CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210583Orig1s000

CLINICAL REVIEW(S)

Clinical Review and Decisional Memo
Robert Shibuya, MD and Sharon Hertz, MD
NDA 210583, Resubmission
Anjeso (meloxicam injection)

CLINICAL REVIEW AND SUMMARY REVIEW FOR REGULATORY ACTION

Application Type	Class 2 Resubmission
Application Number(s)	210583
Priority or Standard	Standard
Submit Date(s)	September 24, 2018
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Division/Office	Division of Anesthesia, Analgesia, and Addiction Products/ODE2
Reviewer Name(s)	Robert Shibuya, MD
Division Director	Sharon Hertz, MD
Review Completion Date	See stamp on electronic signature page
Established/Proper Name	Meloxicam injection
(Proposed) Trade Name	Anjeso
Applicant	Recro Pharma
Dosage Form(s)	Injection
Applicant Proposed Dosing Regimen(s)	For intravenous injection every 24 hours
Applicant Proposed Indication(s)/Population(s)	"…management of moderate to severe pain, alone or in combination with (b) (4) analgesics"
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Not applicable.

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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
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

This is a Class 2 New Drug Application (NDA) resubmission for Anjeso, a reformulation of the meloxicam moiety for intravenous (IV) injection only. The meloxicam molecule is a non-steroidal, anti-inflammatory drug (NSAID) originally approved in 2000. According to the Orange Book (January 2019), 51 NDAs or ANDAs containing meloxicam are approved, all for oral administration. Meloxicam is not approved for acute pain. If approved, Anjeso would be the only meloxicam-containing drug approved in the US for IV administration.

RECRO Pharma (the Applicant) originally sought an indication of management of moderate to severe pain with a suggested dosage regimen of 30 mg IV every 24 hours (Q24h). In the original NDA review, deficiencies with both duration of action and onset of analgesia were identified. In this resubmission, RECRO proposes to add "alone or in combination with (b) (4) analgesics" to the indication and to add other prose to the Dosage and Administration Section of the package insert (PI) to address these deficiencies.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Cross-Discipline Team Leader Review and Summary Review for Regulatory Action for the original NDA concluded that the Applicant had not demonstrated the clinical meaningfulness of the findings on the primary endpoints...primarily due to lack of support from the results on the secondary analyses…" The secondary endpoints noted in Section 1 (Benefit Risk Assessment) from the combined Decisional Memo include: 1. "…the analgesic effect does not persist through the dosing interval…", 2. Results for time to meaningful pain relief and time to first rescue use indicate a delayed onset of action that is not appropriate for an IV analgesic for acute pain." And 3. "The frequent use of rescue medication suggests that Anjeso does not provide analgesia suitable to manage postoperative pain."

Thus, while the adequate and well-controlled studies showed a difference in the primary endpoint (a summed pain intensity difference over 24 or 48 hours), the Agency has not concluded that Anjeso is efficacious for the initial proposed indications "Indicated in adults for the management of moderate to severe pain."

At the End-of-Review meeting (July 18, 2018), the Applicant was told that the deficiencies could be addressed through additional studies and/or labeling. The revised labeling submitted in the supplement included (b) (4) During this review cycle, after a thorough review of the available pharmacokinetic and efficacy data for Anjeso, and assessments of pertinent regulatory

precedents for context, it is clear that Anjeso does not meet the expectations of a physician for an IV analgesic. The available data do not support that this formulation of meloxicam is fit for use for the proposed indication.

1.3. Benefit-Risk Assessment

The only new clinical data submitted were blinded safety data from ongoing studies. Because, as will be discussed later in this review, the Applicant failed to adequately address the deficiencies in efficacy, the benefit-risk assessment remains unchanged from the first review cycle. This review contains some refinement of the Division's assessment of efficacy but no change to the conclusion that the Applicant did not demonstrate clinically meaningful efficacy to support the proposed indications

1.4. Patient Experience Data

No patient experience data are contained in this resubmission.

2. Therapeutic Context

2.1. Analysis of Condition

The descriptions of the clinical problem and importance of acute pain are well summarized in Dr. Jiang's review of the NDA. There have been no substantive changes to the prevalence, assessment, or management of acute pain since the CR Action.

2.2. Analysis of Current Treatment Options

The Analysis of Current Treatment Options is addressed in Dr. Jiang's review signed by Drs. Jiang and Lloyd on May 1 and 2, 2018. While the field of multimodal analgesia continues to evolve, we are not aware of consensus advances in treatment options that would affect regulatory decision making subsequent to the Complete Response (CR) action on the original NDA.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The regulatory history prior to the May 23, 2018 Complete Response Action is addressed in Dr. Jiang's review. The regulatory activities pertinent to this review are the Complete Response

Letter (CRL) and an End-of-Review meeting that occurred on July 18, 2018.

The CRL contains 1 clinical deficiency, 1 nonclinical deficiency, and 2 product quality deficiencies. The nonclinical and quality deficiencies pertained to extractables/leachables.

The clinical deficiency contains two components.

a. "…the results of the secondary analyses, including pain intensity difference over time curves, SPID18- 24, and SPID42-48, indicate that the analgesic effect does not persist through the dosing interval.
b. "…the results for time to meaningful pain relief and time to first rescue use indicate a delayed onset of action that is not consistent with expectations for an intravenous analgesic for acute pain, and the frequent use of rescue medication suggests that ANJESO does not provide analgesia suitable to manage postoperative pain."

The Division also requested that the Applicant submit more detailed analyses of bleeding events and anemia with any resubmission and to amend the agreed Pediatric Study Plan to add the juvenile toxicity study to the timeline.

Key discussion points and agreements from that meeting follow.

1. The Applicant proposed (b) (4).
2. The Applicant (b) (4)
3. Potential remedies discussed ranged from new clinical studies to evaluate a shorter dosing interval "and/or proposing labeling to address the concerns identified."
4. The applicant was advised that the resubmission must:
    a. "…supply a compelling argument to address the…" [end of dose failure] and how this would be addressed in labeling
    b. "provide labeling recommendations to address the delayed time of onset"

There is another relevant product that warrants further description, NDA 209588, Buvaya (buprenorphine sublingual spray). This is a reformulation of buprenorphine for an indication of moderate to severe acute pain when the use of an opioid is appropriate. This product was the subject of a Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee that occurred on May 22, 2018. The pivotal efficacy study for Buvaya showed that the median time to meaningful pain relief (using the two-stopwatch method) ranged from 92-166 minutes (~1.5-2.75 hours). The analogous metric for Anjeso is 2-3 hours. When asked whether the data support a finding of efficacy for Buvaya, the meeting minutes read:

Overall, the committee agreed that the efficacy findings were not sufficient, because of the

> delayed time to onset of analgesia, to support the indication of "management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate." The committee generally agreed that even though there is a tremendous public health need for other alternative medications for acute pain, with a delayed time to onset and weak efficacy, Buvaya did not show clinical efficacy as a schedule III controlled substance…

3.2. Summary of Presubmission/Submission Regulatory Activity

The End-of-Review meeting is described in Section 3.1

3.3. Foreign Regulatory Actions and Marketing History

Anjeso is not currently marketed in foreign countries.

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

4.1. Office of Scientific Investigations (OSI)

No new clinical studies were submitted; no inspections were conducted.

4.2. Product Quality

The Office of Product Quality (OPQ) reviewed the resubmission. Briefly, there were two deficiencies related to leachables noted in the CRL. The OPQ review team concluded that the screening for leachables and root cause analysis for the leachables detected that were not observed during the extraction study were adequate. OPQ has recommended Approval for this resubmission.

4.3. Clinical Microbiology

There were no microbiology deficiencies noted in the initial review and no manufacturing changes have occurred, so this section is not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The CRL noted one nonclinical deficiency related to extractables and leachables. The Pharmacology/Toxicology review of the resubmission indicates that the Applicant re-evaluated the leachables and "…none of the eight extractable compounds were detected above the AET [analytical evaluation threshold] in any of the samples evaluated." The

Pharmacology/Toxicology team has found that the Applicant has adequately addressed the CRL deficiency and is recommending approval for this resubmission.

4.5. Clinical Pharmacology

There were no Clinical Pharmacology deficiencies noted in the CRL. As described in Section 5.2, following, a key element of the Applicant's response was a pharmacokinetic (PK) modeling simulations. Drs. Deep Kwatra and Yun Xu reviewed the simulations. The clinical pharmacology team found the simulations and resultant data to be acceptable. (b) (4)

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Consistent with the End-of-Review agreement that the Applicant may address the CRL deficiencies by submitting revised labeling with scientific justification, no new clinical trials were submitted. Thus, Sections 6 (Efficacy) and 7 (Integrated Review of Effectiveness) are not applicable. The Applicant submitted an updated Integrated Summary of Safety, discussed in Section 8 which does not change the overall picture of the safety or the risk-benefit relationship of this drug.

The substance of my review of the material contained in this resubmission will be contained in Section 5.2, immediately following and Section 10, Labeling Recommendations.

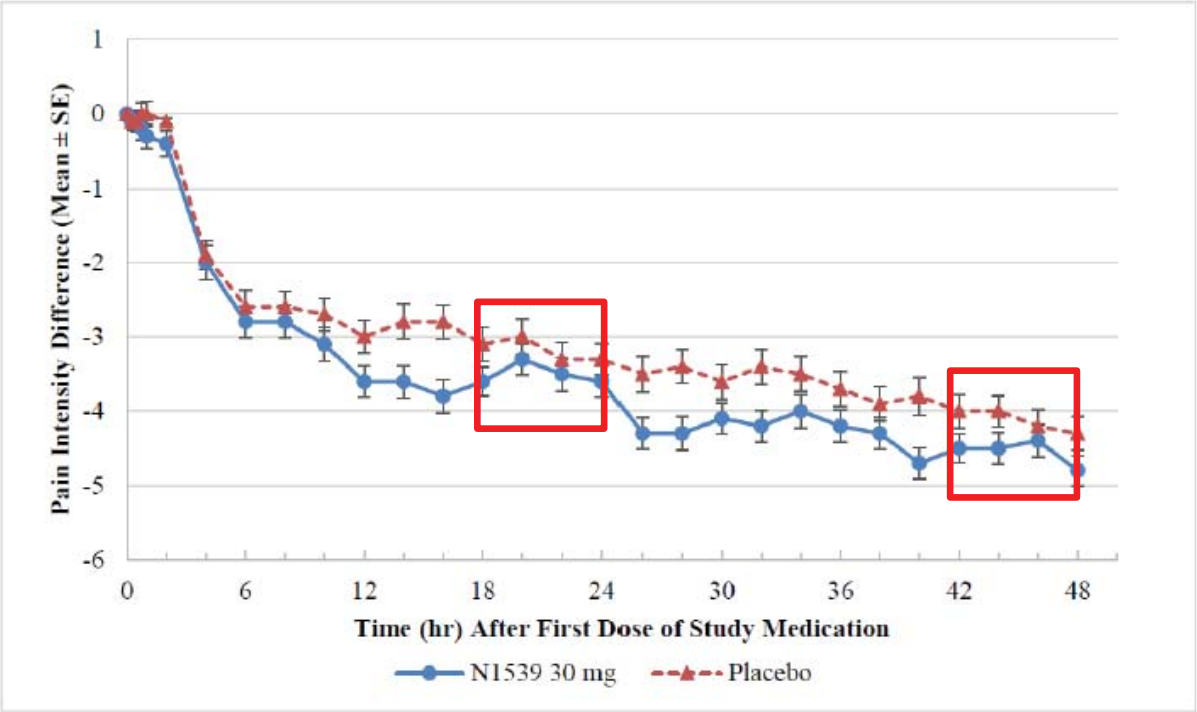
5.2. Review Strategy

Existing data:

There are two clinical deficiencies. The first deficiency is that, while the Applicant proposed every 24-hour dosing in the original NDA, the clinical trial data show end-of dose failure at 18 hours. Inspection of the Pain Intensity Difference vs. time curves for Studies 015

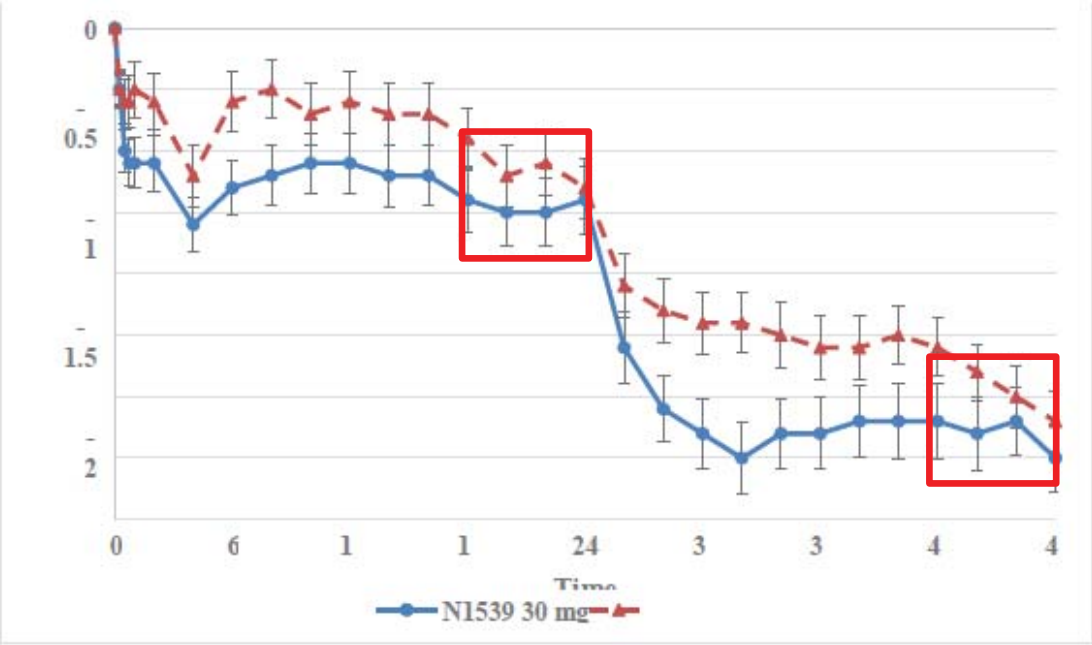
(abdominoplasty) and 016 (bunionectomy) show how the placebo and active pain curves lose separation (red boxes) in Hours 18-24 after each dose of study drug (Figures 1 and 2).

Figure 1: Pain intensity difference over time, Study 015 (abdominoplasty)



Source: Clinical Study Report, Study 015, Figure 2

Figure 2: Pain intensity difference over time, Study 016 (bunionectomy)



Source: Clinical Study Report, Study 016, Figure 2

The second clinical deficiency pertains to the onset of action of the drug. Drugs administered by the intravenous route are expected to act rapidly, typically within a few minutes. In Phase 3 studies, Anjeso showed a long latency to onset of meaningful analgesia which was in the range of 2 to 3 hours. This is shown in Tables 1 and 2, below, showing the median time to meaningful pain relief. Onset of analgesia is conventionally measured using the two-stopwatch method. Patients are dosed and two stopwatches are started simultaneously. Patients are told to stop the first stopwatch at the first perceptible pain relief and the second at the first meaningful pain relief. The accepted metric for the onset of analgesia is the median time to meaningful pain relief when confirmed by a preceding perceptible pain relief measurement.

Table 1: Two-stopwatch data, Study 015 (abdominoplasty)

Parameter / Statistic	N1539 30 mg (N=110)	Placebo (N=109)
Time to First Perceptible PR (hr)		
Subjects Achieved Endpoint, n (%)	63 (57.3)	45 (41.3)
25% (95% CI)	0.26 (0.23, 0.41)	0.37 (0.22, 0.88)
50% (95% CI)	0.76 (0.5, 0.89)	1.28 (0.96, NA)
75% (95% CI)	1.69 (1.03, 2.24)	NA (3.94, NA)
Log-Rank Test	0.0050	
Time to Meaningful PR (hr)		
Subjects Achieved Endpoint, n (%)	32 (29.1)	27 (24.8)
25% (95% CI)	1.04 (0.69, 2.01)	1.23 (0.96, 2.27)
50% (95% CI)	3.02 (2.01, 4.43)	2.92 (1.71, NA)
75% (95% CI)	4.43 (3.18, NA)	NA (3.94, NA)
Log-Rank Test	0.5096	

Source: Clinical Study Report, Study 015, Table 9

Table 2: Two-stopwatch data, Study 016 (bunionectomy)

Parameter / Statistic	N1539 30 mg (N=100)	Placebo (N=101)
Time to First Perceptible PR (hr)		
Subjects Achieved Endpoint, n (%)	66 (66.0)	59 (58.4)
25% tile (95% CI)	0.18 (0.14, 0.27)	0.25 (0.16, 0.35)
50% tile (95% CI)	0.52 (0.35, 0.74)	1.59 (0.48, 2.00)
75% tile (95% CI)	4.45 (1.03, 8.06)	4.00 (2.00, 8.75)
Log-Rank Test	0.1228	-
Time to Meaningful PR (hr)		
Subjects Achieved Endpoint, n (%)	46 (46.0)	40 (39.6)
25% tile (95% CI)	0.56 (0.44, 0.95)	2.03 (0.62, 2.38)
50% tile (95% CI)	2.16 (1.00, 12.01)	3.19 (2.39, 4.82)
75% tile (95% CI)	12.01 (2.62, 12.01)	8.75 (4.35, 11.79)

Log-Rank Test	0.1048	-

Source: Clinical Study Report, Study 016, Table 9

The initial NDA review also noted that the median time to first rescue occurred 1 to 2 hours after the first dose (1.08 hrs Table 7, Study 015 and 1.99 hrs; Table 7, Study 016). In Study 015, the rescue opioid was administered two hours prior to meaningful analgesia. Thus, on the basis of these two metrics, the contribution of Anjeso to the outcome of meaningful analgesia is uncertain.

New Data/Rationale in this submission:

The Applicant submitted no new clinical data but addressed the deficiencies through revisions to the proposed labeling supported with a healthcare provider (HCP) survey and interviews. The Applicant's overall strategy is summarized in Table 3 following, followed by a more detailed description of the Applicant's arguments.

Table 3: Proposed remedies for clinical deficiencies

Remedy #	Deficiency	Proposed Remedy	New argument/information to support
1	End-of-dose failure	Add "**alone or in combination with** (b) (4) **analgesics**" to Section 1: Indication [**bold** added]	Applicant is positioning Anjeso as part of a multimodal analgesia regimen. (b) (4)
2	End-of-dose failure	Add (b) (4) to Section 2: Dosage & Administration [**bold** added]	Same as above.
3	End-of-dose failure	Add " (b) (4) to Section 2 [**bold** added]	(b) (4)
1	Long onset of action	Add "**alone or in combination with** (b) (4) **analgesics" to indication**."	See Remedy #1.

		To Section 1 [**bold** added]	
2	Long onset of action	Add (b) (4) to Section 2 [**bold** added]	See Remedy #1.
4	Long onset of action	Add " (b) (4) to Section 2. [**bold** added]	Tested in a healthcare provider survey and qualitative interviews.

Remedies 1 and 2:

(b) (4)

Remedy 3:

(b) (4)

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(b) (4)

Remedy 4:
Remedy 4 proposes to add (b) (4) ” to the Dosage and Administration Section.

A two-part study consisting of qualitative interviews and a survey provides some information around this proposal. Unfortunately, the original supplement of September 2018 included only

a superficial summary of this research. In response to an Information Request, more detail was submitted.

