 (0.0%)	2 (2.7%)	1 (2.0%)	49 (9.6%)
≥ 75 Years	16 (5.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (3.1%)
Sex					
Male	101 (32.9%)	11 (14.5%)	17 (22.7%)	10 (20.0%)	139 (27.4%)
Female	206 (67.1%)	65 (85.5%)	58 (77.3%)	40 (80.0%)	369 (72.6%)
Race					
White	179 (58.3%)	39 (51.3%)	55 (73.3%)	29 (58.0%)	302 (59.4%)
Black or African American	114 (37.1%)	32 (42.1%)	17 (22.7%)	20 (40.0%)	183 (36.0%)
Asian	4 (1.3%)	3 (3.9%)	2 (2.7%)	1 (2.0%)	10 (2.0%)
Native Hawaiian or Other Pacific Islander	3 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)
American Indian or Alaska Native	3 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)
Multiple	4 (1.3%)	2 (2.6%)	1 (1.3%)	0 (0.0%)	7 (1.4%)
Ethnicity					
Hispanic or Latino	26 (8.5%)	15 (19.7%)	18 (24.0%)	7 (14.0%)	66 (13.0%)

Not Hispanic or Latino	279 (90.9%)	60 (78.9%)	56 (74.7%)	41 (82.0%)	436 (85.8%)
Not Reported	1 (0.3%)	1 (1.3%)	1 (1.3%)	2 (4.0%)	5 (1.0%)
Unknown	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Height (cm)					
N	307	76	75	50	508
Mean (SD)	167.8 (9.9)	166.3 (10.0)	166.8 (8.9)	166.7 (7.9)	167.3 (9.6)
Median	166.5	164.5	165.1	166.8	166.0
Min ; Max	139.7 ; 200.0	151.0 ; 199.0	149.9 ; 191.0	152.4 ; 182.9	139.7 ; 200.0
Weight (kg)					
N	307	76	75	50	508
Mean (SD)	83.0 (17.3)	75.6 (17.0)	74.2 (15.6)	79.5 (15.5)	80.2 (17.2)
Median	81.6	73.3	74.0	75.2	78.0
Min ; Max	45.0 ; 132.4	52.0 ; 131.0	46.0 ; 112.9	52.2 ; 111.0	45.0 ; 132.4
BMI (kg/m²)					
N	307	76	75	50	508
Mean (SD)	29.4 (5.3)	27.2 (5.1)	26.6 (5.3)	28.5 (4.8)	28.6 (5.3)
Median	28.9	26.7	26.0	27.7	28.1
Min ; Max	18.7 ; 44.6	18.0 ; 39.8	17.1 ; 40.0	20.8 ; 39.3	17.1 ; 44.6

Source: Applicant's submission (Integrated Summary of Safety Report, page 16)

8.1.3. Adequacy of the safety database:

The safety population is an adequate representation of the treatment population of subjects with post-operative pain due to bunionectomy, non-laparoscopic general surgery, orthopedic, or plastic surgery.

8.2. Adequacy of Applicant's Clinical Safety Assessments

8.2.1. Issues Regarding Data Integrity and Submission Quality

A Data Fitness assessment was performed in collaboration with the Office of Computational Science (OCS). The data integrity and submission quality were adequate for this review and had no effect on the safety review.

8.2.2. Categorization of Adverse Events

AFT-MXIV-07
Adverse events (AE) and serious adverse events were defined in the study protocol and were defined appropriately. The protocol did not contain a definition for "treatment emergent" adverse events. The severity of AEs and relationship to study drug was defined, however, a grading scale to assess severity was not identified.

As AFT-MXIV-07 used a bunionectomy pain model, the Sponsor specified the following in the study protocol:

> "Normal postoperative sequelae, including pain, itching, bruising, numbness, bleeding, burning, tingling, and edema at the surgical site, will not be recorded as AEs unless they are of greater severity and/or intensity than would be expected in the surgeon/investigator's opinion."

The collection of adverse event data continued through the final follow-up visit that occurred within 5-9 days after surgery.