This work proceeded in two parts. The work was contracted by RECRO but conducted by (b) (4), an independent contractor. Part 1 was a series of qualitative telephone interviews with physician specialists (anesthesiologists, general surgeons, orthopedic surgeons, and colorectal surgeons). The objective was to recruit board-certified physicians who would be "prototypical prescribers" of drugs used postoperatively. Interviewees were asked relevant demographic and practice questions. They were then provided with the proposed PI for Anjeso ("blinded") and asked to read it as if they were reading a PI of a new drug for the first time. Interviewees were asked about:

1. Ease of comprehension and clarity
2. Phrases/sentences that could cause confusion
3. Preferences between text and alternatives
4. Other comments

Part 2 of the project consisted of a "quantitative" survey to assess the PI for clarity, clinical relevance, "alignment with expectations," and "whether the Full PI provided physicians clear information to appropriately utilize the product with their patients." Similar to Part 1 (interviews), the study was to recruit physicians likely to prescribe the drug, if approved. Presumably, the survey was web-based (it is described as "online"). The study was "blinded" in that it did not identify Anjeso. Neither part explicitly excluded investigators in completed or ongoing trials.

Respondents were then shown five Package Insert Sections (Indication and Usage, Dosage and Administration, Clinical Trials, Mechanism of Action, and Clinical Trials) one at a time and asked about each section. After reading each section, respondents were asked to rate the following on a 1-7 numerical rating scale (1=strongly disagree; 7 = strongly agree) for:

- Clarity: "How well I understood the language"
- Clinical Relevance: "Information is meaningful to me and my practice"
- Alignment with Expectation: "The type of information is aligned with, or exceeds, my expectation for this class of product"

Respondents then read the full PI and rated on the same metrics. They were asked to rate a fourth category "Confident to Consider – The information gives me what I would need to consider utilization of Product X postoperatively, in those patients I would feel comfortable using an IV NSAID." If respondents did not rate the PI as 1-4, they were asked what they would have wanted to know.

Highly summarized results appear in Table 7, below.

Table 7: Summarized results of HCP interviews and survey

	Interview	Survey
N (n)	34 (12 anesthesiologists, 8 general surgeons, 7 orthopedic surgeons, 7 colorectal surgeons.	150 (75 anesthesiologist, 30 general surgeons, 30 orthopedic surgeons, 15 colorectal surgeons)
Key findings relevant to this action	31/34 stressed importance of multimodal analgesia for postoperative pain management	Applicant considered a positive score as 5-7 (1 = strongly disagree; 7 = strongly agree) All Sections scored ≥90% "positive" with the exception of: Indication/Usage: 87% for alignment with expectations D&A: 89% clinical relevance Adverse Reactions: 85% for alignment with expectations Clinical Studies: 82-86% for all three
	27/34 stated that they are not fully satisfied with current options	"Overall, the proposed IV meloxicam PI was thought to be clear and understandable with almost all physicians stating the information provided within the PI would give them confidence in prescribing IV meloxicam to their patients and an understanding of where this product would fit into their postoperative pain management protocols and techniques."
	The PI is similar to other non-opioid products used in the post-operative setting.	
	For Section 1, "…alone or in combination with (b) (4) analgesics" was preferred to "…alone or in combination with (b) (4) analgesics"	
	14/34 thought "time to meaningful pain relief" was vague and subjective.	
	Wide onset of action (15 min to 3 hrs) is "potentially" longer than expected for IV NSAIDs.	
	Prose about potential need for rescue was clear (b) (4) .	

The Applicant concluded that the dosing regimens (b) (4) are acceptable and understandable. Apparently, there were some issues with the interpretation of language warning of the slow onset of analgesia.

6. Review of Relevant Individual Trials Used to Support Efficacy

Not applicable

7. Integrated Review of Effectiveness

- Not applicable.

8. Review of Safety

Dr. Jiang conducted a complete review of the safety of Anjeso in his May 2018 review. The resubmission contains a safety update and 3 appendices (Tables, literature searches, and narratives).

8.1. Safety Review Approach

Blinded safety data from three ongoing studies are available. Given the unremarkable safety findings from the initial NDA review, my review was largely limited to review of the SAE narratives to detect any new safety signals. The Applicant provided a table of the common adverse events compared to the pooled safety data in patients that was useful for the review.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

According to the Cross-Discipline Team Leader/Decisional Memo from Drs. Lloyd and Fields, at the time of the CR Action, the database consisted of three Phase 2 studies and three Phase 3 studies as well as the studies conducted to support the clinical pharmacology requirements. A total of 1,099 postoperative patients had been exposed to Anjeso at at least 30 mg and 526 patients had received at least 3 doses. The Serious Adverse Events were summarized in Table 8, following.

Table 8: Serious Adverse Events at the time of the CR Action

Parameter	Placebo N=517	N1539 5-15 mg N=327	N1539 30 mg N=910	N1539 60 mg N=189
Subjects with ≥1 SAE, n (%)	15 (3)	5 (2)	15 (2)	0
Number of reported SAEs	18	5	21	0
Blood and lymphatic system disorders, n (%)				
Anemia	0	0	1 (0.1)	0
Cardiac disorders, n (%)				
Coronary artery disease	1 (0.2)	0	0	0
Gastrointestinal disorders, n (%)				
Intestinal perforation	0	0	1 (0.1)	0
Jejunal stenosis	1 (0.2)	0	0	0
Nausea	1 (0.2)	0	0	0
Omental infarction	0	0	1 (0.1)	0
Small bowel obstruction	0	0	2 (0.2)	0
Ileus	0	0	0	0
General disorders and administration site conditions, n (%)				
Sudden death	1 (0.2)	0	0	0
Hepatobiliary disorders, n (%)				
Hepatocellular injury	1 (0.2)	0	0	0
Infections and infestations, n (%)				
Abdominal abscess	1 (0.2)	0	0	0
Diverticulitis	0	0	1 (0.1)	0
Incision site infection	0	1 (0.3)	1 (0.1)	0
Mesenteric abscess	0	0	1 (0.1)	0
Pneumonia	0	0	1 (0.1)	0
Postoperative abscess	1 (0.2)	0	0	0
Postoperative wound infection	1 (0.2)	0	0	0
Septic shock	0	0	1 (0.1)	0
Injury, poisoning and procedural complications, n (%)				
Anastomotic ulcer	1 (0.2)	0	0	0
Femoral neck fracture	0	0	1 (0.1)	0
Fracture	1 (0.2)	0	0	0
Incisional hernia	1 (0.2)	0	0	0
Post procedural hemorrhage	1 (0.2)	1 (0.3)	1 (0.1)	0
Post procedural pulmonary embolism	1 (0.2)	0	3 (0.3)	0
Postoperative ileus	1 (0.2)	1 (0.3)	1 (0.1)	0
Tendon injury	0	0	1 (0.1)	0
Wound Healing complications, n (%)				
Wound dehiscence	0	1 (0.3)	0	0
Investigations, n (%)				
Liver function test abnormal	1 (0.2)	0	0	0
Metabolic and nutrition disorders, n (%)				
Hypervolaemia	0	0	1 (0.1)	0
Nervous system disorders, n (%)				
Dizziness	1 (0.2)	0	0	0
Renal and urinary disorders, n (%)				
Acute kidney injury	0	0	2 (0.2)	0
Respiratory, thoracic and mediastinal disorders, n (%)				
Dyspnoea	1 (0.2)	0	0	0
Respiratory arrest	1 (0.2)	0	0	0
Respiratory distress	0	0	1 (0.1)	0
Gynecological, n (%)				
Vaginal hemorrhage	0	1 (0.3)	0	0

Source: CDTL/DD memo, May 23, 2018

The CDTL/DD Memo concurred with Dr. Jiang's summary that, "the overall safety profile of [Anjeso] is consistent with what has been observed in patients treated with NSAIDs as a class, particularly one that is administered IV over a short duration."

In the May 2018 CRL, the following was conveyed, verbatim.

> When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.
>
> 1. Describe in detail any significant changes or findings in the safety profile.
> 2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
>   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
>   - Present tabulations of the new safety data combined with the original application data.
>   - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
>   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
> 3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
> 4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
> 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
> 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
> 7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
> 8. Provide English translations of current approved foreign labeling not previously submitted.

Additional exposures to Anjeso in the safety update were derived from one Phase 1 and two Phase 3 studies, summarized in Table 9, below.

Table 9: Ongoing studies contributing subjects/patients to safety update

Study ID	Design	Population	# of new subjects/patients	# planned	Dosing Regimen
REC-17-021	OL, crossover	HV	6		30 mg single-dose
REC-17-024	P, DB, PC	Colo-rectal surgery	35 (blinded)	50 (randomized 1:1)	30 mg Q24h (1st dose 30 min prior to surgery)
REC-17-025	P, DB, PC	Total knee replacement	27 (blinded)	200 (randomized 1:1)	30 mg Q24h (1st dose after spinal and before start of surgery)

OL=open-label, R=randomized; DB=double-blind; PC=placebo-controlled, HV=healthy volunteer

8.2.2. Relevant characteristics of the safety population:

The persons dosed with Anjeso since the CR action are healthy volunteers or typical post-surgical patients who would be eligible for treatment with an NSAID.

8.2.3. Adequacy of the safety database:

The safety data was considered sufficient for the original review. The resubmission adds blinded data from a small number of patients.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Given that data from only an additional 68 people (of 268 planned) are available, no inspections were requested or conducted for this resubmission. The studies are being conducted under Good Clinical Practice guidelines.

8.3.2. Categorization of Adverse Events

The safety update does not specify the version of MedDRA used. The protocols indicate that the definitions of adverse event and serious adverse event are consistent with applicable regulations.

8.3.3. Routine Clinical Tests

The protocols require routine laboratory and ECG monitoring.

8.4. Safety Results

8.4.1. Deaths

No deaths have been reported in the ongoing clinical trials.

8.4.2. Serious Adverse Events

A total of 10 new SAEs were reported. Again, treatments are blinded at this time.

Subject (b) (6) (Study 24 [colo-rectal surgery]) experienced a polyp in the ethmoid sinus that presented as diplopia. He underwent uncomplicated sinus surgery with resolution.

Subject (b) (6) (Study 24) experienced post-operative vomiting, resulting in wound dehiscence and bowel evisceration. He was taken back to the operating room and the defect repaired with resolution.

Subject (b) (6) (Study 24) experienced ileus and urinary retention following her colectomy. She was treated with nasogastric decompression, parenteral nutrition, and Tamsulosin with resolution.

Subject (b) (6) (Study 24) also developed ileus following a robotic right colectomy for Crohn's disease. He was treated with nasogastric decompression and holding opioids with resolution.

Subject (b) (6) (Study 24) is a 73-year old black man with multiple medical problems including Type 2 diabetes mellitus. He underwent colectomy and received blinded study drug between (b) (6). He was discharged on (b) (6). Four days after discharge, he presented to the Emergency Department with confusion and diaphoresis and his serum glucose was 28 mg/dL. His hypoglycemia was medically managed and he was discharged after resolution.

Subject (b) (6) (Study 24) also developed ileus following a colectomy. He was treated with nasogastric decompression, milk of magnesia, simethicone, and colase with resolution.

Subject (b) (6) (Study 24) was readmitted for a wound infection five days following his last dose of blinded study drug. He was treated with IV antibiotics and "management" of incisional site cellulitis. This SAE is still resolving at the time of submission.

Subject (b) (6) (Study 25 [total knee replacement]) experienced dysphagia while eating on the day of surgery and after receiving his first dose of blinded study drug. He underwent endoscopy and was diagnosed with esophageal stricture and esophagitis. He underwent dilation and treatment with pantoprazole. The event was considered resolved.

Subject (b) (6) (Study 025) is a 64-year old Hispanic woman with multiple medical problems. Following a total knee replacement, she developed a pulmonary embolus that declared itself with wheezing, mild dyspnea, and unilateral lower extremity edema and pain. She was treated with enoxaparin and supportive measures and started on rivaroxaban. This SAE is resolving at the time of submission.

Subject (b) (6) (Study 025) is a 76-year old white man with multiple medical problems who underwent total knee replacement. Two days after discharge, he presented with difficulty breathing and coughing. He was found to have an oxygen saturation of 77% on room air. DVT prophylaxis was provided during his hospitalization although he was only discharged on aspirin, 81 mg. His workup revealed right heart strain from a large pulmonary embolism. He was treated with anti-coagulation and antibiotics because of some consolidation in the right lower and middle lobes. This event is reported as resolving at the time of submission.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No adverse events leading to discontinuation occurred in persons exposed to Anjeso since the CR action.

8.4.4. Significant Adverse Events

Given the small quantity of additional blinded safety data, I have no comments for this section.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The Applicant provided a table summarizing the Treatment-Emergent Adverse Events for the Phase 1 study (Study 21) which is reproduced below (Table 10).

Table 10: TEAEs, Study 021

Subject Number	Preferred Term/ Description	Relationship	Intensity	Outcome	Action Taken
(b) (6)	Back Pain/ Back Soreness	Not Related	Mild	Recovered/ Resolved	Not applicable
	Headache/ Headache	Possibly Related	Mild	Recovered/ Resolved	Drank a caffeinated beverage
	Nausea/ Nausea	Not Related	Mild	Recovered/ Resolved	Not applicable
	Presyncope/ Vasovagal Attack	Not Related	Mild	Recovered/ Resolved	Not applicable
	Headache/ Increased Frequency of Stress Headaches	Possibly Related	Mild	Recovered/ Resolved	Not applicable
	Myalgia/ Left Rhomboid Pain	Not Related	Mild	Recovered/ Resolved	Not applicable

Source: Safety update, Table 2

For the studies in patients (Studies 024 and 025), the Applicant provided summary tables showing adverse event intensity and relatedness and brief descriptions of severe adverse events that do not show any worrisome trends.

The table (Table 11) showing the rates of common adverse events by System Organ Class and Preferred Term in the ongoing studies and completed studies in patients is worth further mention.

Table 11: Most Commonly Occurring (>1 Subject) Treatment-Emergent Adverse Events in Studies REC-17-024 and REC-17-025 Combined

	Phase 3b Studies[a]	Phase 2/3 Studies[b]	
Parameter	Blinded Subjects N=62 n (%)	N1539 30 mg N=910 n (%)	Placebo N=517 n (%)
Subjects with ≥1 TEAE	54 (87.1)	497 (54.6)	296 (57.3)
Gastrointestinal disorders			
Nausea	25 (40.3)	189 (20.8)	131 (25.3)
Vomiting	6 (9.7)	42 (4.6)	38 (7.4)
Constipation	5 (8.1)	61 (6.7)	25 (4.8)
Ileus	5 (8.1)	1 (0.1)	1 (0.2)
General disorders and administration site conditions			
Pyrexia	5 (8.1)	11 (1.2)	9 (1.7)
Infections and infestations			
Cellulitis	2 (3.2)	7 (0.8)	0
Metabolism and nutrition disorders			
Hypophosphataemia	6 (9.7)	2 (0.2)	0
Hypokalaemia	4 (6.5)	6 (0.7)	2 (0.4)
Hypomagnesaemia	3 (4.8)	4 (0.4)	1 (0.2)
Hypocalcaemia	2 (3.2)	0	1 (0.2)
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	2 (3.2)	2 (0.2)	1 (0.2)
Nervous system disorders			
Headache	4 (6.5)	51 (5.6)	54 (10.4)
Dizziness	3 (4.8)	32 (3.5)	25 (4.8)
Psychiatric disorders			
Insomnia	3 (4.8)	13 (1.4)	11 (2.1)
Anxiety	2 (3.2)	2 (0.2)	4 (0.8)
Renal and urinary disorders			
Oliguria	3 (4.8)	0	0
Respiratory, thoracic and mediastinal disorders			
Paranasal sinus hypersecretion	2 (3.2)	0	0
Wheezing	2 (3.2)	1 (0.1)	0
Skin and subcutaneous tissue disorders			
Pruritus	6 (9.7)	31 (3.4)	15 (2.9)
Vascular disorder			
Hypotension	13 (21.0)[c]	11 (1.2)	8 (1.5)
Hypertension	4 (6.5)	5 (0.5)	4 (0.8)

Source: Safety update, Table 8, page 13/17

Table 11 shows that the incidence of adverse events in the ongoing studies in colo-rectal surgery and knee replacement are higher than those in the prior studies (predominantly bunionectomy and abdominoplasty). This is not surprising given the difference in

demographics, expected co-morbidities, and morbidity of the surgical procedures currently under study.

8.4.6. Laboratory Findings

While all ongoing three studies require the collection of laboratory, vital sign, and ECG data, given the low overall accrual (68/268 [25%]), I am not requiring the Applicant to submit tables of blinded laboratory data. Should a clinically significant lab abnormality occur, it would be reported as an adverse event.

8.4.7. Vital Signs

As in 8.4.6, I have elected not to require that the Applicant submit blinded vital sign data.

8.4.8. Electrocardiograms (ECGs)

As in 8.4.6, I have elected not to require that the Applicant submit blinded ECG data.

8.4.9. QT

As in 8.4.6, I have elected not to require that the Applicant submit blinded ECG data.

8.4.10. Immunogenicity

Not applicable

8.5. Analysis of Submission-Specific Safety Issues

In the Complete Response Letter, the Applicant was instructed to submit 1. Significant changes in the safety profile, 2. A retabulation of the reasons for premature trial discontinuation by incorporating drops out from new trials, 3. Data pertaining to bleeding events and anemia by procedure and dose, and 4. Other routine safety data.

Some of the requests specified in the CRL were moot. For example, no premature discontinuations occurred in the ongoing studies so the updated table was not necessary. I reviewed the tables for bleeding/anemia and wound healing events which do not change the overall picture of the safety of this drug. Patients treated with active drug have a slight excess of bleeding/anemia events regardless of surgery type and there is a small imbalance in wound healing events, also favoring placebo. The differences are small but consistent. For example, the largest difference occurs in the categories of bleeding and wound healing for orthopedic surgeries. Patients treated with Anjeso 30 mg had bleeding and wound rates of 3.1% and 4.2% compared to 1.6% and 2.8% of patients treated with placebo. In non-orthopedic surgeries, the corresponding rates were 4.2% and 5.5% vs. 2.6% and 3.7%. There no worrisome bleeding or anemia adverse events reported in the new clinical data.

The product continues to have an adverse event profile consistent with an immediate-release NSAID used in a post-surgical population.

8.5.1. [Name Safety Issue]

Not applicable.

8.6. Safety Analyses by Demographic Subgroups

Not applicable.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

Not applicable.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

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

Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

8.9.2. Expectations on Safety in the Postmarket Setting

- Not applicable.

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Not applicable.

9. Advisory Committee Meeting and Other External Consultations

There was no Advisory Committee convened for this resubmission.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

I recommend a Complete Response (CR) Action for this NDA resubmission and labeling is premature at this point.

As described in Section 8 (Safety), the only new clinical data do not further inform the safety of this product. As there are no new efficacy data, the substance of this review is a reassessment of the available efficacy data.

The Applicant was asked to address two efficacy deficiencies observed in the Phase 3 clinical trials. On average, the drug does not work for the intended dosing interval of 24 hours and the Phase 3 studies showed an unacceptably long latency to the onset of analgesia. The two-stopwatch data show that the median time to meaningful analgesia can be as long as 3 hours with the drug, well outside the expectation of a physician for an analgesic for acute use, and after the median time to first use of rescue medication. On average, the drug works for 15-18 hours once onset of effect occurs, after which the pain curves for active and placebo converge.