AFT-MXIV-11
Adverse events (AE) and serious adverse events were defined in the study protocol and were defined appropriately. The study protocol also provided definitions for “treatment emergent” and “treatment related” adverse events. Treatment-emergent adverse events (TEAEs) are defined as events that emerge during treatment, having been absent pre-treatment, or that worsen relative to the pre-treatment status (ICH E9). Treatment-emergent adverse events that are considered by the Investigator to be “probably” or “definitely” are treatment-related adverse events (TRAEs). These appear to be defined appropriately.

The severity of AEs and relationship to study drug was defined by a sponsor-proposed scale; alternate grading scales were not used.

TEAEs that occurred at any timepoint during the treatment period were coded to MedDRA System Organ Class Code and Preferred Term and tabulated as frequencies and percentages.

The collection of adverse event data continued within 7 ± 2 days after the last dose of study drug at which time any additional adverse event and concomitant medication data was collected.

8.3.3 **Routine Clinical Tests**

AFT-MXIV-07
Routine clinical tests were collected at various time points post-operatively.
Vital signs were evaluated at Time 0, after the first dose on Day 1, then each morning prior to dosing, and at discharge or early termination. Clinical laboratories and urinalyses were performed at screening only and not performed prior to discharge from the inpatient unit. Physical exams were performed on the day of surgery only.

AFT-MXIV-11
Routine clinical tests were collected at various time points post-operatively.
Vital signs were evaluated at Time 0, prior to and following first dose infusion on Day 1, then each morning prior to dosing and at discharge or early termination. ECGs were conducted prior to surgery, at 48 hours after the first dose and after the last dose/prior to discharge.
Physical exams were performed prior to surgery on Day 1 if screening was not performed within 7 days of surgery. Physical exams were then completed after the last dose, prior to discharge, and at the follow-up visit (7 +/- 2 days after last dose). Urinalyses and clinical labs were performed at screening, Day 1 prior to surgery, and prior to discharge.

8.3. Safety Results

8.3.1. Deaths

There were no deaths in any clinical trials conducted with Combogesic IV.

8.3.2. Serious Adverse Events

No SAEs were reported for the pivotal Phase 3 efficacy study, AFT-MXIV-07.

Two subjects experienced SAEs during the safety and exposure study, AFT-MXIV-11, which were hypotension and intestinal obstruction. Both subjects required hospitalization and resulted in discontinuation from the study.

The following are concise summaries from the Applicant's narrative summaries provided in the Summary of Clinical Safety:

1. SAE of hypotension: This occurred in a 67-year-old female s/p abdominoplasty surgery who developed hypotension (primary event), diaphoresis, nausea, dizziness, shortness of breath and inability to control her bowel approximately 2 hours after receiving her second dose of Combogesic IV. She was hospitalized and the SAE was considered resolved on the same day.
2. SAE of intestinal obstruction: This occurred in a 69-year-old male s/p knee replacement surgery. He completed the 48-hour treatment period consisting of 8 doses. Approximately 24 hours after the last dose, he developed symptoms of intestinal obstruction and was hospitalized. He was discharged from the hospital nine days after admission and was fully recovered with no additional adverse events by telephone the following day. The patient was considered discontinued from the study due to the SAE since he did not complete the in-person follow-up visit.

One SAE occurred across the three Phase 1 studies in AFT-MXIV-01. A subject experienced a bilateral ankle fracture from a fall while hiking. This SAE occurred during the washout period of the study 4 days after having received a half-dose of Combogesic IV. The subject was hospitalized, underwent surgery and was withdrawn from the study.

These 3 SAEs are unlikely to be related to study drug.

8.3.3. Dropouts and/or Discontinuations Due to Adverse Effects

From the Applicant's Summary of Clinical Safety regarding AFT-MXIV-11:

> "The safety population (n = 232) included all participants who received at least one dose of the study drug. There were 17 early withdrawals, 14 of which were during the treatment period. These included 6 discontinuations due to AEs, each of which were considered 'not related' or 'unlikely' related to the study drug."

As noted in Table 22, none of the participants that were withdrawn from AFT-MXIV-07 were from the Combogesic IV group. Six participants withdrew from AFT-MXIV-11, the open-label safety and exposure study, due to AEs, one of which occurred during the follow-up period (SAE: intestinal obstruction).

Table 16 Tabulation of individual discontinuations due to AEs in the pooled safety population (intravenous formulation)

Study	Subject Identification	Treatment	AE MedDRA preferred Term
AFT-MXIV-07	(b) (6)	ACETAMINOPHEN	Pyrexia
AFT-MXIV-07		IBUPROFEN	Angioedema
AFT-MXIV-07		IBUPROFEN	Infusion site pain
AFT-MXIV-11		COMBOGESIC® IV	*Primary event:* Tachycardia *Secondary event:* Chest pain
AFT-MXIV-11		COMBOGESIC® IV	Primary event: Hypotension *Secondary events:* Nausea; Dizziness; Hyperhidrosis; Anal incontinence; Dyspnoea
AFT-MXIV-11		COMBOGESIC® IV	Intestinal obstruction
AFT-MXIV-11		COMBOGESIC® IV	Infusion site extravasation
AFT-MXIV-11		COMBOGESIC® IV	Infusion site pain
AFT-MXIV-11		COMBOGESIC® IV	Confusional state

Source: Applicant's submission (ISS, page 40)

Additionally, the Sponsor notes that in order to evaluate the local tolerance to study medication at the infusion site, no other drug will be administered through the cannula dedicated to the infusion of Combogesic IV.

8.3.4. Significant Adverse Events

As presented in the next section (8.3.5).

8.3.5. Treatment Emergent Adverse Events and Adverse Reactions

The most common TEAEs in the safety population are presented in the table below.

Table 17 shows that infusion site pain occurred with higher frequency in the Combogesic IV treatment group compared to the ibuprofen, acetaminophen, and placebo treatment groups.

Table 17 Common TEAEs (occurring in ≥ 2% of Combogesic® IV-treated participants) in safety population (intravenous formulation) by Preferred Term

Preferred Term	Combogesic® IV N=307		Ibuprofen N=76		Acetaminophen N=75		Placebo N=50		Total N=508	
	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events
Any Class, Any Term	182 (59.3%)	436	58 (76.3%)	131	45 (60.0%)	112	39 (78.0%)	110	324 (63.8%)	789
Infusion site pain	54 (17.6%)	64	7 (9.2%)	8	0 (0.0%)	0	1 (2.0%)	1	62 (12.2%)	73
Nausea	50 (16.3%)	69	26 (34.2%)	33	25 (33.3%)	28	16 (32.0%)	23	117 (23.0%)	153
Dizziness	22 (7.2%)	30	7 (9.2%)	8	7 (9.3%)	8	9 (18.0%)	11	45 (8.9%)	57
Constipation	22 (7.2%)	23	4 (5.3%)	4	4 (5.3%)	4	4 (8.0%)	4	34 (6.7%)	35
Infusion site extravasation	20 (6.5%)	21	5 (6.6%)	5	2 (2.7%)	2	7 (14.0%)	8	34 (6.7%)	36
Vomiting	19 (6.2%)	29	5 (6.6%)	8	11 (14.7%)	12	1 (2.0%)	1	36 (7.1%)	50
Headache	17 (5.5%)	19	5 (6.6%)	5	5 (6.7%)	5	10 (20.0%)	11	37 (7.3%)	40
Somnolence	12 (3.9%)	12	6 (7.9%)	7	6 (8.0%)	7	3 (6.0%)	4	27 (5.3%)	30
Pruritus	9 (2.9%)	9	4 (5.3%)	4	3 (4.0%)	3	2 (4.0%)	2	18 (3.5%)	18
Polyuria	9 (2.9%)	9	1 (1.3%)	1	0 (0.0%)	0	2 (4.0%)	2	12 (2.4%)	12
Procedural nausea	8 (2.6%)	8	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	8 (1.6%)	8
Hyperhidrosis	6 (2.0%)	6	4 (5.3%)	4	4 (5.3%)	4	3 (6.0%)	4	17 (3.3%)	18

Source: Applicant's submission (ISS, page 20)

In AFT-MXIV-07, common AEs were AEs that were reported in more than 10% of the 276 participants randomized to treatment in this study and are summarized in the following Table.

AEs coded to Gastrointestinal Disorders or Nervous System Disorders accounted for 60% of AEs (GI: 190, NS: 107, Total: 493). The Applicant notes that this is consistent with the postoperative setting and what has been observed in their previous postoperative pain studies conducted with the oral FDC 500/150 (acetaminophen/ibuprofen).