Factors favoring an Approval Action for Anjeso

1. If approved, Anjeso would represent the fifth non-opioid analgesic approved for IV administration. The approved products are:

a.	Toradol (ketorolac)	NDA 19698	Approved 1989
b.	Caldolor (ibuprofen)	NDA 22348	Approved 2009
c.	Ofirmev (acetaminophen)	NDA 22450	Approved 2010
d.	Dyloject (diclofenac)	NDA 22396	Approved 2014

Later in this review, cross-study comparisons to Caldolor, Ofirmev, and Dyloject are made. Toradol was excluded based on the inaccessibility of detailed clinical trial data from the 1989 approval.

2. While not established from a regulatory perspective, the meloxicam moiety is reported to have relative COX-2 specificity although most reports indicate that COX-2 selectivity is lost at high plasma concentrations (Gates 2005). In addition, some literature also indicates that the "oxicams" may be pharmacologically different from other NSAIDs by "exhibiting a novel binding pose" in the COX channel (Xu 2014). Given idiosyncrasies between patients, it is possible that these properties might benefit certain patients.

3. Given that multimodal analgesia is now standard-of-care for inpatient management of acute pain, having another choice of a parenteral non-opioid favors approval of Anjeso.

While there are three interrelated theoretical reasons favoring the approval of Anjeso, I recommend a Complete Response for this NDA for three, also interrelated, reasons summarized immediately below and fully explained later.

1. Anjeso lacks expected attributes of an IV drug that render it unfit for use for the proposed indication.
2. Even though Anjeso met the statistical threshold for efficacy on the primary endpoint (SPID), it does not appear that the drug product is effective in the intended population.
3. The PK-PD correlation appears weak. Thus, the clinical deficiencies do not appear to be remediable (b) (4)

Physician expectations for drugs administered via the intravenous route

When compared to oral administration, intravenous administration of drugs incurs certain risks and costs, summarized below.

1. IV administration is associated with a number of risks including line infection/sepsis, bleeding, phlebitis, thrombosis, etc.
2. IV administration imposes additional burdens on the healthcare system such as nursing time, documentation, and equipment requirements.
3. Patients with poor IV access may require a central line or special cannulation techniques, incurring higher cost and risks (pneumothorax, bleeding).
4. Some IV drugs cause pain on injection (potassium chloride, propofol) or are known to extravasate easily (promethazine).
5. Some drugs can only reasonably be administered orally due to local effects (activated

charcoal, sucralfate) or the need for activation by bowel bacteria (sulfasalazine).

6. While other factors affect cost, the higher manufacturing costs of a sterile injection for IV administration generally results in a higher unit cost to the healthcare system.

The risks and costs of IV administration are justified under certain circumstances, summarized as follows.

1. When a patient is nil per os (NPO)
2. When a rapid pharmacologic response is required/desired
3. When rapid titration based on clinical signs and symptoms is required/desired
4. When plasma concentrations that exceed those attained by oral administration are required for efficacy (antibiotics)
5. When the drug is a peptide or otherwise destroyed in the gastrointestinal tract
6. When the drug either has poor oral absorption, high first-pass effect, or poor oral tolerability

Reasons 5 and 6 do not apply to meloxicam, an orally bioavailable small molecule, approved as a tablet. Thus, the fit between Anjeso and clinical requirements for an IV acute analgesic is limited to a discussion of NPO status, rapidity of therapeutic onset, and titratability of the drug product. The importance of plasma concentrations of meloxicam is also related to these issues.

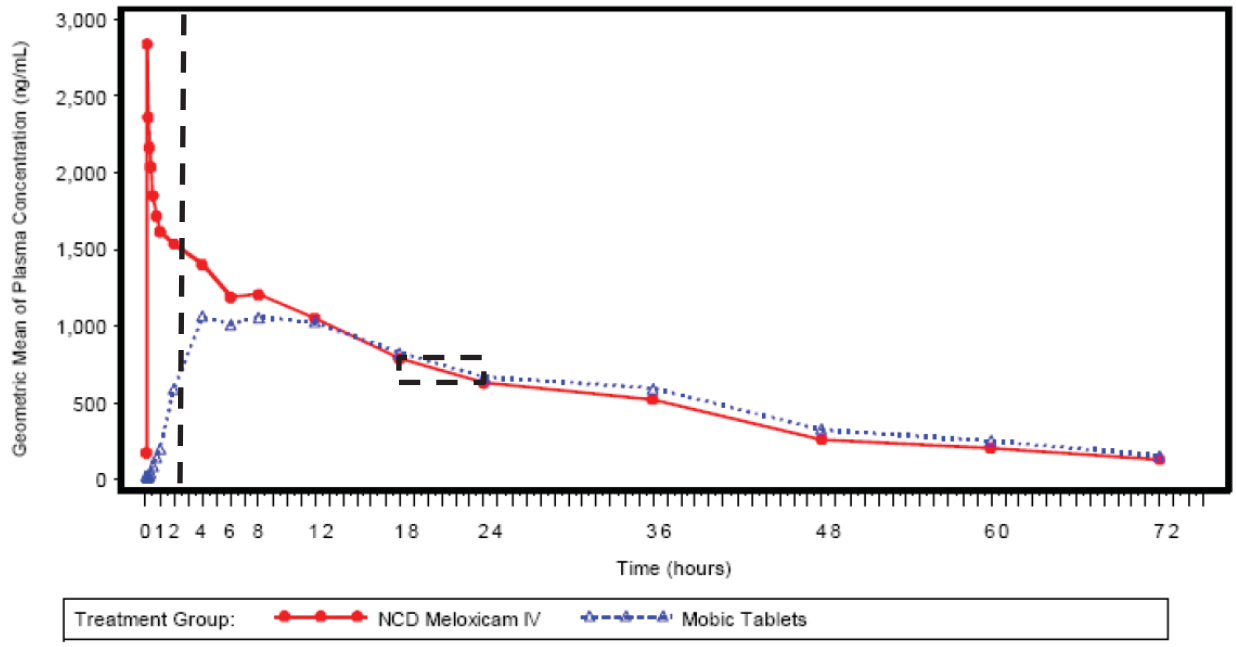
An IV formulation of meloxicam would be expected to be usable in a NPO patient if it had a rapid onset and be easily titratable. There are multiple opioid analgesics (most notably morphine, hydromorphone, and fentanyl) used by parenteral (including IV) routes routinely in medical practice. While these drugs were approved prior to routine use of the two-stopwatch method, clinical experience shows that opioids administered IV have an onset of action within a few minutes and are readily titrated due to short half-life (particularly fentanyl and its analogs).

As noted above, there are three injectable non-opioids approved since 2009 (Ofirmev, Caldolor, and Dyloject). The NDAs for Ofirmev and Dyloject contained studies that used the two-stopwatch method. The median times to meaningful pain relief were 27 minutes (Ofirmev, Study CPI-APA-304), 41 minutes (Dyloject Study DFC-005), and 51 minutes (Dyloject Study DFC-004). As noted in Regulatory History, a sublingual formulation of buprenorphine (reviewed at Advisory Committee) was not approved, in part, due to an onset of the action in the range of 90-160 minutes. Again, Anjeso has an onset of action in the range of 130 to 180 minutes.

While non-opioid IV analgesics are not routinely titrated to effect, the half-lives of acetaminophen, ibuprofen, and diclofenac imply that those drug products would be more titratable. Those products allow every 6-hour dosing, compared to the every 24-hour dosing for meloxicam.

Being able to titrate a drug to clinical effect requires a strong pharmacokinetic-pharmacodynamic (exposure-response) correlation. Figure 4, below shows the concentration-time curve for the pivotal comparative bioavailability study (Study n1539-01) that compared Anjeso to Mobic tablets.

Figure 4: Mean plasma concentration-time profiles after administration of Anjeso and Mobic (30 mg)

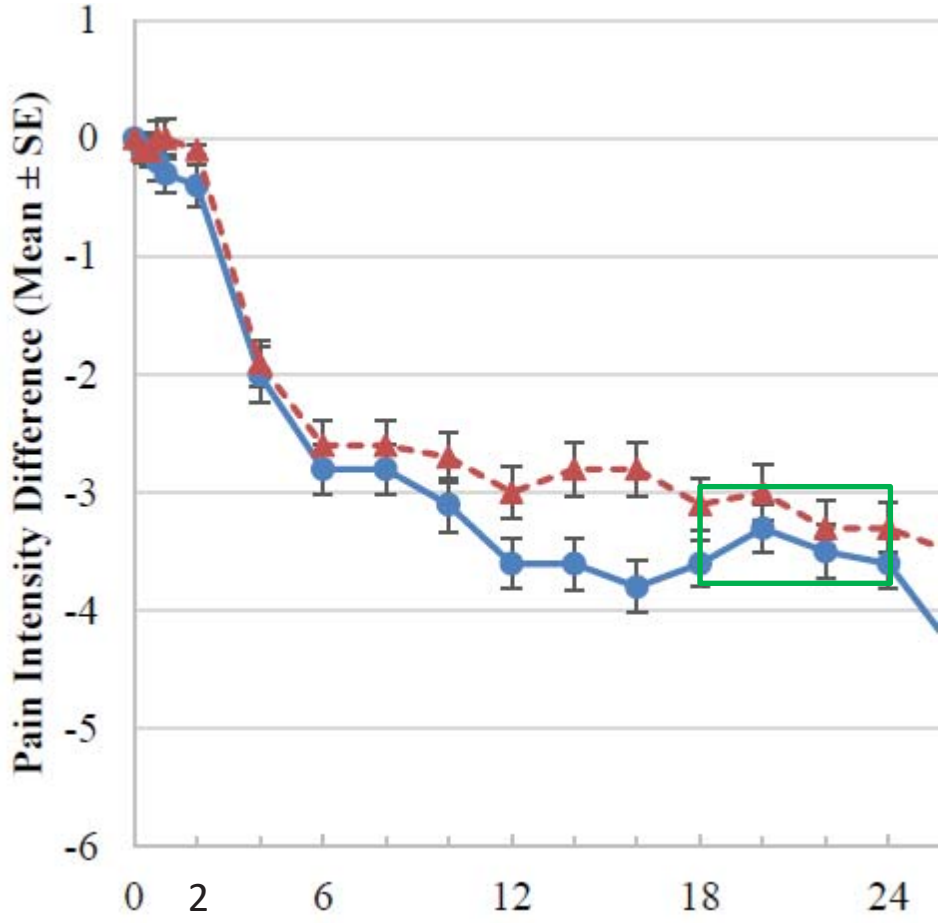


Source: Clinical Study Report, Study a1539-01, Figure 11.4.1, page 44/1528

I have added a dashed vertical line to the figure to represent the median time to meaningful pain relief (average = 2.5 hours between Studies 15 and 16). It is clear that Anjeso delivered high plasma meloxicam concentrations well before patients reported pain relief. I also added a dashed box to highlight the decrease in plasma meloxicam concentration between Hours 18 and 24. Estimating the concentrations by inspection of the Y-axis, the meloxicam concentration only decreases from ~1700 ng/mL to ~1500 ng/mL over the last 6 hours of the dosing interval. I additionally note that Study n1539-03, a multiple-dose PK study, shows a similar small drop in plasma meloxicam between Hours 18 and 24 (1979 vs. 1758 ng/mL).

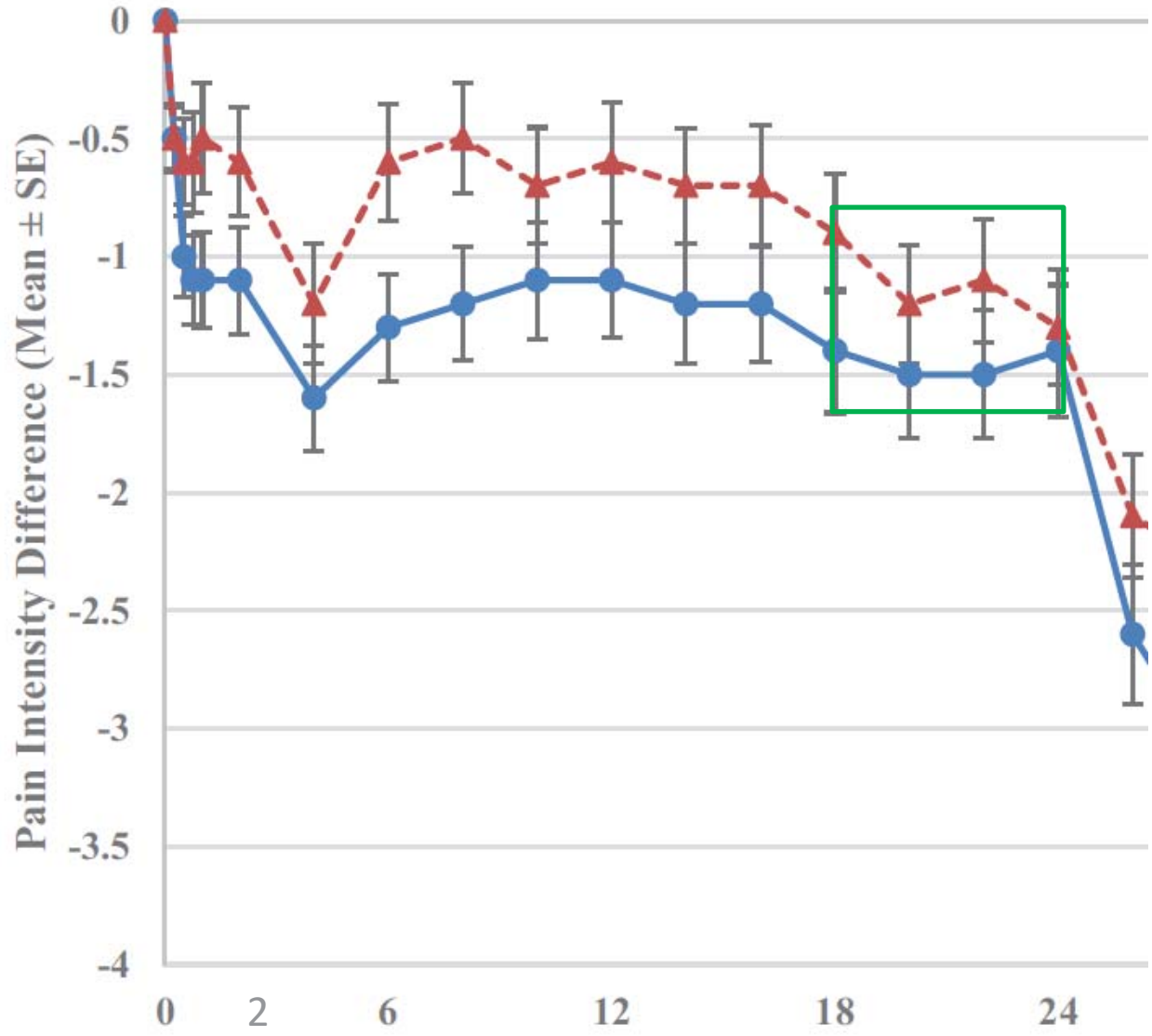
Although repetitive of material in Section 5.2, for convenient comparison to the PK data, Figures 5 and 6 show the change in pain intensity vs. time curve from Studies 015 and 016, respectively. I have added a box around the last six hours of the dosing interval to highlight the end-of-dose failure.

Figure 5: Summary of pain intensity difference values (mean ± SE), Study 015 (abdominoplasty)



Source: Clinical Study Report, Study 015, Figure 2

Figure 6: Summary of pain intensity difference values (mean ± SE), Study 016 (bunionectomy)



Source: Clinical Study Report, Study 016, Figure 2

Comparison of the three figures leads to the conclusion that the exposure-response relationship for Anjeso appears to be weak. Given the lack of apparent exposure-response relationship, we would not predict that the ability to rapidly control plasma drug concentrations with IV administration will be useful for Anjeso.

Is Anjeso effective in the intended population?

INDICATION

The resubmission seeks an indication of "…management of moderate to severe pain, alone or in combination with (b) (4) analgesics." This prose effectively represents two indications:

1. Monotherapy for moderate to severe pain
2. As adjunctive therapy, also for moderate to severe pain.

The analogous approved products, Ofirmev, Caldolor, and Dyloject have the following relevant indications (deleting fever and pediatric language), summarized in Table 12.

Table 12: Indications for approved IV NSAIDS

Tradename	Active drug	Relevant Approved Indications
Ofirmev	Acetaminophen	Management of mild to moderate pain
		Management of moderate to severe pain with adjunctive opioid analgesics
Caldolor	Ibuprofen	Management of mild to moderate pain
		…and the management of moderate to severe pain as an adjunct to opioid analgesics
Dyloject	Diclofenac	Management of mild to moderate pain
		Management of moderate to severe pain alone or in combination with opioid analgesics

There is a lack of consensus around what comprises "mild," "moderate," and "severe" pain. However, compared to the approved products, RECRO is seeking an indication as monotherapy for a higher degree of pain (moderate to severe pain) and also proposes not to specify the adjunctive analgesic (opioid).

PATIENTS STUDIED

Anjeso was studied in patients status post abdominoplasty and bunionectomy. The three relevant comparators conducted studies in the following populations (Table 13).

Table 13: Patient populations for IV NSAIDs

Tradename	Population studied
Ofirmev	Laparoscopic laparotomy
	Knee and hip replacement
Caldolor	Mixed surgical population (abdominal, pelvic, and orthopedic surgery)
Dyloject	Dental surgery
	Abdominal and pelvic surgery
	Orthopedic surgery

Laparoscopic abdominal surgery and dental surgery are generally considered to result in less post-operative pain than surgeries such as knee replacement or abdominoplasty. With the exception of two studies, the surgical models used in the other three programs approximate the patients studied in the Anjeso Phase 3 studies.

KEY EFFICACY RESULTS

The Agency discourages the use of cross-study comparisons for many excellent reasons including differences in study design, patient populations, outcome measures, practice trends over time, and biologic variability, among others. However, the pivotal studies supporting the Anjeso NDA failed to include relevant comparators. Thus, it becomes necessary to use data from other clinical programs to provide context from which to assess Anjeso. Relevant metrics for the most relevant approved comparators are tabulated below (Table 14), compared to Anjeso. I have excluded the primary endpoint (summed pain intensity difference) because there is a wide variety of methodologies for calculation of that metric that render the SPIDs from different studies not directly comparable.

Table 14: Cross-study comparisons: IV NSAIDs

Tradename	Study	Median time to meaningful pain relief (min)	% needing rescue in first 24 hours	Time to first rescue (hr)	% Reduction in opioid used vs. placebo
Anjeso	REC-15-015	180	88	1	21.5
Anjeso	REC-15-016	130	83	2	16.2
Caldolor	CPI-CL-008	Not collected	N/A (add on study)	Not reported	21.5
Dyloject	DFC-001	Not collected	Not reported	6.5	
Dyloject	DFC-004	51	72	2.53	39.3
Dyloject	DFC-005	41	74	3.76	41.3
Ofirmev	CPI-APA-304	27	40	10	
Ofirmev	RC2103002	Not collected	87*	3	

*Study used an "add-on" model where all patients were primarily managed with patient-controlled analgesia (morphine). It is not clear why this metric was not 100%

On the basis of these cross-study comparisons, Anjeso had the slowest onset of an action by a wide margin. With the exception of Ofirmev Study RC2103002, where a high rate of opioid use is expected due to study design, a higher proportion of patients required rescue analgesia in the pivotal Anjeso trials. That implies that Anjeso has the worst performance as monotherapy.