Notably, AFT-MXIV-07 showed that the incidence of vomiting was higher in the Combogesic IV group compared with the ibuprofen and placebo groups, but not the acetaminophen group. The Applicant suggests that the vomiting reported by patients in the Combogesic IV group is attributable to the acetaminophen component of the combination, rather than a unique effect. There were no other differences in the incidence of common AEs between the Combogesic IV group and the other groups for Study AFT-MXIV-07. However, vomiting was not classified as a common TEAE in Study AFT-MXIV-11. Moreover, vomiting occurred at a frequency that was less than the monotherapies in the safety population (pooled data from multiple-dose studies).

Table 18 Common Treatment-Emergent Adverse Events, Study AFT-MXIV-07

SOC/PT	Combogesic IV (n=75)	Ibuprofen (n=76)	APAP (n=75)	Placebo (n=50)	Total (n=276)
Any Class, Any Term	69.3%	76.3%	60%	78%	70.3%
Nausea	29.3%	34.2%	33.3%	32%	32.2%
Vomiting	**21.3%**	6.6%	**14.7%**	2%	12%
Dizziness	17.3%	9.2%	9.3%	16%	12.7%
General disorders/administration site conditions	20%	22.4%	10.7%	26%	19.2%

Skin and SQ tissue disorders	14.7%	19.7%	13.3%	14%	15.6%

Source: Reviewer-generated Table from Applicant's submission (Summary of Clinical Safety, page 18)

In AFT-MXIV-11, the most common TEAEs (occurring in ≥ 2% of the study population) are noted in the Table below. The most common TEAEs were related to infusion site pain, nausea, and infusion site extravasation. The system organ classes of these common AEs (administration site, gastrointestinal, and nervous) were similar to AFT-MXIV-07. Of the remaining common TEAEs, the Applicant offers that while they were not previously observed in patients in AFT-MXIV-07, none of these TEAEs are considered novel or significant safety concerns as they have been observed in previous clinical trials with the Applicant's oral FDC 500/150 (acetaminophen/ibuprofen) and/or are known effects of acetaminophen or NSAIDs.

Table 19 Common TEAEs Occurring during the Treatment Period in ≥ 2% of Study Participants, Study AFT-MXIV-11

Preferred Term	Combogesic® IV N=232	
	Patients	Events
Infusion site pain	44 (19.0%)	49
Nausea	28 (12.1%)	32
Infusion site extravasation	18 (7.8%)	19
Constipation	18 (7.8%)	19
Headache	13 (5.6%)	13
Dizziness	9 (3.9%)	12
Polyuria	9 (3.9%)	9
Procedural nausea	8 (3.4%)	8
Somnolence	7 (3.0%)	7
Diarrhoea	5 (2.2%)	5
Alanine aminotransferase increased	5 (2.2%)	5

Source: Applicant's submission (Summary of Clinical Safety, page 19)

Lastly, of the 89 subjects who received full-dose Combogesic IV in the Phase 1 pharmacokinetic studies, only two subjects experienced adverse events within 24 hours of being dosed; these AEs included one incident of nausea and one incident of upper respiratory tract infection.

8.3.6. Laboratory Findings

The Applicant provided a pooled summary table of shifts to abnormal for the three single-dose PK studies (AFT-MXIV-01, -06 and -12). Out of 89 subjects in the full-dose Combogesic IV group, only 1 subject had a shift from normal to high in AST; there were no shifts in other liver function tests. There were normal to low shifts in hemoglobin and hematocrit in the full-dose Combogesic IV group that were not considered clinically significant by the investigator.

For multiple-dose studies, the Applicant noted that AFT-MXIV-07 was not "...specifically designed to detect any abnormal laboratory values which might be associated with using acetaminophen and ibuprofen in a fixed combination." Labs values were checked at screening only.

However, AFT-MXIV-11 included an assessment of clinical laboratory values at baseline and at the end of treatment. Of 228 patients with both a baseline and an end-of-treatment evaluation, 68 and 65 had normal to low shifts in hemoglobin and hematocrit, respectively. In this open-label, uncontrolled study, these subjects underwent non-laparoscopic general, orthopedic or plastic surgery. Only three subjects had shifts resulting in values considered clinically significant, all of which were classed as TEAEs 'not related' to the study drug.

Shifts in liver function tests of ALT and AST from normal to < 3x ULN occurred in 10.5% and 9.6% of subjects with available evaluations, respectively. Elevations of AST and ALT to > 3x ULN occurred in 2.6% and 2.2% (n=5/232) of subjects with available evaluations, respectively. Elevations were transient, as levels reduced to normal, or to lower levels, in participants with repeated laboratory tests conducted at follow-up.

The Applicant notes that elevations in hepatic enzymes observed in AFT-MXIV-11 occur at a comparable frequency to similar products containing ibuprofen alone. The Applicant offers that approved labeling for ibuprofen products in the United States states that elevations in transaminases at < 3x ULN may occur in up to 15% of NSAID-treated patients including ibuprofen, and elevation of >3x ULN have been reported in approximately 1% of NSAID-treated patients in clinical trials.

Importantly, with review of the pooled safety data between AFT-MXIV-07 and AFT-MXIV-11, it appears that the majority of elevations of AST and ALT occurred on Day 2 of treatment with Combogesic IV and did not occur in any other treatment group.

Moreover, the types and incidence of shifts in hematology and chemistry parameters were comparable in subjects exposed for ≥ 5 days compared to those exposed for ≤ 48 hours. The types and incidence of TEAEs observed later in the study at Days 4-5 were comparable to those observed earlier in the study at Days 1-2. Increases in platelets occurred in 6 subjects treated for ≥ 5 days compared to none in subjects treated for ≤ 48 hours, however none of these elevations resulted in platelet values considered clinically significant.

Reviewer's comment: It appears that elevations in transaminases > 3x ULN are occurring at a slightly higher but comparable frequency in Study AFT-MXIV-11 compared to what is in approved labeling for ibuprofen products (1% vs. 2.2-2.6%). Since AFT-MXIV-11 is a single-arm study of Combogesic IV, no direct comparisons can be made to acetaminophen or ibuprofen. The elevations in transaminases do not appear to be occurring with longer exposures (5 days). The proposed labeling for Combogesic IV notes that laboratory monitoring should be considered as clinically indicated since GI bleeding, hepatotoxicity and renal injury can occur without warning.

8.3.7. Vital Signs

There were no clinically significant changes from baseline in vital signs in Study AFT-MXIV-07 and Study AFT-MXIV-11 at each time point assessed.

8.3.8. Electrocardiograms (ECGs)

Electrocardiograms (ECGs) were not performed in Study AFT-MXIV-07.

ECG was performed in Study AFT-MXIV-11 at screening (within 30 days before surgery), on Day 1 (if screening was not performed within 7 days of surgery), and at 48 hours after the first dose and after the last dose/prior to discharge. A proportion of subjects (7.8%) experienced a shift from normal to abnormal (not clinically significant), however a greater proportion (19.0%) experienced a shift from abnormal (not clinically significant) to normal. Additionally, the profile of shifts from baseline to end of treatment was comparable between subjects exposed for ≤ 48 hours compared to those exposed for ≥ 5 days. There were no shifts resulting in abnormal readings that were also considered clinically significant by the investigator.

8.3.9. QT

Not applicable; no thorough QT clinical trials were conducted.

8.3.10. Immunogenicity

Not applicable; there are no immunogenicity safety issues related to Combogesic IV.

8.4. Analysis of Submission-Specific Safety Issues

There were no submission-specific safety issues for this application.

8.5. Safety Analyses by Demographic Subgroups

No specific safety analyses were performed by demographic subgroups for the two Phase 3 clinical studies included in the determination of safety of Combogesic IV, AFT-MXIV-07 and AFT-MXIV-07.

8.6. Specific Safety Studies/Clinical Trials

No specific safety studies were conducted were conducted to evaluate a specific safety concern for this application.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

Refer to the Pharmacology and Toxicology review.

8.7.2. Human Reproduction and Pregnancy

There have been no adequate and well-controlled studies of Combogesic IV in pregnant women.