Consistent with the slow onset of action and need for rescue, the latency to first rescue was also consistently shortest in the Anjeso trials and was earlier than time to onset. Last, as an indirect measure of the effectiveness of Anjeso as adjunctive analgesia, I note that it was generally outperformed by the comparator analgesics for reduction in rescue opioid used. Again, while I am cognizant of the hazards of cross-study comparisons, Anjeso has consistently performed worse than the approved drugs.

RECRO has proposed an indication for more severe pain (b) (4) . However, the cross-study comparisons show that Anjeso generally performed at the low end of the approved drugs. Anjeso does not appear to be effective for the proposed indications, particularly the monotherapy indication.

(b) (4)

Can dosing adjustment address the clinical deficiencies?

Meloxicam offers some theoretical pharmacological advantages due to its relative COX-2 selectivity and unique interaction with the binding site. However, in his review of the original NDA, Clinical Pharmacology Reviewer Dr. Deep Kwatra noted the slow onset of action of oral meloxicam, its poor water solubility, and he specifically noted that the molecule is not approved for acute pain. Thus, it is unclear to me whether meloxicam is a good choice of drug for this indication and route of administration. While our Biometrics team has not conducted a formal PK-PD correlation of this drug product, as discussed previously in this review, the available information demonstrate a poor correlation between plasma meloxicam levels and reported pain intensity. The lack of PK-PD correlation renders remedies that rely on dosing adjustment of dubious value. It is possible that there is something intrinsic to the meloxicam molecule that makes it ill-suited to this application. Given all of this uncertainty, the Applicant will have to demonstrate better efficacy in a relevant population or that the drug meets the expectation of an IV analgesic in combination with other drugs or that a multimodal regimen including meloxicam confers some safety advantage.

I do not consider the Applicant's proposals (b) (4) will address the end-of-dose failure and there are no good data to inform the safety of doing so.

The following comments should be conveyed to the Applicant

1. Anjeso has an onset of action in the range of 2 to 3 hours. Given the costs and risks of intravenous (IV) administration and prescriber expectations for IV drugs, this finding renders Anjeso unfit for use as an IV drug for acute pain.
2. Re-review of the efficacy and pharmacokinetic data show that efficacy (e.g. measures of pain intensity) of the product is not well correlated with drug concentration data at the same time point. Specifically, while very high plasma meloxicam concentrations are achieved shortly after the first dose, as mentioned in #1, pain relief is not experienced until Hour 2 or 3. The pharmacokinetics data alone also did not clearly explain the end-of-dose failure. Plasma meloxicam decreases by approximately 200 ng/mL from Hour 18 to 24 (from ~1700 to ~1500 ng/mL). This relatively small decrease in plasma meloxicam concentration may not be adequate to explain the loss of efficacy over the same time period. These observations make it unlikely that (b) (4) will effectively address the efficacy deficiencies observed without additional data.
3. Review of pertinent safety data are inadequate (b) (4)
4. Comparison to similar products showed that Anjeso is either the worst or nearly the worst for several metrics related to usefulness as an acute, IV analgesic. These metrics include onset of analgesia and those related to use of rescue such as the proportion of patients using rescue. The high rates of rescue used (83% and 88%) raise doubt about the efficacy of Anjeso as monotherapy.
5. While Anjeso may be useful as part of multimodal analgesia, the development program submitted to date to not contain adequate information informing the appropriate use of Anjeso as combination therapy.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

As this product is not being approved, discussion of a REMS is premature.

12. Postmarketing Requirements and Commitments

From the clinical perspective, this product is subject to the Pediatric Research Equity Act requirements. There is already an approved Pediatric Study Plan. The plan requires a juvenile toxicology study and two clinical studies. The timelines for the overall pediatric program will have to be re-assessed following the Applicant's response to this Complete Response Action.

13. Appendices

13.1. References

Gates BJ, Nguyen TT, Setter SM, Davies NM. Meloxicam: a reappraisal of pharmacokinetics, efficacy, and safety. Expert Opinion on Pharmacotherapy 2005;6:12:2117-2140.

Xu S, Rouzer CA, Marnett LJ. Oxicams, a Class of NSAIDs and beyond. IUBUM Life. 2014 December;66(12):803-8011.

13.2. Financial Disclosure

Not Applicable

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/

ROBERT B SHIBUYA
03/22/2019 10:34:51 AM

SHARON H HERTZ
03/22/2019 10:38:07 AM

Combined Cross-Discipline Team Leader (CDTL) Review and Summary Review for Regulatory Action

Date	(electronic stamp)
Cross-Discipline Team Leader	Joshua Lloyd, MD
Deputy Division Director	Ellen Fields, MD, MPH
NDA	210583
Applicant	Recro Pharma, Inc.
Date of Submission	July 26, 2017
PDUFA Goal Date	May 26, 2018
Proprietary Name	Anjeso
Established or Proper Name	Meloxicam
Dosage Form(s)	Intravenous injection
Applicant Proposed Indication(s)/Population(s)	Management of moderate-to-severe pain
Applicant Proposed Dosing Regimen(s)	30 mg once daily, administered by intravenous bolus injection over 15 seconds
Recommended Regulatory Action	Complete Response

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Anjeso is a once daily 30 mg injectable formulation of the nonsteroidal anti-inflammatory drug meloxicam that was developed for the proposed indication of the management of moderate-to-severe pain. The Applicant conducted two Phase 3 studies to evaluate the efficacy of Anjeso compared to placebo for the treatment of postoperative pain. Both pivotal efficacy studies demonstrated a statistically significant difference between Anjeso and placebo on the primary endpoint. However, the results of the secondary analyses indicate that the analgesic effect does not persist through the dosing interval resulting in a significant period of inadequate analgesia of approximately six hours. Additionally, the results for time to meaningful pain relief and time to first rescue use indicate a delayed onset of action that is not consistent with expectations for an intravenous analgesic for acute pain. In the abdominoplasty study, median time to meaningful pain relief occurred approximately two hours after median time to first rescue use, indicating that meaningful pain relief may have been more associated with the dose of oral oxycodone than Anjeso. The frequent use of rescue medication by the vast majority of patients also suggests that Anjeso does not provide analgesia suitable to manage postoperative pain. Although the safety profile is generally consistent with that of other NSAIDs, the efficacy results indicate that Anjeso is not appropriate for use as an intravenous analgesic in the setting of acute pain.

Additionally, there are unresolved product quality and nonclinical issues related to extractables and leachables testing.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pain is associated with a variety of injuries and illnesses and impacts millions of Americans' lives each year • Acute pain is generally self-limited and typically requires treatment for no more than up to a few weeks • Postoperative pain is an important category of acute pain	Acute pain may be initially managed with intravenous analgesics in a hospital setting followed by oral analgesic therapy. Adequate pain control is a critical component of patient's postoperative recovery.
Current Treatment Options	• Acute pain is generally managed with one or more of the following analgesics: 1) Acetaminophen (oral and IV) 2) NSAIDs (oral and IV) 3) Immediate-release opioid products (e.g., hydrocodone, oxycodone) in combination with other analgesics (e.g., acetaminophen, ibuprofen) 4) Single-ingredient opioid products (oral and IV)	Oral meloxicam is available for use in chronic conditions; however, it is not appropriate for use as an acute analgesic as formulated in currently approved products due to a prolonged Tmax and, therefore, onset of action. Although an IV formulation of meloxicam is not currently available, other IV NSAID formulations, including ibuprofen, diclofenac, and ketorolac, are available.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant submitted results from two Phase 3 randomized clinical trials evaluating the analgesic efficacy of once daily dosing with 30 mg of Anjeso (meloxicam) compared to placebo. One of the studies was conducted in patients who underwent abdominoplasty, and the other was conducted in patients who underwent bunionectomy. • The primary endpoints were summed pain intensity difference (SPID) over 24 hours (SPID24) for the abdominoplasty study and SPID48 for the bunionectomy study. A primary endpoint that evaluates efficacy over multiple dosing intervals is preferred for acute pain studies. Therefore, the Agency additionally evaluated SPID48 for the abdominoplasty study. • The Applicant demonstrated a statistically significant difference between Anjeso and placebo on the primary endpoints and the SPID48 for the abdominoplasty study. • However, the results on several secondary endpoints did not support the clinical relevance of the primary results for the proposed acute pain indication. Specifically: 1) Pain intensity difference curves over time and analyses of SPID over the latter part of the 24-hour dosing interval demonstrated that the analgesic effect does not persist through the dosing interval, resulting in a significant period of inadequate analgesia of approximately six hours. 2) Results for time to meaningful pain relief and time to first rescue use indicate a delayed onset of action that is not appropriate for an IV analgesic for acute pain. In the abdominoplasty study, median time to meaningful pain relief occurred approximately two hours after median time to first rescue use, indicating that meaningful pain relief may have been more associated with the dose of oral oxycodone than Anjeso. 3) The frequent use of rescue medication suggests that Anjeso does not provide analgesia suitable to manage postoperative pain.	The Applicant has not demonstrated the clinical meaningfulness of the findings on the primary endpoints for Anjeso for the proposed indication, primarily due to lack of support from the results on the secondary analyses discussed.
Risk and Risk Management	• The Applicant provided an adequately sized safety database to evaluate the safety of Anjeso for the proposed indication. • The overall safety profile of Anjeso is consistent with what has been observed in patients treated with NSAIDs as a class, particularly one that is administered IV over a short duration • Higher frequencies of bleeding events/anemia were observed in certain populations of patients (e.g., open abdominal hysterectomy) treated with	Overall, the safety profile of Anjeso is consistent with other NSAIDs, particularly for one that is administered IV over a short duration. There are unresolved product quality and nonclinical issues related to extractables and leachables testing.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Anjeso compared to placebo. Further analysis is needed to evaluate the frequency of these events by postoperative subpopulations. • There are unresolved product quality and nonclinical issues related to extractables and leachables testing.	

2. Background

Anjeso[1] is an injectable formulation of meloxicam, a nonsteroidal anti-inflammatory drug (NSAID) of the enolic acid (oxicam) class that is relatively selective for COX-2 inhibition, particularly at lower doses. Anjeso is administered as a once daily 30 mg intravenous injection for patients with acute pain (e.g., postoperative) and has a proposed indication of the management of moderate-to-severe pain. The Applicant submitted a 505(b)(2) NDA for Anjeso relying on the Agency's previous findings for Mobic (meloxicam) tablets (NDA 20938), which were approved in April, 2000, and carry indications in osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis. Meloxicam is available in multiple oral formulations to treat these chronic painful and/or inflammatory conditions. Multiple NSAIDs are available in oral and injectable dosage forms for acute pain conditions, and opioids and acetaminophen are also used in this setting. If approved, Anjeso would be the first injectable meloxicam product and the first meloxicam product indicated for acute pain.

Anjeso was developed under IND 105,172 and the Division held multiple meetings with the Applicant where, among other things, agreement was reached on the overall safety and efficacy data that would be required for an NDA submission. On multiple of these occasions, the Division expressed concern over the once daily dosing regimen for an intravenous (IV) analgesic and the fact that neither plasma levels nor analgesic effect appear to be sustained over the 24-hour period after dosing. Due to this concern, the Division requested that the Applicant provide analyses to support evidence of analgesia over the latter part of the dosing interval.

3. Product Quality

The drug product is an intravenous formulation of meloxicam; is a sterile, opaque, pale-yellow, aqueous dispersion packaged in a clear glass vial; and does not require reconstitution (i.e., "ready-to-use"). Each milliliter (ml) contains 30 mg of meloxicam, povidone, sodium deoxycholate (b) (4) sucrose, and water for injection. The formulation employs proprietary NanoCrystal Colloidal Dispersion technology, which is intended to increase the dissolution rate of meloxicam and provide a faster onset of action to treat acute pain.

Sterilization (b) (4) which the microbiology review team found to be adequate. A 48-month expiry was granted for drug product stored under long-term conditions of 25°C. The manufacturing facilities were deemed acceptable, and DMF (b) (4) for the drug substance was found to be adequate. The request for a categorical exclusion from the requirement to prepare an environmental assessment was determined to be acceptable.

However, the product quality team is recommending a complete response due to an inadequate assessment of extractables/leachables of the drug product. Specifically, the Applicant did not provide adequate leachables testing through the shelf-life of the drug product and there was

[1] Also referred to as N1539

lack of a correlation between the extractables and leachables testing (i.e., leachables detected that were not also observed in the extractables study). The product quality team has provided comments for the Applicant regarding these deficiencies. I concur with the conclusions reached by the product quality review team.

4. Nonclinical Pharmacology/Toxicology

Nonclinical data were required to support the systemic safety of the higher exposures achieved with Anjeso compared to the referenced product (refer to Section 5 of this review), as well as local safety, including blood compatibility studies, due to the change in route of administration from the referenced product.

The Applicant conducted repeat-dose toxicology studies in rats, rabbits, and minipigs at durations of up 28 days in rats and minipigs. The nonclinical team noted that there were "no significant adverse systemic findings aside from the gastrointestinal toxicities typically associated with compounds in the NSAID class" and that "the systemic safety of the product is considered adequately justified for the intended clinical use from the nonclinical perspective." A 28-day repeat-dose intravenous (IV) study in minipigs was conducted with the 30 mg/ml formulation to address the local safety of the to-be-marketed (TBM) product. According to the nonclinical review, the minipig IV study "showed very slight to well-defined erythema at IV and perivascular injection sites, but no correlating microscopic changes. In addition, no hemolysis or changes in macroscopic appearance were associated with the TBM 30 mg/mL formulation. Therefore, the local safety of the product is considered adequately justified from the nonclinical perspective."

However, the nonclinical review team found that the application did not adequately evaluate extractables and leachables. According to the nonclinical review:

> The NDA did not include an adequate extractables and leachables evaluation to justify the safety of potential leachables arising from the container closure system and from (b) (4) manufacturing contact materials. Although appropriate extraction and analytical methods were employed, there were several compounds detected in extraction studies and in an aged drug product sample that were either not identified or not adequately justified for safety. The Applicant argued that if a compound, identified or unidentified, was detected in an extraction study but not in the aged product, that it must not be a true leachable. However, the aged product evaluation included only one drug product batch at only one time point on stability (e.g., 14 months). This is insufficient alone to make any conclusions in this regard as leachables may be produced at earlier or later time points on stability and sampling from several batches over the course of stability program is best practice for definitive leachables testing to provide reasonable assurance of capturing peak levels of individual leachables. Since the Applicant dismissed these unknown compounds, the definitive leachables study, which appropriately tested three batch at numerous time points on stability, only targeted two organic leachables (b) (4)). Neither leachable was detected at levels greater than 5 mcg/day in any batch at any time point. However, the extractable/leachable evaluation should have identified the unknown extractables and targeted them in the definitive leachables study.

The nonclinical team has provided comments for the Applicant regarding these deficiencies. I concur with the conclusions reached by the nonclinical review team.

5. Clinical Pharmacology

As described in the clinical pharmacology review, the Applicant conducted four Phase 1 studies to evaluate the pharmacokinetics (PK) of Anjeso, including an evaluation of relative bioavailability between Anjeso and the referenced product Mobic. Anjeso is proposed to be given as a once daily 30 mg IV bolus injection administered over 15 seconds. Whereas, the maximum approved dose for Mobic is 15 mg once daily by mouth.

Meloxicam has a prolonged absorption (i.e., Tmax of 5 to 6 hours) and slow onset of action when administered orally owing to its poor water solubility. Meloxicam is currently approved for chronic indications only. Anjeso was developed to enhance the dissolution rate of meloxicam with the intention of achieving a more rapid onset of action more appropriate for use in an acute pain setting.

The Applicant studied two formulations of Anjeso over the course of development. A 25.5 mg/ml formulation was used in early studies followed by the 30 mg/ml to-be-marketed (TBM) formulation, which was used in some of the Phase 1 and Phase 2 studies and all of the Phase 3 studies. The clinical pharmacology review team noted that the ingredients were the same for both formulations and that the ratio of active pharmaceutical ingredient to excipients are identical. Although the Applicant did not conduct a PK study comparing the two formulations, the clinical pharmacology review team concluded that the PK information obtained using the 25.5 mg/ml formulation may support the TBM formulation because there are relatively small differences between formulations and the PK parameters are similar between formulations based on cross-study comparison.

A single 30 mg IV dose of Anjeso produced an approximately 2-fold higher AUC and 4-fold higher Cmax compared to 15 mg of Mobic administered orally. The Tmax for Anjeso was achieved shortly after administration, consistent with IV dosing, and the half-life was approximately 23 hours as compared to approximately 26 hours for Mobic. Individual and pooled analyses demonstrated that overall and peak meloxicam exposures with Anjeso increased proportionally over the doses administered (i.e., up to 180 mg). Steady state was achieved after seven consecutive days of once daily dosing with a slightly higher than two-fold increase in AUC. An evaluation of the effect of renal impairment on meloxicam PK with Anjeso was conducted in older subjects with mild renal impairment compared to healthy younger subjects with normal renal function, which did not identify a meaningful clinical difference in Cmax or AUC for meloxicam between groups.

The Applicant submitted data from a concentration-QT (C-QT) study (REC-15-019) to evaluate the QT prolonging potential of Anjeso, and this was evaluated by the QT-interdisciplinary review team (QT-IRT). Although the study only employed a placebo control (i.e., no positive control), the QT-IRT concluded that Anjeso does not prolong the QTc interval.

I concur with the conclusions reached by the clinical pharmacology review team that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The Applicant conducted two adequate and well-controlled Phase 3 clinical trials to evaluate the efficacy of Anjeso compared to placebo for the treatment of postoperative pain to support the proposed indication.

Study REC-15-015

Study REC-15-015 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial in patients with moderate-to-severe pain following abdominoplasty surgery. Patients received once daily treatment with Anjeso over 48 hours and were eligible to receive a third dose prior to discharge. Oxycodone 5 mg by mouth every 2 hours as needed for pain was available as a rescue analgesic; however, patients were encouraged to wait at least one hour after receiving study drug prior to requesting rescue analgesia. Pain intensity was rated on an 11-point numeric rating scale (NRS), and the primary endpoint was the summed pain intensity difference (SPID) from 0 to 24 hours (SPID24). Time to first perceptible pain relief and meaningful pain relief were evaluated using the double stopwatch method. Time to first rescue medication use and frequency of rescue medication use were also evaluated.

A total of 219 patients were randomized with the vast majority having completed the 48-hour pain assessment and the study (approximately 98% and 95%, respectively). Too few patients discontinued treatment or the study to identify trends in reasons for discontinuation. The majority of patients were female (98%) and Caucasian (63%), with a mean age of approximately 40 years.

The difference in SPID24, the primary endpoint, between treatment groups was statistically significant. Dr. Zhou, statistical reviewer, confirmed a similar finding on the SPID48 in order to evaluate efficacy over multiple dosing intervals. However, pain intensity difference curves and an analysis of SPID18-24 and SPID42-48 showed that there was no significant difference between Anjeso and placebo over the last six hours of the dosing interval indicating a significant end-of-dose failure for analgesia.

Approximately 88% and 91% of patients in the Anjeso and placebo groups, respectively, used rescue medication over the 48 hours following randomization with a median time to first rescue in each group of approximately one hour. The mean number of rescue medication doses was 3.4 and 1.6 in the first and second 24 hours of dosing, respectively, for the Anjeso group, compared to 4.2 and 2.6 for the placebo group, respectively. More patients in the

placebo group used rescue medication than the Anjeso group; however, patients in the Anjeso group still required a mean of 17 mg of oxycodone in the first 24 hours.