8.7.3. Pediatrics and Assessment of Effects on Growth

There were no events of pediatric exposure reported in the submission. Combogesic IV was not studied in subjects younger than 18 years of age.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no overdose, withdrawal and rebound studies conducted for this submission.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

The Applicant provided a safety update of Combogesic IV (referred to as Maxigesic IV) including an updated Periodic Safety Update Report (PSUR) detailing the worldwide post-marketing safety surveillance for this product. The PSUR covered a reporting period of approximately 17 months (from June 21, 2020, to November 30, 2021). Between 2019 and 2020, Maxigesic IV (paracetamol 1000 mg/ibuprofen 300 mg/100 mL intravenous infusion) was approved and marketed in Australia, New Zealand, United Arab Emirates, Germany, and Austria. Maxigesic IV and its other product names have since received marketing registration approval in numerous European Union and non-European Union countries. No new safety signals or risks were identified during the reporting period.

8.8.2. Expectations on Safety in the Postmarket Setting

As stated above, the drug-drug combination of Combogesic IV is marketed in several countries outside the United States. No new safety signals were identified during the reporting period covered in the PSUR. The individual components, acetaminophen and ibuprofen, are FDA-approved as an injection formulation for treatment of pain and have well-characterized safety profiles. No concerning safety issues were identified during the review when acetaminophen and ibuprofen were administered concurrently as Combogesic IV.

Combogesic IV will be administered in an inpatient setting with oversight by medical professionals. At this time, there are no concerns or potentially important differences in how the drug will be administered in the postmarket setting compared to its use in clinical studies. Though Combogesic IV could potentially be used off-label for management of fever, there are no anticipated safety concerns at this time.

Notably, patients aged 75 and over made up 5.2% of the safety database and therefore, were not adequately represented. This demographic included 16 subjects from Study AFT-MXIV-11, the open-label safety and exposure study.

8.8.3. Additional Safety Issues From Other Disciplines

Nonclinical deficiencies will result in a Complete Response for this application. The nonclinical deficiencies include inadequate data from leachable studies to permit substantive toxicological risk assessment. In order to resolve this deficiency, the nonclinical review team requests that the Applicant submit a revised toxicological risk assessment for all leachable compounds detected above the 5 mcg/day threshold.

8.9. Integrated Assessment of Safety

Combogesic IV (acetaminophen 1000 mg/ibuprofen 300 mg) is a drug-drug combination product consisting of two marketed drug products of an approved formulation and route of administration, Ofirmev (IV acetaminophen) and Caldolor (IV ibuprofen), at maximum total daily doses less than (ibuprofen) or equal (acetaminophen) to doses in approved labeling. The proposed maximum total daily dose of Combogesic IV is 4000 mg acetaminophen and 1200 mg ibuprofen in 24 hours. Additionally, there are no drug-drug interactions between acetaminophen and ibuprofen.

The clinical development program generated safety data from 307 patients treated with Combogesic IV from two Phase 3 multiple-dose studies (AFT-MXIV-07 and AFT-MXIV-11), including 50 subjects exposed for 5 days. Safety data were also generated from 89 subjects exposed to single doses of Combogesic IV from three Phase 1 single-dose studies.

The safety data generated from the two Phase 3 multiple-dose studies did not show any serious safety signals including no strong evidence of overlapping toxicities between acetaminophen and ibuprofen when dosed for 48 hours or 5 days.

Infusion site pain occurred at a higher rate in the Combogesic IV treatment arm compared to the comparator arms among the safety population.

From the clinical standpoint, there were no serious safety concerns identified in the course of this review. However, Combogesic IV is recommended for a Complete Response due to the Applicant not providing adequate data from the leachable studies to permit a substantive toxicological risk assessment. In order to resolve the deficiency, the Applicant must submit a revised toxicological risk assessment for all leachable compounds detected above the 5 mcg/day threshold.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this application as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The label is being reviewed. The following sections have been amended and/or modified: Contraindications, Warning and Precautions, Adverse Reactions, Use in Specific Populations, and Clinical Studies.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

12. Postmarketing Requirements and Commitments

In order to comply with the Pediatric Research Equity Act (PREA), the Applicant submitted a pediatric study plan. The Agency agreed with a deferral of all assessments of safety and effectiveness of Combogesic IV for under 2 years and between 2 to 17 years in the communication dated March 9, 2020.