Overall, less than 27% of patients experienced meaningful pain relief within the first 12 hours with a median time to meaningful pain relief of approximately 3 hours for both treatment groups. Notably, the median time to meaningful pain relief occurred approximately two hours after the median time to first rescue use. The Kaplan-Meier estimates of time to meaningful pain relief were not statistically significant between the two treatment groups.

Study REC-15-016

Study REC-15-016 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial in patients with moderate-to-severe pain following unilateral bunionectomy. This study was designed similarly to Study REC-15-015; however, the primary endpoint was SPID48.

A total of 201 patients were randomized with the vast majority having completed the 48-hour pain assessment and the study (approximately 95% and 97%, respectively). Similar to the prior study, too few patients discontinued treatment or the study to identify trends in reasons for discontinuation. The majority of patients were female (85%) and Caucasian (64%), with a mean age of approximately 47 years.

The difference in SPID48, the primary endpoint, between treatment groups was statistically significant. However, pain intensity difference curves demonstrated a narrowing of the difference between Anjeso and placebo towards the end of the dosing interval. Additionally, an analysis of SPID18-24 and SPID42-48 showed that there was no significant difference between Anjeso and placebo over the last six hours of the dosing interval. Similar to the prior study, these results indicate a significant end-of-dose failure for analgesia.

Approximately 83% and 98% of patients in the Anjeso and placebo groups, respectively, used rescue medication over the 48 hours following randomization with a median time to first rescue of approximately 2 hours in each group. However, the Kaplan-Meier estimates of time to first rescue use was statistically significant between the two treatment groups in this study as opposed to the prior study. The mean number of rescue medication doses for the Anjeso group was 4.1 and 1.7 in the first and second 24 hours of dosing, respectively, compared to 5.2 and 2.7 for the placebo group, respectively. More patients in the placebo group used rescue medication than the Anjeso group; however, patients in the Anjeso group still required a mean of 21 mg of oxycodone in the first 24 hours.

Overall, less than 50% of patients experienced meaningful pain relief within the first 12 hours with a median time to meaningful pain relief of approximately 2.2 hours for the Anjeso group and 3.2 hours for the placebo group. However, the Kaplan-Meier estimates of time to meaningful pain relief were not statistically significant between the two treatment groups.

Study REC-15-017

Study REC-15-017 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial evaluating the safety of Anjeso following a variety of surgical procedures. Although this study did not assess pain intensity or other measures of analgesia, it evaluated opioid consumption between groups, reported as an IV morphine equivalent dose. The study demonstrated slightly lower opioid consumption with numerically less nausea, vomiting, pruritus, and dizziness for the Anjeso group as compared to placebo. However, this study was not adequately designed to determine if any reduction in opioid consumption was clinically-relevant (e.g., improvement on a prespecified clinically-relevant opioid-related safety outcome).

Summary

Both pivotal efficacy studies demonstrated a statistically significant difference between Anjeso and placebo on the primary endpoint. However, the results of the secondary analyses indicate that the analgesic effect does not persist through the dosing interval resulting in a significant period of inadequate analgesia (i.e., of approximately six hours). Additionally, the results for time to meaningful pain relief and time to first rescue use indicate a prolonged onset of action that is not appropriate for an intravenous analgesic. In the abdominoplasty study, median time to meaningful pain relief occurred approximately two hours after median time to first rescue use, indicating that meaningful pain relief may have been more associated with the dose of oral oxycodone than Anjeso. The frequent use of rescue medication by the vast majority of patients also suggests that Anjeso is not suitable as a standalone analgesic. For these reasons, both the clinical and statistical review teams are recommending a complete response action for this application, and I concur with their conclusions.

8. Safety

The Applicant submitted a safety database in postoperative patients that consisted of three Phase 2 studies, the two pivotal Phase 3 efficacy studies, and an additional placebo-controlled Phase 3 study that was designed to evaluate the safety of Anjeso in postsurgical patients (Study REC-15-017; briefly described in Section 7 above). As was discussed with the Applicant during development, a safety database that consisted of at least 1,000 exposures, with at least half of those exposed to multiple doses, was required due to the higher exposures to meloxicam with Anjeso as compared to the referenced product. The Applicant was advised to include as many patients as possible for durations up to seven days due to when steady state is achieved.

The extent of exposure included a total of 1,099 postoperative patients exposed to the 30 mg dose or higher (i.e., 60 mg) with 903 patients exposed to 2 or more doses, 526 patients exposed to 3 or more doses, and 4 patients exposed to 7 or more doses. An additional 327 patients received lower doses of Anjeso in the range of 5 to 15 mg and additional healthy subjects were exposed to Anjeso in the context of the Phase 1 studies. A total of 293 postoperative patients

exposed to the 30 mg dose or higher were male, 132 were 65 years of age or older, and 96 were high risk, defined as 65 years of age or older with mild renal impairment.[2]

A 39-year old placebo-treated patient died due to complications of the toxic effects of methamphetamine after having withdrawn from the study to address a personal issue. No other deaths were reported in the program. Serious adverse events (SAEs) were reported in 15 (2.9%) patients in the placebo group (including the subject who died), 5 (1.5%) patients in the Anjeso 5 to 15 mg group, and 15 (1.6%) patients in the Anjeso 30 mg group. No SAEs were reported in patients in the Anjeso 60 mg group. Many of the SAEs are typical of a postoperative population but may also be seen in the setting of NSAID therapy (e.g., bleeding, poor wound healing, acute kidney injury). However, no overall trends were observed with respect to comparison of Anjeso to the placebo group or within the doses of the Anjeso groups. SAEs are summarized in the table below:

[2] The Division requested safety be evaluated in this high risk group and noted that the minimum number of patients in this category that would be necessary to constitute an adequate evaluation would depend on the PK in this group compared to younger healthy subjects. The Applicant submitted PK data to suggest that there was not a meaningful clinical difference in Cmax or AUC for meloxicam between older subjects with mild renal impairment and healthy younger subjects with normal renal function. Refer to Section 5 of this review.

Parameter	Placebo N=517	N1539 5-15 mg N=327	N1539 30 mg N=910	N1539 60 mg N=189
Subjects with ≥1 SAE, n (%)	15 (3)	5 (2)	15 (2)	0
Number of reported SAEs	18	5	21	0
Blood and lymphatic system disorders, n (%)				
Anemia	0		1 (0.1)	
Cardiac disorders, n (%)				
Coronary artery disease	1 (0.2)		0	
Gastrointestinal disorders, n (%)				
Intestinal perforation	0	0	1 (0.1)	0
Jejunal stenosis	1 (0.2)		0	
Nausea	1 (0.2)	0	0	0
Omental infarction	0		1 (0.1)	
Small bowel obstruction	0	0	2 (0.2)	0
Ileus	0	0	0	0
		0		0
General disorders and administration site conditions, n (%)		0		0
Sudden death	1 (0.2)	0	0	0
Hepatobiliary disorders, n (%)		0		0
Hepatocellular injury	1 (0.2)		0	
Infections and infestations, n (%)		0		0
Abdominal abscess	1 (0.2)		0	
Diverticulitis	0		1 (0.1)	0
Incision site infection	0	0	1 (0.1)	
Mesenteric abscess	0		1 (0.1)	0
Pneumonia	0	0	1 (0.1)	0
Postoperative abscess	1 (0.2)	0	0	0
Postoperative wound infection	1 (0.2)	1 (0.3)	0	0
Septic shock	0	0	1 (0.1)	0
		0		0
		0		0
		0		0
		0		

Injury, poisoning and procedural complications, n (%)				
Anastomotic ulcer	1 (0.2)		0	
Femoral neck fracture	0		1 (0.1)	
Fracture	1 (0.2)		0	
Incisional hernia	1 (0.2)		0	0
Post procedural hemorrhage	1 (0.2)	0	1 (0.1)	0
Post procedural pulmonary embolism	1 (0.2)	0	3 (0.3)	0
Postoperative ileus	1 (0.2)	0	1 (0.1)	0
Tendon injury	0	0	1 (0.1)	0
Wound Healing complications, n (%)		1 (0.3)		0
		0		0
Wound dehiscence		1 (0.3)		0
Investigations, n (%)		0		
Liver function test abnormal	1 (0.2)		0	
Metabolic and nutrition disorders, n (%)				0
Hypervolaemia	0 0	1 (0.3)	0 1 (0.1)	
Nervous system disorders, n (%)		0		0
Dizziness	1 (0.2)		0	
Renal and urinary disorders, n (%)		0		0
Acute kidney injury	0		2 (0.2)	
Respiratory, thoracic and mediastinal disorders, n (%)		0		0
Dyspnoea	1 (0.2)		0	
Respiratory arrest	1 (0.2)	0	0	0
Respiratory distress	0		1 (0.1)	
Gynecological, n (%)		0		0
Vaginal hemorrhage		0		0
		0		0
		1 (0.3)		0
	0		0	

Source: Dr. Jiang, clinical reviewer

Very few postoperative patients discontinued taking Anjeso due to an adverse event. One patient in the 5 to 15 mg Anjeso group discontinued (maculopapular rash) and two patients in the 30 mg Anjeso group discontinued (localized edema, post-procedural pulmonary embolism).

Among the common adverse events, nausea, headache, vomiting, and dizziness were most commonly reported. Some of the typical opioid-related adverse events were reported at higher frequencies in the placebo group as compared to the Anjeso group.

The Applicant analyzed adverse events of special interest related to concerns associated with NSAID therapy, including bleeding, cardiovascular, hepatic, injection site reactions, renal, thrombotic, and wound healing events, as well as safety in patients 65 years of age and older with mild renal impairment (high risk group) compared to younger patients with normal renal function.

These analyses revealed a higher frequency of bleeding events/anemia with Anjeso, particularly in the 5 to 15 mg and 60 mg dose groups, compared to placebo. Some of these events required blood transfusion. Dr. Jiang noted this result was largely driven by the Phase 2 study N1539-04. Study N1539-04, which enrolled patients undergoing open abdominal hysterectomy, and the other Phase 2 studies, which included patients undergoing laparoscopic abdominal surgery, were the studies that involved a range of doses of Anjeso. Further analysis of pooled safety data is necessary to determine if particular surgical subpopulations may be at increased risk for bleeding events/anemia in the presence of an IV NSAID due to the nature of the procedure. Adverse events were generally comparable between the high risk group and younger patients with normal renal function with the exception of anemia and constipation, which occurred at a higher frequency in the high risk group. Analyses on the remaining adverse events of special interest did not identify a particular new safety concern associated with IV administration of meloxicam.

Dr. Jiang concluded that "the overall safety profile of [Anjeso] is consistent with what has been observed in patients treated with NSAIDs as a class, particularly one that is administered IV over a short duration."

9. Advisory Committee Meeting

An Advisory Committee was not convened for this application.

10. Pediatrics

The Applicant reached an agreed Pediatric Study Plan (PSP) with the Division, in consultation with the Pediatric Review Committee (PeRC), as communicated in an agreement letter dated June 29, 2016. The Applicant's pediatric plan was discussed at PeRC on April 11, 2018, and includes a request for a partial waiver in patients less than one year of age and a deferral of studies in the remaining age groups. The deferred studies consist of an evaluation of

pharmacokinetics (PK), safety, and efficacy in 1 to <2 years of age and PK and safety in 2 to <17 years of age. The PK results in 2 to <17 are intended to support extrapolating the analgesic efficacy from adults to pediatric patients two years of age and older. The PSP also includes a juvenile toxicology study to be completed prior to conducting studies in patients <2 years of age; however, this study was not included in the PSP timeline. PeRC recommended that the juvenile toxicology study be included in the timeline in the PSP and that this be communicated to the Applicant in the action letter.

11. Other Relevant Regulatory Issues

Clinical Site Inspections

Jenn Sellers, MD, PhD, from the Office of Scientific Investigations (OSI) completed the Clinical Inspection Summary for this application. Two clinical investigator sites, one from each pivotal efficacy study, were selected for audit by the Agency. OSI found that

> The clinical sites of Drs. Leiman and Pollak were inspected in support of this NDA. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.
>
> The preliminary classification of both inspections (of Drs. Leiman and Pollak) was No Action Indicated (NAI).

Financial Disclosures

The Applicant provided certification that there were no financial interests or arrangements to disclose.

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Anjeso, to be acceptable. DMEPA also provided comments on the proposed package insert and the carton and container labeling. DMEPA's comments on the carton and container labeling were sent to the Applicant, and DMEPA found the revised carton and container labeling based on these comments acceptable. The Division of Pediatric and Maternal Health (DPMH) reviewed the proposed pregnancy and lactation labeling and supporting information submitted by the Applicant.

Additional labeling recommendations were not discussed with the Applicant given the deficiencies in the application at this time.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A REMS is not required for this application.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

If the deficiencies can be adequately addressed, pediatric studies based on the requirements of the Pediatric Research Equity Act will be required.

14. Recommended Comments to the Applicant

Deficiencies

Although you have demonstrated a statistically significant difference between Anjeso and placebo on the primary endpoint in Studies REC-15-015 and REC-15-016, the results of the secondary analyses, including pain intensity difference over time curves, SPID18-24, SPID42-48, indicate that the analgesic effect does not persist through the dosing interval resulting in a significant period of inadequate analgesic effect with your product (i.e., of approximately six hours). Additionally, the results for time to meaningful pain relief and time to first rescue use indicate a prolonged onset of action that is not appropriate for an IV analgesic, and the frequent use of rescue medication suggests that Anjeso is not suitable as a standalone analgesic.

Additional Comments

We have the following comments/recommendations that are not approvability issues:

Safety

Analyze and report the frequency of bleeding events and anemia (adverse events of special interest analysis) by surgical procedure and by dose based on the pooled Phase 2 and 3 postoperative safety data. Also analyze and report the frequency of these events for each of the Phase 2 and Phase 3 studies separately and tabulate the data by dose. With each table, summarize if any of the events were classified as serious, if any treatments were required, and any outcomes for the patients included in each of the tables and/or provide links to this information in the application.

Pediatrics

We note that your agreed pediatric study plan (PSP) includes a juvenile toxicology study. However, you have not included the timeline for conducting this study in Section 10 **Timeline of the Pediatric Development** Plan of the PSP. Submit an updated PSP with your resubmission that includes the juvenile toxicology study in the timeline.

Deputy Division Director Comments

I concur with Dr. Lloyd on the regulatory action and recommend a complete response for this application. I also concur with the reasons for the action as stated in Dr. Lloyd's review. The Applicant has not provided data to support the efficacy of Anjeso for the proposed indication.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSHUA M LLOYD
05/23/2018

ELLEN W FIELDS
05/23/2018

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	210583
Priority or Standard	Standard
Submit Date(s)	July 26, 2017
Received Date(s)	July 26, 2017
PDUFA Goal Date	May 26, 2018
Division/Office	DAAAP/ODE2
Reviewer Name(s)	Timothy T. Jiang
Review Completion Date	(Electronic stamp)
Established/Proper Name	Meloxicam
(Proposed) Trade Name	ANJESO
Applicant	Recro
Dosage Form(s)	IV
Applicant Proposed Dosing Regimen(s)	30 mg, once-a-day
Applicant Proposed Indication(s)/Population(s)	Indicated in adults for the management of moderate to severe pain
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	N/A

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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
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

N1539 (proposed trade name: ANJESO) is a new parenteral form of the nonsteroidal anti-inflammatory drug (NSAID) of the enolic acid class, meloxicam, which was first approved for oral use in the United States in 2000 for the management of chronic indications such as osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis in children two years of age and older.

By dissolving the active meloxicam moiety by using the proprietary NanoCrystal technology, N1539 was formulated for intravenous bolus administration. The proposed indication for N1539 is the management of moderate to severe pain in adults. The to-be-marketed dose of N1539 is 30 mg once daily, administered by intravenous (IV) bolus injection over 15 seconds

1.2. Conclusions on the Substantial Evidence of Effectiveness

The N1539 Phase 3 clinical program was designed with a primary endpoint that evaluated the effect of N1539 on moderate to severe pain after surgery. The primary endpoint was the time-weighted sum of pain intensity difference (SPID) as compared to placebo. In the Phase 3 studies (REC-15-015, and REC-15-016), the study drug was used in randomized, double-blind, placebo-controlled clinical trials in two different pain models (abdominoplasty and bunionectomy). Patients with inadequately controlled pain symptoms could request rescue analgesia (oral oxycodone 5 mg administered up to every two hours). To account for the use of rescue medications, pain intensity (PI) was measured prior to a rescue use and was carried forward to replace PI scores collected within two hours following this rescue use.

The once daily dosing of this parenteral analgesic met the primary endpoints, SPID24 and SPID48, in abdominoplasty (REC-15-015) and bunionectomy (REC-15-016), respectively. However, the efficacy as an acute analgesic at the proposed dosing interval is not established due to the failure in key secondary endpoints:

<u>End-of-dosing failure</u>
The analyses of pain intensity difference (PID) show that there were no significant differences during the last six hours of the dosing interval in both studies. The secondary analysis evaluating analgesic effect over the last six hours of 24-hour dosing interval demonstrated no difference in pain intensity (SPID18-24) over the last six hours between treatment and control in both surgical models suggesting that the proposed dosing interval is not appropriate. The lack of an analgesic effect over a six-hour long period at the end of 24-hour dosing is clinically significant for inadequate lasting pain relief.

Delayed Onset

A short time to first rescue use and delayed meaningful pain relief in both models (though it is more pronounced in abdominoplasty than bunionectomy) suggests an onset of action that is not appropriate for an IV analgesic in an acute pain setting. For REC-15-015 (abdominoplasty), the mean times to first rescue were 1.08, and 1.09 hours for study drug and placebo respectively, and the times to meaningful pain relief were 3.02 and 2.92 hours respective. For REC-15-016 (bunionectomy), the mean times to first rescue were 1.99 vs. 2.09 hours respectively for study drug and placebo; the times to meaningful pain relief were 2.16, and 3.19 hours respective.

A meaningful pain relief is typically achieved within the first hour for an IV NSAID analgesic, and the time to achieve meaningful pain relief for study drug is delayed by that standard.

It is noted the time to meaningful pain relief were evaluated using the double-stop watch method without regarding first use of rescue. Therefore, it is noted that for both studies, albeit more pronounced in abdominoplasty, the time to meaningful pain relief was achieved only after the first rescue. For abdominoplasty, in the treatment arm, the time to first rescue was one hour and the time to meaningful pain relief was about three hours. The meaningful pain relief was achieved temporally two hours after oral dose of 5 mg oxycodone. Therefore, it could be argued that the meaningful pain relief was, at least partially, achieved by the 5 mg Oxycodone given earlier.

With the end-of-dosing failure and the delayed onset, the frequent rescue of about four times (up to 20 mg Oxycodone) over 24 hours even in the active treatment arm is expected.

In conclusion, the end-of-dosing failure and the delayed onset suggest that the N1539, given 30 mg IV daily, is not suitable as an analgesic for use in the management of acute pain at the proposed dosing interval. Therefore, I recommend a Complete Response action for this application.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

N1539 is a new parental form of the NSAIDs meloxicam, formulated for administered intravenous bolus. Applicant proposed N1539 30 mg given once daily for the management of moderate to severe pain.

The efficacy of N1539 for the management of acute moderate to severe pain was not established in the two pivotal Phase 3 trials (REC-15-015 and REC-15-016). Phase 3 studies were multicenter, randomized, double-blind, placebo-controlled, parallel trials following abdominoplasty, and bunionectomy. Patients with inadequately controlled pain symptoms could request rescue analgesia (oral oxycodone 5 mg administered up to every two hours). To account for the use of rescue medications, pain intensity (PI) was measured prior to a rescue use and was carried forward to replace PI scores collected within two hours following this rescue use.

In both trials, the primary endpoints were met i.e., a greater proportion of patients treated with N1539 achieved statistically significantly higher mean SPID scores over the prespecified time interval (SPID24 in abdominoplasty and SPID48 in bunionectomy) compared to placebo. However, the primary endpoints were not supported by analyses on several important secondary endpoints in both trials to support an acute pain indication. The analyses on the secondary endpoints demonstrated no difference in SPID18-24 (end-of dosing failure), delayed onset of pain relief (delayed time to meaningful pain relief, early time to first rescue, and time to meaningful pain relief being temporally associated with administration of first rescue), and a high frequency of rescue medication use, even in the active treatment arm. The times to meaningful pain relief were about two hours and three hours, respectively in abdominoplasty and bunionectomy even in the treatment arm. Meaningful pain relief is typically achieved within the first hour for an IV NSAID analgesic, and the time to achieve meaningful pain relief for study drug is delayed by that standard. In addition, since time to meaningful pain relief were evaluated without considering rescue use, it could be argued that the meaningful pain relief was only achieved by the first rescue (5 mg oral oxycodone) at least in the abdominoplasty study as the meaningful pain relief was achieved about two hours (at about three hours) after the first rescue (at about one hour). The overall efficacy results suggest that N1539 given at 30 mg once daily has an end-of-dosing failure as given at the proposed dose interval, and delayed onset which is not suitable as an acute analgesic.

From safety perspective, there are no serious adverse effects (SAEs) attributed to N1539 in the Phase 3 studies, the common adverse effects (AEs) were consistent with historical knowledge of an NSAID's safety profile, particularly one that is administered IV over a short duration.

Clinical Review
Timothy T. Jiang
NDA210583
Meloxicam Injection (ANJESO)

I recommend a Complete Response action for this application as the Applicant has not developed a parental NSAIDs which is suitable for an acute indication with a rapid onset and the analgesic efficacy lasting the duration of the intended dosing interval.

Although the Applicant noted a slight reduction in opioid analgesic use and a slight decrease in some opioid related AEs with N1539 (Anjeso) as compared to the placebo group, in order to obtain a claim around opioid sparing, the Applicant would need to provide replicated evidence supporting the clinical relevance of any reduction in opioid usage. This may be possible by evaluating whether there is a clinically-meaningful improvement in safety for one or more pre-specified opioid-related safety outcomes (e.g., respiratory, gastrointestinal), or a clinically relevant proportion of patients who do not require opioid analgesics when compared to an appropriate control.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute pain can be caused by many events or circumstances • Symptoms can last hours, days, or weeks and are commonly associated with tissue injury, inflammation, a surgical procedure, childbirth, or a brief disease process Clinical symptoms of acute pain often include increased heart rate, blood pressure, and respiratory rate, shallow respiration, agitation or restlessness, facial grimaces, or splinting • Acute pain is a combined constellation of unpleasant sensory, emotional, and mental experiences and associated with autonomic, endocrine-metabolic, physiological, and behavioral responses • Post-surgical pain is a major form of acute pain	Inadequate acute pain control can result in increased morbidity or mortality Effective postsurgical analgesia is an essential component in the care of the surgical patient
Current Treatment Options	• Current treatments for acute pain from surgery includes opioids, acetaminophen (APAP), and NSAIDs	A multimodal strategy including NSAIDs for acute pain has been advocated IV NSAIDs with long acting and rapid onset will be clinically useful

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Two Phase 3 studies won the primary endpoints (SPID24 or SPID 48), but failed in key secondary endpoints: • End-of-dosing failure (equally pronounced in two surgical models) as demonstrated by: No difference in SPID18-24 Frequent rescue (up to 20 mg Oxycodone over first 24 hours) • Delayed onset (abdominoplasty is more pronounced than bunionectomy) as demonstrated by: Short time to first rescue use Delayed meaningful pain relief Meaningful pain relief after first rescue Frequent rescue (up to 20 mg Oxycodone over first 24 hours)	Simply demonstrating efficacy throughout the dosing period is not adequate N1539 given at 30 mg once daily has an end of dosing failure as given at the proposed dose interval, and a delayed onset which is not suitable as an acute analgesic
Risk and Risk Management	• Oral meloxicam has been approved since 2000 • One unrelated death in placebo group • No SAEs attributed to the study drug • Incident of common AEs such as nausea, vomiting, dizziness was comparable between study drug and placebo • No adverse effects on wound healing	Size of the safety database was adequate to characterize safety profile The overall safety experience is consistent with that of an NSAID, particularly one that is administered IV over a short duration

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	[Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	Pain intensity
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	Wound healing
	□ 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	[Sec 2.1 Analysis of Condition]
	□ 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	[Current Treatment Options]
	□ 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 an unpleasant sensory and emotional experience usually arising from actual or potential tissue damage which last hours, days, or weeks (typically last less than three months). Acute pain can be caused by many events or circumstances. Symptoms are commonly associated with tissue injury, inflammation, a surgical procedure, childbirth, or a brief disease process.

Clinical symptoms of acute pain often include increased heart rate, blood pressure, and respiratory rate, shallow respiration, agitation or restlessness, facial grimaces, or splinting. Acute Pain is a combined constellation of unpleasant sensory, emotional, and mental experiences associated with autonomic, endocrine-metabolic, physiological, and behavioral responses.

Apart from adversely affecting the patient's comfort, acute pain can also result in increased patient morbidity or mortality. Inadequate acute pain management can increase risk for chronic pain, especially in the post-surgical setting.

According to International Association for the Study of Pain (IASP), in the United States alone, nearly 100 million surgeries take place annually. More than 80% of these surgical patients report postoperative pain. Over 70% of emergency department visits are due to pain; acute headache alone accounts for 2.1 million of these visits. Acute pain is also a common problem in family practice, sports medicine, and especially in internal medicine. Adequate acute pain treatment can improve patient quality of life and satisfaction with care, as well as enhance clinical resource management and reduce long-term costs of care.

2.2. Analysis of Current Treatment Options

Current treatments for acute pain includes opioids, acetaminophen (APAP), and NSAIDs. There are multiple formulations of meloxicam available in this country for oral and topical administration. If approved, N1539 will be the first meloxicam for parenteral administration. There are also three approved parenteral NSAIDs as the table below.

Table 1 Lists Currently Available Injectable NSAIDs

Product	Year of Approval	Indication
Ketorolac tromethamine	1989	Short-term (up to 5 days) management of moderately severe, acute pain that requires analgesia at the opioid level.
Ibuprofen	2009	Management of mild to moderate pain, and moderate to severe pain as an adjunct to opioid analgesics, and for the reduction of fever

Diclofenac	2014	Management of acute moderate to severe pain

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This product is not currently marketed in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following are the highlights of the regulatory activities that occurred during the development of N1539.

IND 105172 was opened in April 2009, the key comments made to the Sponsor as follows:

- A dental study is not adequate
- A variety of post-operative pain models will be required

An EOP2 was held in December, 2010, the key comments conveyed to the Sponsor as follows:

- Dosing interval
  - The once daily dosing regimen is unusual for a parenteral analgesic
  - While a 24-hour primary efficacy endpoint has been used as part of the data to support efficacy for parenteral products in the past, the 24-hour period represented multiple doses
  - It does not appear that the plasma levels are sustained throughout the 24-hour time after dosing
  - Specifically evaluate pain intensity during the second 12-hour period of the dosing interval
  - Simply demonstrating efficacy throughout the dosing period is not adequate
- Study renally impaired patients and elderly patients (above the age 65), and wound healing

A second EOP2 after change of ownership was held in August, 2015, the key comments conveyed to the Sponsor as follows:

- Dosing interval
  - determining your proposed dosing regimens based on single-dose studies, along with the results of the dose-ranging study

- Accept mini-abdominoplasty (under the umbilicus) as a surgical model for the Phase 3 study; while prefer SPID 48 accept SPID 24 for this surgical model
- Evaluation of a cohort of "high risk" subjects defined as those aged >65 years with mild renal impairment (GFR 60-89 mL/min/1.73 m2)
- Total exposure of at least 1000 subjects to multiple doses

A Pre-NDA meeting was held in January, 2017, the following items summarized the understandings reached between the Applicant and the Division.

- While a 24-hour primary efficacy endpoint has been used as part of the data to support efficacy for parenteral products in the past, the 24-hour period represented multiple doses for those products.
- The Sponsor must specifically demonstrate pain intensity relief during the second 12-hour period of the dosing interval.
- The two curves of PID versus time for the two Phase 3 studies both show no difference between study drug and placebo at 24 hours suggesting end-of-dose failure.
- Only a total of 17 male subjects exposed to study drug in the two efficacy studies.

3.3. Foreign Regulatory Actions and Marketing History

This product is not currently marketed in the foreign countries.

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

4.1. Office of Scientific Investigations (OSI)

The Applicant reported that all clinical studies in this application were conducted in accordance with applicable regulatory guidances and relevant sections of the International Conference on Harmonization guidelines.

The safety and efficacy of N1539 were evaluated in two key studies (REC-15-015 and REC-15-016). These two studies were audited on-site at GCP inspections of two clinical inspection sites as the table below, the site selection tool was used to identify these two sites.

Table 2 Sites of Inspection

Site #/ Name of CI/ Address	Protocol #/ # of Enrolled Subjects	Inspection Dates	Classification
Site #3 **Leiman, David, M.D.** 2001 Hermann Drive Houston, TX 77004	Protocol: REC-15-015 Subjects: 66	04-08 Dec 2017	NAI*
Site #3 **Pollak, Richard, D.P.M.** 8042 Wurzbach Road, Suite 420 San Antonio, TX 78229	Protocol: REC-15-016 Subjects: 73	13-20, Mar 2018	NAI*

Source: Clinical Inspection Summary (CIS)
Scientific Investigations (OSI) reviewer Dr. Jenn Sellers concluded that the studies appear to have been conducted adequately, and the data generated by these two sites and submitted by the Applicant appear to be acceptable in supporting the respective indication.

4.2. Product Quality

The deficiencies in the extractable/leachable from the container closure system have been identified as follows:

1. *An insufficient sample size was used to evaluate the presence of the leachables at greater than 5ug/day on stability.*

2. *According to USP <1663> and <1664>, there must be a good correlation between the extractables and leachables identified such that leachables are not identified that are also not found to be extractables. A lack of correlation may imply that the extractable study was not conducted vigorously enough to extract all possible impurities.*

Please see Dr. Ciby Abraham's CMC review for detail. There are no approvability issues from quality microbiology perspective, please also see Dr. Christine Craig's review for detail.

4.3. Clinical Microbiology

N/A

4.4. Nonclinical Pharmacology/Toxicology

The same issues in the extractable/leachable have been identified as in CMC review as follows:

The NDA did not include an adequate extractables/leachables evaluation to justify the safety of potential leachables in the drug product. The structures of six potential

leachable compounds (e.g., [redacted]) were not fully elucidated, but were detected at above the AET and at levels exceeding the requested qualification threshold of 5 mcg/day. In addition, the compound [redacted] was detected at above 5 mcg/day from extractions with [redacted] manufacturing contact material and an unknown compound ([redacted]) was detected at above 5 mcg/day from the aged drug product. Your rationale to dismiss these compounds as not being potential leachables because they were not detected in both the extraction studies and one lot of aged drug product at one time point is unacceptable as leachables may be produced at earlier or later time points on stability and sampling from several batches over the course of the stabilty studies, which is best practice for definitive leachables testing, would be needed to provide reasonable assurance of capturing peak levels of individual leachable compounds. In addition, the definitive leachables stability testing was inadequate since it only targeted two compounds and did not monitor for all compounds detected in the extraction studies over the 5 mcg/day threshold, including those unknown compounds which need to be identified if they are present as a leachable over the recommended qualification threshold of 5 mcg/day. Note that the results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any [redacted] manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation.

Please see Dr. Armagha Emami's review for detail.

4.5. Clinical Pharmacology

There are no approvability issues identified from clinical pharmacology perspective, please see Dr. KWATRA, DEEP's review for detail. The single ascending dose crossover pharmacokinetics, and relative bioavailability study (Study 1539-01) revealed that the Tmax for N1539 given 30 mg IV was 0.08 hour as shown in the table below.

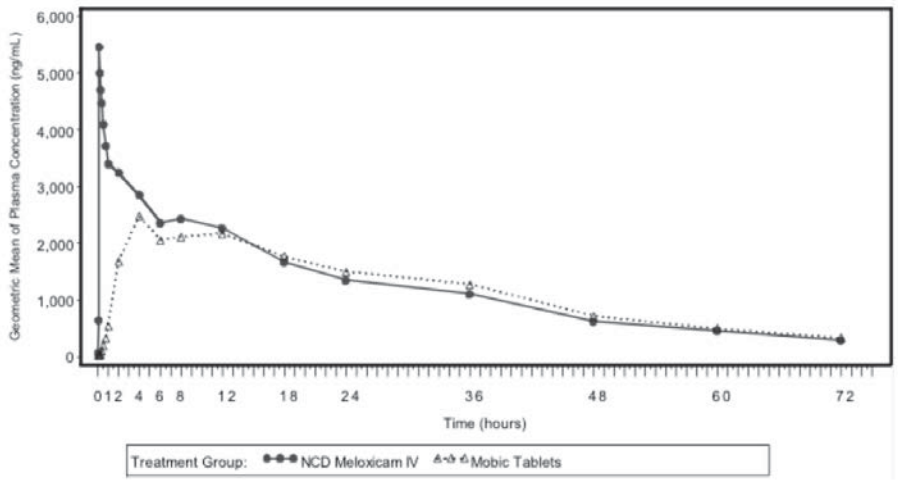
Table 3 Single-dose N1539 Pharmacokinetic parameters

Parameter	Meloxicam 15 mg		Meloxicam 30 mg		Meloxicam 60 mg	
	N1539 N = 7	Mobic Tablet N = 7	N1539 N = 7	Mobic Tablet N = 7	N1539 N = 7	Mobic Tablet N = 7
C_{max}[a], ng/mL						
Mean (SD)	2850.00 (228.76)	1221.9 (289.5)	5562.86 (1114.86)	2611.4 (571.6)	11,338.57 (1734.46)	4810.0 (867.5)
C_{min}[b], ng/mL						
Mean (SD)	663.29 (221.23)	699.00 (195.54)	1375.71 (298.38)	1521.43 (280.32)	2452.86 (408.15)	2465.71 (384.14)
AUC_t, ng•h/mL						
Mean (SD)	46,094.8 (14,565.8)	42,949.2 (11,662.8)	92,575.9 (18,456.0)	88,340.6 (16,547.1)	156,042.6 (24,041.4)	146,677.3 (21,925.3)
CV	0.3	0.3	0.2	0.2	0.2	0.1
GM	44,094.8	41,463.0	90,988.8	86,875.0	154,517.0	145,356.0
AUC_∞, ng•h/mL						
Mean (SD)	57,314.4 (27,233.2)	53,988.8 (23,207.7)	107,508.7 (34,443.0)	104,400.0 (30,656.2)	171,229.0 (34,439.1)	163,854.7 (32,916.7)
CV	0.5	0.4	0.3	0.3	0.2	0.2
GM	52,043.9	49,880.7	103,275.9	100,572.6	168,495.9	161,247.4
t_{max}, h						
Mean (SD)	0.08	6.57 (4.12)	0.08	6.86 (5.87)	0.08	5.14 (2.27)
Median (min, max)	0.08 (0.08, 0.08)	4.00 (2.00, 12.0)	0.08 (0.08, 0.08)	4.00 (2.00, 18.0)	0.08 (0.08, 0.08)	4.00 (2.00, 8.00)
$t_{½}$, h						
Mean (SD)	27.3 (15.7)	26.4 (12.1)	23.3 (9.36)	23.4 (8.78)	20.3 (4.32)	20.6 (5.14)
Median (min, max)	24.4 (11.7, 51.0)	28.0 (11.6, 48.1)	22.1 (14.5, 42.6)	20.3 (16.1, 41.1)	18.7 (16.0, 29.3)	19.5 (15.9, 30.3)

Source: Clinical Pharmacology Review

The mean plasma concentration over time of N1539 vs oral meloxicam 30 mg is presented in the figure below, a rapid Tmax is observed.

Figure 1 Mean Plasma Concentration After a Single Dose of N1539



Source: Clinical Pharmacology Review

4.6. Devices and Companion Diagnostic Issues

N/A

4.7. Consumer Study Reviews

N/A

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 4 listed Studies to Support this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety						
15-015	Double blind, parallel	30 mg IV daily	SPID24	219	Abdominoplasty	4 in US
15-016	Double blind, parallel	30 mg IV daily	SPID48	201	Bunionectomy	4 in US
02	Double blind, parallel with active comparator	15 to 60 mg IV daily Motrin 400 mg	SPID24	230	Dental surgery	1 in US
04	Double blind, parallel with active comparator	5 mg to 60 mg IV daily Morphine 60 mg	SPID24 and TOTPAR24	486	Open abdominal hysterectomy	14 in Poland, Serbia, and Republic of Georgia
15-014	Double blind, parallel	30 to 60 mg IV daily	SPID48	59	Bunionectomy	1 in US
Studies to Support Safety						
15-017	Double blind	30 mg IV daily	Safety	721	Major surgeries	46 in US, Canada, Australia, and New Zealand
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
15-018	Open label	30 mg IV daily	Safety	12	Subjects with renal impairment or	1 in US

					other higher risk subjects	
15-019	Double blind	180 mg, 120 mg and 30 mg IV	Safety (QTc)	48	Healthy subjects	1 in US

5.2. Review Strategy

The Applicant identified two Phase 3 trials (Study REC-15-015 and REC-15-016) as contributing to evidence of efficacy for the study drug. These two studies were reviewed thoroughly for study design and conduct, as well as assessment of the Applicant's efficacy conclusions. The Applicant's efficacy results were also reanalyzed by the statistical reviewer, Dr. Zhou. There are three Phase 2 dose-range studies, which are summarized in the review.

A Phase 3 safety study (Study REC-15-017) is a randomized, multicenter, double-blind, placebo-controlled evaluation of the safety of N1539 in adult subjects following major surgery which also collected total opioid consumption. This is study is reviewed in correspondent efficacy section (7.2.2) and safety section (8.5.13)

6. Review of Relevant Individual Trials Used to Support Efficacy

SUMMARY OF PHASE 2 STUDIES

Study 02 (N1539-02)
Study 02 was entitled "A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Adaptive Design, Single-Dose Study of IV N1539 in the Treatment of Pain Secondary to Dental Impaction Surgery." The objectives of this clinical study were to evaluate the analgesic efficacy and assess the safety and tolerability of single doses of N1539 (25.5 mg/mL) 15, 30, and 60 mg.

Eligible subjects underwent surgical extraction of > two third molars, of which at least one was a complete or partial mandibular impaction. Following dental surgery, subjects were dosed when their PI rating was moderate or severe on a 4-point Likert Scale (with categories of none, mild, moderate, or severe). Subjects who did not report pain at this level within five hours following completion of surgery were excluded from the study.

An adaptive design was used to assess whether the chosen dosages were on the linear portion of the analgesic dose-effect curve. The initial cohort evaluated 90 subjects, and the blind was broken to analyze the safety and efficacy data to determine the dose for the next cohort. Following the interim analysis, a second cohort was evaluated. Subjects in the first cohort were randomized to placebo, N1539 15 or 60 mg, or Motrin 400 mg. Subjects in the second cohort were randomized to placebo; N1539 15, 30, or 60 mg; or Motrin 400 mg.