Deferral of pediatric studies was requested for the following reasons by age group:

For ages 2 to less than 17:
In 2019, the sponsor noted that it was not possible to begin the study in 2 - < 17 years until the Phase 3 safety study in adults, AFT-MXIV-11 was completed.

For ages less than 2 years:
A juvenile animal study is needed prior to the submission of a protocol for the clinical study in 0 -2 years. The sponsor anticipated difficulties in recruiting sufficient patients in the birth – 3 month age group, because although intravenous acetaminophen appears to be a safe and effective analgesic in neonates/infants, NSAIDs such as ibuprofen are restricted for pharmacologic closure of patent ductus arteriosus, and there are safety concerns about its use in this age group. Importantly, ibuprofen is not an approved analgesic in infants younger than 3 or 6 months, depending on the jurisdiction.

Of note, the Applicant submitted an updated version of the previously agreed PSP with their NDA submission detailing that timelines for their proposed studies were pushed back by 1 year for feasibility/dose-ranging, juvenile animal studies, and the clinical study in subjects aged 2- < 17. The Division sent an IR to the Applicant asking for an explanation for the delay in timelines. The Applicant noted that the delays are due to multiple extended COVID-19-related lockdowns and disruptions in both New Zealand and the USA. The agreed PSP was finalized in March 2020, the beginning of COVID-19-related lockdowns. The Division agrees with the Applicant's explanation and the proposed changes in timelines of nonclinical and clinical pediatric assessments.

PREA PMRs:

Non-Clinical:

(b) (4)

2.A juvenile animal study to address the safety of acetaminophen and ibuprofen on the development of potential target organs such as the liver, kidney, lung, and testes before initiation of a clinical study of Combogesic® IV in neonates/infants from birth to 2 years of age.

a. Submission of protocol for Juvenile Animal Study to FDA: December 2022
b. Initiation of Juvenile Animal Study: March 2023
c. Completion of Juvenile Animal Study: September 2023
d. Final report date: December 2023

Clinical:

1) A pharmacokinetic and safety study of Combogesic® IV (acetaminophen 1000 mg + ibuprofen 300 mg, per 100 mL solution for intravenous infusion) in pediatric patients aged 2 to less than 17 years for the short-term management of mild to moderate acute pain.

a. Submission of protocol: Q3 2022
b. Initiation of study: Q4 2022
c. Completion of study: Q3 2023
d. Submission of final report: Q4 2023

2) An efficacy, safety, and pharmacokinetic study of Combogesic® IV (acetaminophen 1000 mg + ibuprofen 300 mg, per 100 mL solution for intravenous infusion) in infants from birth to less than 2 years of age for the short-term management of mild to moderate acute pain.

a. Submission of protocol: March 2023
b. Initiation of study: June 2023
c. Completion of study: September 2025
d. Submission of final report: December 2025

13. Appendices

13.1. References

Not Applicable.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): AFT-MXIV-01, AFT-MXIV-06, AFT-MXIV-12, AFT-MXIV-07, AFT-MXIV-11

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 14 investigators are listed below		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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 ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (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 ☐	No ☐ (Request explanation from Applicant)

Site Name Investigator
Study: AFT-MXIV-11 Combogesic IV orthopedic, general or plastic surgery Study
CRG Dr. Ira Gottlieb
CH Dr. Gregory Ruff
SCT Dr. Simon Carson
CGM Dr. Nigel Gilchrist

Study: AFT-MXIV-7 Combogesic IV bunionectomy pain Study
ORI Dr. Stephen Daniels
CRG Dr. Ira Gottlieb

Study: AFT-MXIV-12 Combogesic IV PK (test & reference products) Study
IPRC Dr. Majdi Abu Awida
IPRC Dr. Usama Harb
IPRC Mohammed Bader (study director)
IPRC Dr Naji Najib (IPRC Chairman)

Study: AFT-MXIV-06 Combogesic IV PK (commercial US brands) Study
CCST Dr Richard Robson
CCST Dr. Anne Dick
CCST Dr. Alex Cole
CCST Dr. Chris Wynne

Study: AFT-MXIV-01 Combogesic IV (BA/BE IV/oral) Study
CCST Dr Richard Robson

CCST Dr. Anne Dick
CCST Dr. Devione Wakka
CCST Dr. Chris Wynne

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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