A total of 230 subjects were enrolled in the study, including 30 subjects randomized to placebo, 50 subjects randomized to Motrin, and 50 subjects each randomized to the N1539 15, 30, and 60 mg treatment groups. The mean age of subjects was 19.5 – 20.4 years across treatment

groups.

SPID24 was the primary endpoint for this study, using a 100-mm visual analogy scale (VAS) of pain. Subjects who received rescue medication prior to 24 hours had their pain intensity (PI) scores recorded immediately prior to rescue, and this PI score was carried forward through 24 hours for the SPID computation (ie, using the last observation carried forward, LOCF, methodology). Overall, there was a statistically significant difference between the groups favoring N1539 for the SPID24

Table 5 Summary of SPID24 (Study N1539-02)

Statistic	Placebo N = 30	Motrin 400 mg N = 50	N1539			Overall N = 230
			15 mg N = 50	30 mg N = 50	60 mg N = 50	
LS Mean	-466	-35087	-49576	-58794	-75415	
SE	7062.4	5468.2	5468.1	5474.6	5474.7	
Lower 95% CI	-14383	-45863	-60352	-69583	-86204	
Upper 95% CI	13451	-24312	-38800	-48006	-64627	
p-value[a]						< 0.001

Source: Applicant's submission (Summary of Clinical Efficacy, Page 14)

The secondary endpoint including pain intensity difference (PID), rescue medication, time to perceptible and meaningful pain relief (PR) are generally in favor of N1539.

Reviewer's comments:
In this dose-ranging study, there is a dose-dependent efficacy between 15 mg to 60 mg, while the 30-mg dose was finally selected for the Phase 3 program. However, it must be noted while dental surgery is an appropriate surgical model to study acute analgesic effect of oral NSAIDs, but IV NSAIDs represents an over treatment for this surgical model, which was conveyed to the Applicant when the IND was opened in April, 2009 with questions.

Study 04 (N1539-04)
Study 04 was entitled "A Randomized, Double-Blind, Placebo- and Active-Controlled, Dose-Ranging Study to Evaluate the Analgesic Efficacy, Safety and Tolerability of Intravenous N1539 in Subjects After Open Abdominal Hysterectomy Followed by Optional Continuation of Intravenous N1539 in Responders and Randomization of Placebo and Morphine Subjects to Intravenous N1539."

The objectives of this clinical study were to determine the analgesic efficacy, duration of effect, and safety and tolerability of single doses of N1539 (25.5 mg/mL) 5, 7.5, 15, 30, and 60 mg, to evaluate whether there was a relationship between plasma concentration and PR following administration of N1539, and to obtain safety and efficacy data on subacute dosing with N1539.

Eligible subjects underwent open abdominal hysterectomy. The day after the procedure, following either discontinuation of IV subject-controlled analgesia or a dose of morphine administered in the early morning, subjects were dosed when their PI rating was moderate or severe on a 4-point Likert Scale (with categories of none, mild, moderate, or severe). Subjects who did not report moderate or severe pain within 6 hours after the last dose of morphine were excluded from the study.

A planned and pre-specified analysis was performed after Cohort 1 to determine dosing for Cohort 2. The initial cohort evaluated 180 subjects, and the blind was broken to analyze the safety and efficacy data to determine the dose for the next cohort. Following the interim analysis, a second cohort was evaluated. The study had a 24-hour double-blind phase followed by an open-label phase. Responders to the N1539 treatment and non-responders to placebo or morphine treatment in the double-blind phase were eligible to enter the open-label phase. Only data from the double-blind phase of this study are included in the ISE.

Subjects in Cohort 1 were randomized to receive placebo, morphine, or N1539 (7.5 or 60 mg). Subjects in Cohort 2 were randomized to receive placebo, morphine, N1539 (5, 7.5, 15, 30, or 60 mg). Morphine doses in both cohorts were determined by the Surgeon/Investigator and were typically 0.15 mg/kg (10-15 mg).

A total of 486 subjects were randomized and treated in the study across the two cohorts during the double-blind phase. Twenty-six subjects from Site 21 were excluded from efficacy analyses due to potential bias introduced by unblinded personnel performing blinded assessments during the double-blind phase. Efficacy evaluable subjects (N = 460) were randomized to the following treatment groups: placebo (60 subjects), morphine (60 subjects), N1539 5 mg (60 subjects), N1539 7.5 mg (80 subjects), N1539 15 mg (60 subjects), N1539 30 mg (60 subjects), and N1539 60 mg (80 subjects). The mean age of all subjects in the double-blind phase ranged from 46.9 to 48.5 years across treatment groups.

SPID24 and TOTPAR24 were coprimary endpoints for this study. In these analyses, subjects who received rescue medication prior to 24 hours had their PI or PR scores recorded immediately prior to rescue, and the scores were carried forward through 24 hours for the SPID and TOTPAR calculations (ie, using the LOCF methodology).

The results for SPID24 and TOTPAR24 are presented in the table below. Overall, there was a statistically significant difference between the groups favoring N1539 for the SPID24. there was also a statistically significant difference between the groups favoring N1539 for the TOTPAR24.

Table 6 Summary of SPID24 and TOTPAR24 (Study N1539-04)

Statistic	Placebo N = 60	Morphine N = 60	N1539					Overall
			5 mg N = 60	7.5 mg N = 80	15 mg N = 60	30 mg N = 60	60 mg N = 80	
$SPID_{24}$								
LS Mean	4446.2	-30269.3	-33238.8	-31720.7	-46888.4	-55983.3	-54690.8	
SE	3906.62	3907.81	3905.91	3380.44	3900.22	3899.55	3377.08	
Lower 95% CI	-3231.2	-37949.1	-40914.8	-38364.1	-54553.2	-63646.8	-61327.5	
Upper 95% CI	12123.5	-22589.6	-25562.8	-25077.4	-39223.6	-48319.8	-48054.1	
p-value[a]								<0.001
$TOTPAR_{24}$								
LS Mean	1090.7	2758.9	3127.9	2981.9	3736.1	4131.5	4097.0	
SE	193.82	193.88	193.78	167.71	193.50	193.47	167.55	
Lower 95% CI	709.8	2377.9	2747.0	2652.3	3355.8	3751.3	3767.7	
Upper 95% CI	1471.6	3139.9	3508.7	3311.5	4116.4	4511.7	4426.3	
p-value[a]								<0.001

Source: Applicant's submission (Summary of Clinical Efficacy, Page 17)

The secondary endpoints including rescue medication, SPID for various time points, TOTPAR scores at various intervals, time to perceptible and meaningful PR are generally in favor of N1539.

Reviewer's comments:
In the dose-ranging study, unlike the Study 2 described earlier, there is only an apparent dose-dependent efficacy between 5 mg to 30 mg, while there is no apparent difference between 30 mg and 60 mg.

It is noted that this is an exclusive foreign study in Poland, Serbia, and Republic of Georgia. The Applicant adequately justified the rationales for assuming the applicability to US population as the demographic and baseline characteristic of subjects were generally similar to that of

subjects within the US. In addition, the surgical procedure performed was consistent with the surgical approach in the US.

While an open hysterectomy is an appropriate surgical model. As a Phase 2 dose ranging study, it was not designed as a Phase 3 study with deficiencies as follows:

- A single dose, instead of multi dose study as the Agency preferred
- The method of LOCF used in this study did not address the potential impact of rescue medication use on efficacy assessments, such as a W2LOCF (2-hour windowed LOCF), which carries the prerescue score forward to replace pain intensity scores collected within two hours following each rescue
- Twenty-six subjects from Site 21 were excluded from efficacy analyses due to potential bias introduced by unblinded personnel performing blinded assessments during the double-blind phase

Study REC-15-014

Study 14 was entitled "A Phase 2, Single-Center, Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety, Efficacy, and Pharmacokinetics of N1539 Following Bunionectomy."

The primary objective of this clinical study was to evaluate the safety of N1539 (30 mg/mL formulation diluted to 25 mg/mL prior to administration) administered as an IV bolus over 15-30 seconds in subjects undergoing bunionectomy. Eligible subjects underwent primary unilateral first metatarsal bunionectomy under regional and local anesthesia, with IV sedation. Efficacy assessments included PI, use of rescue medication, and PGA of pain control.

A total of 59 subjects were randomized in the study, including 19 subjects randomized to placebo, 20 subjects randomized to N1539 30 mg, and 20 subjects randomized to N1539 60 mg.

The primary efficacy endpoint for this study was the effect size using SPID48. Analyses of SPID48 as well as SPID over various intervals were computed using the LOCF (primary analysis), baseline observation carried forward (BOCF; sensitivity analysis), and W2LOCF (sensitivity analysis) methods.

The results for SPID48 derived from W2LOCF and LOCF are presented in the table below

Table 7 Summary of SPID48 and W2LOCF Analysis (Study REC-15-014)

Methodology		Placebo N = 20	N1539 30 mg N = 20	N1539 60 mg N = 20
LOCF	Mean ± SD	3588.68 ± 5464.602	-1115.2 ± 5403.460	-605.13 ± 4907.140
	LS Mean	3668.13	-1021.9	-773.86
	p-value[a] vs. placebo		0.0049	0.0076

	Effect size		0.8657	0.8087
W2LOCF	Mean ± SD	-2123.1 ± 7309.385	-9396.5 ± 7141.555	-8070.8 ± 6292.808
	LS Mean	-1991.3	-9241.9	-8350.6
	p-value[a] vs. placebo		0.0007	0.0027
	Effect size		1.0069	0.8738

Source: Applicant's submission (Summary of Clinical Efficacy, Page 20)

The secondary endpoints including responder analysis, rescue use, PGA have mixed results.

Reviewer's comments:
In this dose-ranging study, like the Study 4 described earlier, there is no apparent difference between 30 mg and 60 mg.

6.1. REC-15-015

6.1.1. Study Design

Overview and Objective

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled, evaluation of the efficacy and safety of N1539 following abdominoplasty surgery.

Primary objective:
To demonstrate the analgesic efficacy of N1539 compared with placebo, using the summed pain intensity difference over the first 24 hours (SPID24) in subjects with moderate to severe pain following abdominoplasty surgery

Secondary objectives:
Evaluate the analgesic effects of N1539 versus placebo at various time points using a series of secondary efficacy endpoints for pain intensity, pain relief, and use of rescue medication

Determine the safety and tolerability of N1539 as evaluated with physical examination, vital signs, clinical laboratory tests, ECGs, wound evaluation, and incidence of Adverse Events (AEs) and Serious AEs (SAEs)

Trial Design

This was a Phase 3, randomized, multicenter, double-blind, placebo-controlled evaluation of the efficacy and safety of N1539 in adult subjects undergoing abdominoplasty surgery. The study was planned to enroll approximately 200 subjects (100 subjects per group).

Subjects requiring abdominoplasty surgery, age 18 to 75 years inclusive, were to be screened for participation at four study sites in the United States. Screening was to occur within 28 days before study drug administration. After signing the informed consent, medical history, physical examination, baseline laboratory testing, 12-lead electrocardiogram (ECG), pregnancy testing, and vital sign measurements were to be completed during the screening visit.

On the day of surgery (Day 1), subjects were to undergo abdominoplasty surgery under general anesthesia. Following surgery, IV fentanyl may have been used to maintain analgesia prior to subject meeting postoperative randomization criteria. Subjects were to be evaluated for eligibility for randomization within three hours of the end of surgery (last suture).

Eligible subjects were to be randomized and treated with study drug every 24 hours, and stay at the study site for approximately 48 hours after treatment initiation. After completion of 48 hours of evaluation, subjects could be discharged from the study site. Subjects were eligible to receive a third dose of study drug before discharge at the discretion of the investigator and the subject

All treated subjects were to be followed through 28 days following the last study dose (LSD). All subjects were to return to the study site seven days post-LSD (LSD+7) and 28 days post-LSD (LSD+28) to complete follow-up study assessments.

Efficacy assessments were to include pain intensity, use of rescue medication, time to pain relief, and Patient Global Assessment (PGA) of pain control. Safety assessments were to include monitoring of AEs, clinical laboratory tests, vital sign measurements, wound evaluation, and ECGs. Whole blood samples were to be collected for pharmacokinetic (PK) analysis and inclusion in a separate population PK analysis.

The following summarizes key activities for each phase of this study: 1) Pretreatment Phase, 2) Treatment Phase, 3) Follow-up.]

1. **Pretreatment Phase:**
a. Screening Period (Day -28 to Day -1): Subjects were to be consented and screened.
b. Day of Surgery (Day 1):
    1) Pre-surgery: Subjects were to be admitted to the study site and reassessed for eligibility for the study. Pre-surgery activities were to be conducted.

2) Surgery: Eligible subjects were to undergo abdominoplasty surgery using a standard anesthetic regimen for all subjects as outlined in the surgical procedure guidelines and anesthesia protocol.
3) Postoperative Period: Following surgery, subjects could have analgesia maintained using IV fentanyl until they were evaluated for randomization.

c. Randomization Qualification (Day 1): Following discontinuation of IV fentanyl, subjects were to be assessed for randomization to study treatment. Subjects were eligible for randomization if they met all the postoperative randomization criteria within three hours of the end of surgery.

2. Treatment Phase (Hour 0 through Hour 48)
Once the subject met postoperative randomization eligibility criteria, they were to be randomized in a 1:1 ratio to IV treatment with N1539 30 mg or placebo, administered every 24 hours. Subjects were to be domiciled at the study site throughout the treatment phase.

Randomization and administration of the first dose of study drug was to be within 15 minutes of meeting the qualifying categorical and numeric pain rating scale (NPRS) scores. After randomization, immediately prior to study drug administration, the baseline pain intensity assessment via NPRS was to be completed. Postoperative randomization criteria were to be assessed based on the qualifying NPRS assessment and not the baseline NPRS.

The time of first dose of study drug (Dose 1) was to be recorded as Hour 0. Subjects were to be administered a study dose per their randomization every 24 hours for two doses. Following completion of the Hour 48 study assessments, subjects could receive an additional dose of their randomized treatment prior to discharge, if sufficient pain symptoms were still present, at the discretion of the investigator and the subject.

Subjects with inadequately controlled pain symptoms could request rescue analgesia. Subjects were to be encouraged to wait at least one hour after the first study drug administration before utilizing rescue analgesia, if possible. Pain intensity assessments were to be completed prior to each dose of rescue medication.

Study assessments completed during the treatment phase were to include pain intensity (NPRS), time to pain relief (double stopwatch), PGA of pain control, PK sampling, and vital sign measurement.

3. Follow-up:
After completing the study assessments through Hour 48, subjects could be discharged from the study site. Subjects were to be provided routine standard of care for pain

management after discharge from the study site.

All subjects were asked to return to the study site on LSD+7 and LSD+28 to complete follow-up study assessments.

Study population

Inclusion Criteria

- Male or female 18 to 75 years of age, inclusive
- Undergoing abdominoplasty surgery without collateral procedures
- Be American Society of Anesthesiology (ASA) physical class 1 or 2
- Female subjects were eligible only if all the following apply:
  Not pregnant (female subjects of child bearing potential [FOCBP] must have a negative serum pregnancy tests at screening and negative urine pregnancy test before surgery)
  Not lactating
  Not planning to become pregnant during the study
  Commit to the use of an acceptable form of birth control for the duration of the study through LSD+28
- Body mass index ≤35 kg/m2

Postoperative Randomization Criteria

Subjects were required to meet the following criteria following surgery to be eligible for participation:

- Report moderate or severe pain on a 4-point categorical pain rating scale (with categories of none, mild, moderate, or severe), AND, a score ≥4 on 11-point NPRS within 3 hours of the end of surgery (last suture) on Day 1
- Subject could answer questions and follow commands, and appropriately participate in requisite pain evaluation assessments dictated in the protocol
- The surgical procedure from incision to closure was not longer than three hours
- The subject had no evidence of respiratory insufficiency, clinically significant hypotension, bradycardia, or any other abnormality, during or following surgery that, in the investigator's opinion, significantly increases the risks of study drug administration
- There were no significant deviations from the surgical protocol, anesthetic protocol, or specified pretreatment analgesic regimen, that would, in the opinion of the investigator, put the subject at risk of participation in the trial, confound the analgesic endpoints of the trial or cause concern regarding the subject's ability to participate in the trial

Exclusion Criteria

- Had a known allergy to meloxicam or any excipient of N1539, aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), or to any peri- or postoperative medications used in this study

- Had an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of > 2X the upper limit of normal (ULN), alkaline phosphatase (AP) > 1.5X ULN, or total bilirubin > 1.2X ULN, a prothrombin time (PT) >20% above ULN, or any laboratory abnormality that would place the subject at increased risk for study participation per the judgment of the investigator at screening and/or prior to surgery
- Had a history of or positive test results for HIV, or hepatitis B or C at screening
- Had, as determined by the investigator or the sponsor's medical monitor, a history or clinical manifestations of significant renal, hepatic, cardiovascular, metabolic, neurologic, psychiatric, or other condition that would preclude participation in the study
- Had a history of myocardial infarction or coronary artery bypass graft surgery within the preceding 12 months
- Had a history of migraine (within past 12 months) or frequent headaches (≥ 2 events per week requiring analgesics), seizures, or are currently taking anticonvulsants
- Had active or recent (within six months) gastrointestinal ulceration or bleeding
- Had a known bleeding disorder or be taking agents affecting coagulation
- Had another painful physical condition that, in the opinion of the investigator, may confound the assessments of postoperative pain
- Had evidence of a clinically significant 12 lead ECG abnormality per the judgment of the investigator
- Had a history of alcohol abuse (regularly drinks > four units of alcohol per day; eight oz. beer, three oz. wine, one oz. spirits) within the past five years or a history of prescription/illicit drug abuse
- Had been receiving or have received chronic opioid therapy defined as greater than 15 morphine equivalents units per day for greater than three out of seven days per week over a one month period within 12 months of study treatment initiation
- Used concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs which in the investigator's opinion may exert significant analgesic properties or act synergistically with N1539

Schedules of events

A summary table of study procedures to be performed, and the assigned time points, was provided for the overall study in the table below.

Table 8 Overview of Study procedures

Procedure; Dose/Hour	Screening	Inpatient					Follow-Up	
		Day 1		Day 1 – Day 3			LSD+7 ± 2	LSD+28 ± 4
		Prior to Surgery	Surgery	Dose 1 / Hour 0	Dose 2 / Hour 24	Hour 48		
Informed Consent	X							
Confinement		←	←	X	→	→		
Eligibility Assessment	X	X	X[e]			X		
Demographics and Medical History	X	X						
Physical Examination[f]	X	X				X	X	
Pregnancy Test (FOCBP only)	X[serum]	X[urine]						
Alcohol Breath Test and UDS	X	X						
Clinical Laboratory Tests[a]	X	X				X	X	
HIV and Hepatitis Screening	X							
Vital Signs[b]	X	X		X[d]		X	X	
12 Lead ECG	X	X[c]				X	X	
Adominoplasy Procedure			X					
Study Drug Administration				X	X	X[h]		
Pain Intensity (PI)				X[g]	X[g]	X[g]		
Perceptible and Meaningful PR				X				
PGA of Pain Control					X	X		
PK Sample Collection				X	X			
Wound Evaluation						X	X	X
Prior and Concomitant Medication		←	←	←	X	→	→	→
Adverse Event Monitoring				←	←	X	→	→

a Laboratory tests were to include hematology, chemistry, urinalysis, and coagulation tests.
b Vital signs (VS) included: resting blood pressure, resting pulse, and SpO2. Tests were to be obtained after resting (seated/reclined) for ≥ 5 minutes.
c 12-lead ECG was to be done prior to surgery only if screening ECG was done >7 days before surgery
d VS were to be determined at pre dose, then 0.5, 1, 2, 6, and 24 (pre-Dose 2) hours after Dose 1.
e Postoperative randomization criteria were to be assessed on the day after surgery (Day 1), prior to randomization.
f Height, weight and BMI were to be collected at screening only.
g PI scores were to be assessed at the following time points post Dose 1: 0.25, 0.5, 0.75, 1, and 2 hours. Thereafter PI was to be collected every 2 hours until Hour 48.
h Optional dose could be administered after Hour 48 assessments, prior to discharge, at the discretion of the investigator and subject.

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 16)

Study Endpoints

The primary efficacy endpoint in this study was pain reduction measured by the SPID24.

Statistical Analysis Plan

The objective of the SAP was to reasonably assure that the statistical methodologies to be used for analysis were complete and accurate.
In the development of the study SAP, the following documents were used:
Protocol REC-15-015, 11 December 2015
REC-15-015, eCRF, Final 1.0, 11 January 2016

The principles in the following guidance documents were followed in preparation of the study SAP.

- ICH E3 (1995): Structure and Content of Clinical Study Reports
- ICH E6 (1996): Guideline for Good Clinical Practice
- ICH E9 (1998): Statistical Principles for Clinical Trials

Protocol Amendments

No protocol amendments were issued during the study, and no change to the conduct of the study was implemented.

6.1.2. Study Results

Compliance with Good Clinical Practices

This study was conducted per GCP; US 21 Code of Federal Regulations (CFR) Part 50 (Protection of Human Subjects); US 21 CFR Part 56 (IRBs); US 21 CFR Part 54 (Financial Disclosure); International Conference on Harmonization (ICH) Guidance for Industry, E6 GCP: Consolidated Guidance; the Nuremberg Code; and, where applicable the principles of the Declaration of Helsinki (Recommendations guiding Medical Doctors in Biomedical Research Involving Human Subjects), and with the NH&MRC National Statement on Ethical Conduct in Human Research (2007).

Financial Disclosure

The Applicant's submission included the completed "Certification: Financial Interests

and Arrangements of Clinical Investigators" form (Form FDA 3455). The Applicant indicated that the investigators at each site are certified as having no Financial Arrangement as defined in 21 CFR 54.2.

Patient Disposition

The study screened 500 subjects; a total of 219 subjects were randomized to treatment. Among the randomized subjects, 215 (98.2%) completed the treatment, and 209 (95.4%) completed the LSD+28 follow-up visit. Causes for discontinuing from treatment in the study included: lack of efficacy (three; two in N1539 30 mg group and one in placebo group), and adverse event (one subject in placebo group).

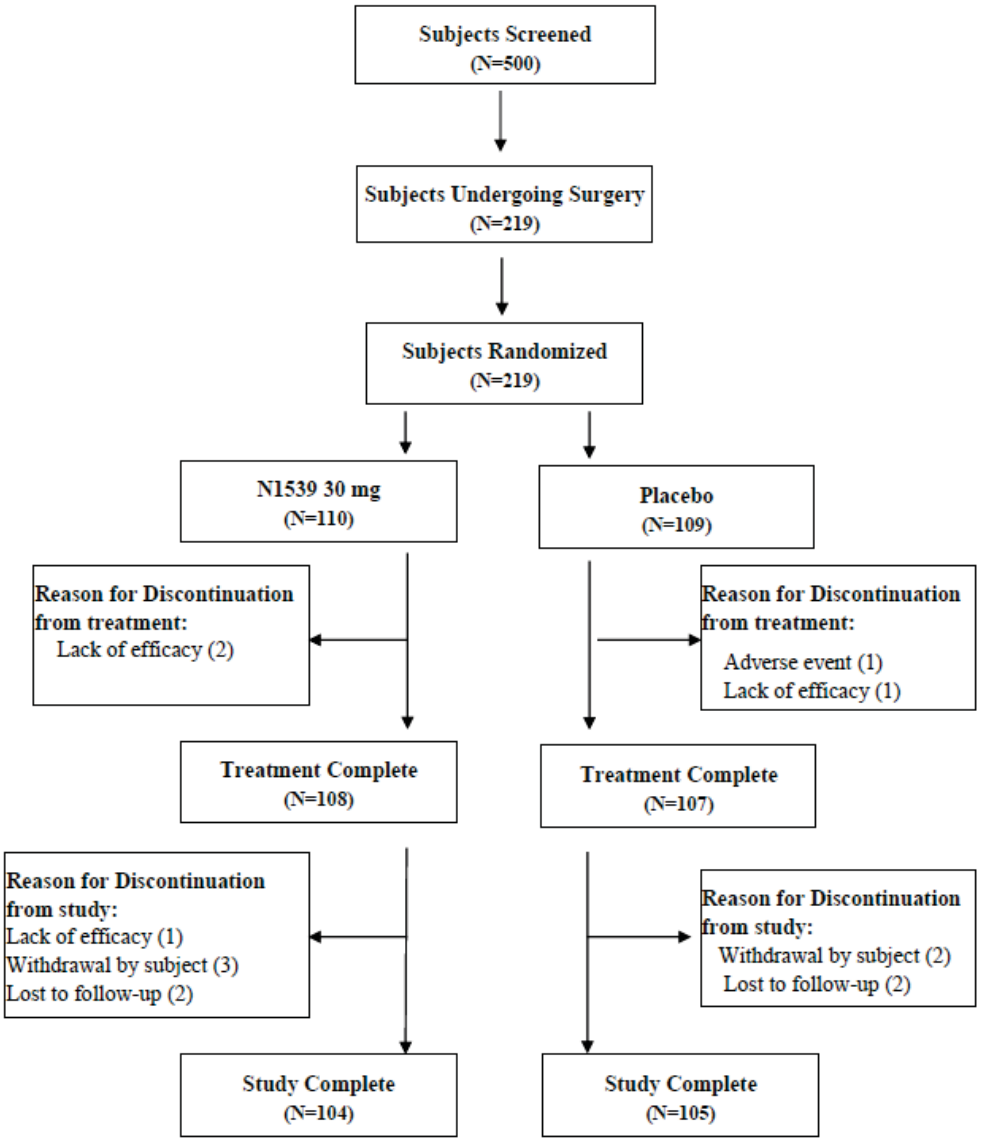


Figure 2 Disposition of Subjects

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 32)

Protocol Violations/Deviations

A total of 13 major deviations were identified in 13 subjects (5.9%). These included nine subjects (five in N1539 30 mg group, four in placebo group) at Site 3 that did not have at least one of the required screening laboratory assessments available for review prior to surgery. Also at Site 3, one subject (N1539 30 mg group) had at screening a three lead ECG rather than a 12 lead ECG, and one subject (placebo group) was enrolled in the study whose alkaline

phosphatase at screening was 159 u/L (normal 42-98 u/L) which was > 1.5 ULN. At Site 2, one subject (N1539 30 mg group) did not meet randomization entry criteria for pain but was randomized (categorical pain scale rated as mild and the required pain intensity for randomization was moderate or severe) and one subject (N1539 30 mg group) had a total bilirubin of 25.7 umol/L (normal 5.1-20.5 umol/L) at screening which was > 1.2 ULN. None of these important deviations were considered to have increased subject risk or had an impact on the study outcomes.

Reviewer's comments:
The major protocol deviations are not expected to affect the overall efficacy results.

Table 9 Summary of Baseline Demographic Characteristics

Variable	N1539 30 mg (N=110)	Placebo (N=109)	Overall (N=219)
Age (yrs) – mean ± SD	38.9 ± 8.40	41.0 ± 9.63	40.0 ± 9.08
Subjects ≥ 65 Years - n (%)	0	2 (1.8)	2 (0.9)
Sex, n (%)			
Male	1 (0.9)	3 (2.8)	4 (1.8)
Female	109 (99.1)	106 (97.2)	215 (98.2)
Race, n (%)			
White	69 (62.7)	69 (63.3)	138 (63.0)
Black or African American	37 (33.6)	36 (33.0)	73 (33.3)
Asian	3 (2.7)	2 (1.8)	5 (2.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.9)	1 (0.5)
Other	1 (0.9)	1 (0.9)	2 (0.9)
Ethnicity, n (%)			
Hispanic or Latino	42 (38.2)	45 (41.3)	87 (39.7)
Not Hispanic or Latino	68 (61.8)	64 (58.7)	132 (60.3)
Baseline Height (m) – mean ± SD	1.6 ± 0.07	1.6 ± 0.08	1.6 ± 0.07
Baseline Weight (kg) – mean ± SD	69.7 ± 9.82	71.8 ± 10.58	70.8 ± 10.24
Baseline BMI (kg/m^2) – mean ± SD	26.5 ± 3.08	26.9 ± 3.16	26.7 ± 3.12
Surgery Duration (hr) – mean ± SD	1.326 ± 0.4828	1.407 ± 0.4411	1.366 ± 0.4633
Time (hr) from End of Surgery to First Dose – mean ± SD	0.853 ± 0.5708	0.855 ± 0.5256	0.854 ± 0.5475

Baseline PI (0-10) – mean ± SD	7.2 ± 1.57	7.4 ± 1.68	-

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 35)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All 219 randomized subjects had at least one medical/surgical history finding prior to receiving study medication. The most common events included: lipodystrophy acquired, cutis laxa, caesarean section, female sterilization, diastasis recti abdominis, hysterectomy and mammoplasty.

The use of concomitant medications was limited to medications that had been at a stable dose for at least 14 days prior to the scheduled surgical procedure, as well as analgesic medications. All 219 subjects utilized prior or concomitant medications during their participation in this study. Frequently used types of non-surgical concomitant medications in the study included: opioids, IV solutions, anti-emetics, beta-Lactam antibiotic, antibiotics for topical use, antithrombotic agents, and drugs for constipation.

Rescue analgesia, oral oxycodone five mg administered up to every two hours as needed to control pain symptoms, was to be available to subjects following the first dose of study treatment through Hour 48 of the treatment phase.

Treatment Compliance, Concomitant Medications

Unblinded study personnel were to administer each dose of study medication while the subject was confined at the study site. The exact date and time each dose was administered was to be recorded in the subject's eCRF.

All medications and other treatments taken by subjects within five days before dosing and during the study were to be recorded in the eCRF.

All medications that had not been at a stable dose for at least 14 days prior to the scheduled surgical procedure were to be prohibited within five half-lives of the specific prior medication (or, if half-life is unknown, within 48 hours) before the surgical procedure

The following medications were prohibited throughout the study (screening through LSD+28): anticonvulsants, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), neuroleptics, or serotonin-norepinephrine reuptake inhibitors (SNRIs). Selective serotonin reuptake inhibitors (SSRIs) were allowed if taken for at least 30 days before the screening period of the study at an unchanged, stable dose. Additionally, gabapentin and pregabalin were

not permitted and administration would have disqualified the subject from the efficacy evaluation.

Regional or neuraxial anesthesia was not to be used during the surgical procedure. No epidural or intrathecal agents were to be used perioperatively, as well as any long-acting local anesthetic agents.

Analgesic medications other than those pre-specified for postoperative use, or for post-randomization rescue use, were prohibited during the treatment period (through Hour 48) including: hydrocodone, codeine, fentanyl, meperidine, tramadol, opioid combinations, acetaminophen, and NSAIDs. Aspirin (acetylsalicylic acid) was prohibited unless taken for cardiac or cardiovascular prophylaxis.

Sedatives (including benzodiazepines) used as minor tranquilizers or hypnotics were not allowed throughout the study unless approved by the investigator and medical monitor.

Rescue medication

Patients with inadequately controlled pain symptoms could request rescue analgesia (oral oxycodone 5 mg administered up to every two hours). To account for the use of rescue medications, pain intensity (PI) was measured prior to a rescue use and was carried forward to replace PI scores collected within two hours following this rescue use.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint in this study was pain reduction measured by the $SPID_{24}$. The primary analysis of the difference between the treatment groups was the W2LOCF analysis. The mean (SD) baseline pain score was 7.2 (1.57) and 7.4 (1.68) for the N1539 30 mg and placebo groups, respectively. The LS mean (standard error [SE]) of $SPID_{24}$ was -4262.1 (214.19) for N1539 30 mg and -3535.7 (215.05) for placebo; the difference in $SPID_{24}$ between the treatment groups was statistically significant (p=0.0145) using the W2LOCF analysis method. A summary of LS Mean $SPID_{24}$ is provided in the table below.

Table 10 Summary of SPID24

Parameter	N1539 30 mg (N=110)	Placebo (N=109)	P-Value
Baseline PI (0-10) – mean ± SD	7.2 (1.57)	7.4 (1.68)	-
$SPID_{24}$ - LS Mean (SE)	-4262.1 (214.19)	-3535.7 (215.05)	0.0145

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 37)

Reviewer's comment: The Applicant's analysis of the primary efficacy endpoint has been confirmed by the Agency's statistical reviewer, Dr. Zhou who has the following additional comments regarding the primary endpoint:

> *In the EOP2 meeting (IND105,172) dated December 9, 2010, the agency stated that the primary efficacy endpoint must reflect multiple-dose efficacy, such as a $SPID_{48}$. Therefore, I also analyzed $SPID_{48}$. The results show that N1539 30 mg was superior to placebo in terms of our preferred primary endpoint $SPID_{48}$ ($p = 0.0039$).*

Sensitivity Analysis

Sensitivity analyses of the $SPID_{24}$ using the LOCF, BOCF, and OBSERVED methods showed that the N1539 30 mg treated subjects had more total pain reduction (i.e., a smaller SPID value) than the placebo treated subjects. The difference between the groups in $SPID_{24}$ was statistically significant using the OBSERVED method (p=0.0197) but not significant using the LOCF and BOCF methods (p=0.2468 and p=0.9832, respectively).

Reviewer's comments: Dr. Zhou concurs that $SPID_{24}$ and $SPID_{48}$ were only statistically significant different between two treatment groups using the OBSERVED analysis method.

Efficacy Results – Secondary and other relevant endpoints

The Sponsor conducted several secondary efficacy analyses. It must be noted that the Applicant did not account for multiple comparisons in their analyses, therefore the p values reported by the Sponsor are not meaningful. The results of these analyses are useful only in descriptive terms and to show trends.

Summed Pain Intensity Difference (SPID)

Analysis of SPID at other intervals included $SPID_6$, $SPID_{12}$, $SPID_{48}$, and $SPID_{24-48}$. Under the W2LOCF primary analysis method, subjects treated with N1539 30 mg had a greater pain reduction (i.e., smaller SPID value) than the placebo treated subjects at each planned interval; the differences between N1539 30 mg and placebo at each interval were statistically significant ($p<0.05$) with exception of the $SPID_6$. A summary of LS Mean SPID data at each planned interval is provided in the table below.

Table 11 Summary of LS Mean SPID

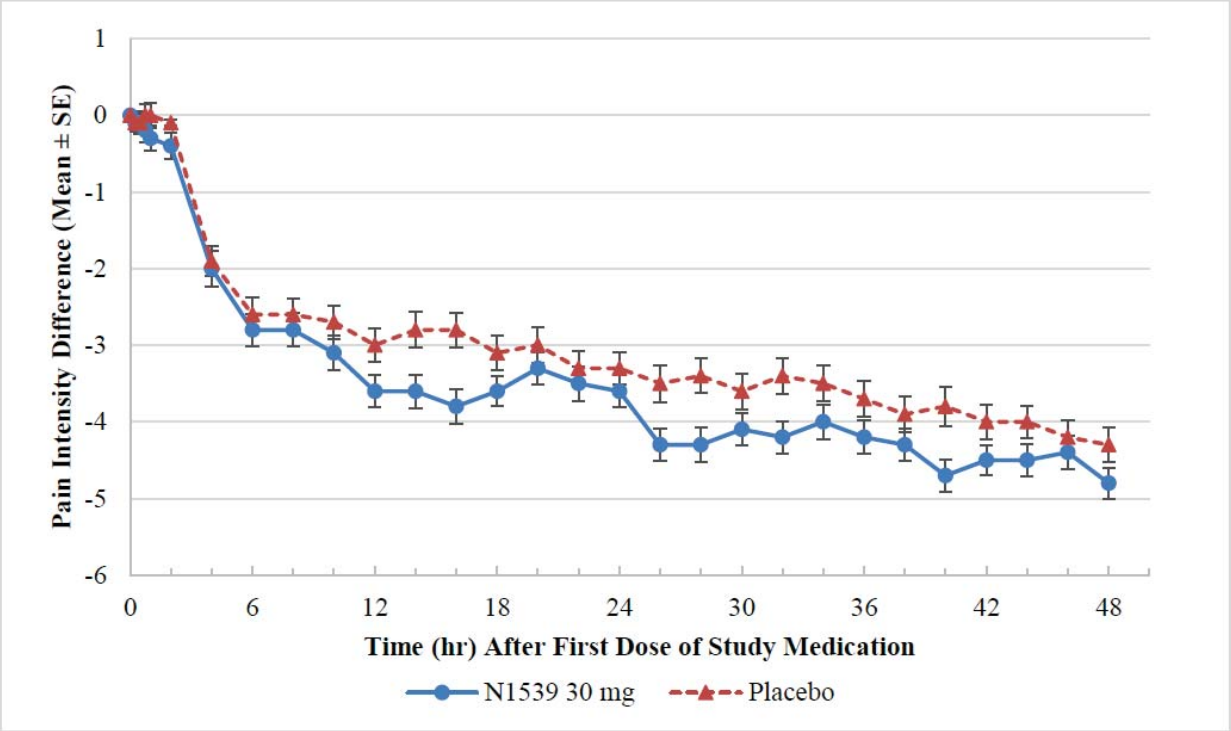
Parameter	N1539 30 mg (N=110)	Placebo (N=109)	P-Value
$SPID_6$	-607.0 (52.45)	-510.9 (52.66)	0.1841
$SPID_{12}$	-1763.8 (104.77)	-1471.1 (105.18)	0.0434

$SPID_{48}$	-10600.0 (442.31)	-8829.2 (444.08)	0.0040
$SPID_{24-48}$	-6337.8 (251.36)	-5293.5 (252.36)	0.0028

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 38)

Pain Intensity Difference (PID)
Pain reduction was measured from PI scores at each time point, using each planned analysis method. A summary of PID scores using the W2LOCF analysis is depicted over the 48-hour treatment period in the figure below.

Figure 3 Pain intensity Difference for N1539 Compared to Placebo Over the First 48 Hours of Treatment



Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 39)

Reviewer's comments:
The two curves of PID versus time show minimal differences between study drug and placebo over the last six hours of the 24-hour dosing interval suggesting end-of-dose failure.

End of Dosing Period Efficacy Assessment

At the request of the Division, the Sponsor provided end of dosing period efficacy assessment. To evaluate the efficacy response at the end of the dosing interval, the following three efficacy endpoints were evaluated at the end of the dosing period:

- SPIDs derived from W2LOCF, the pre-defined primary analysis method SPID, during the second 12 hours ($SPID_{12-24}$, $SPID_{36-48}$) and last 6 hours ($SPID_{18-24}$, $SPID_{42-48}$) of each 24-hour dosing interval, and at increasing intervals (every six hours) throughout the treatment phase (Hour 0-48)
- Proportion of subjects requiring rescue analgesia in each 6-hour interval
- Total number of doses of rescue analgesia per subject in each 6-hour interval

The analyses of proportion of subjects requiring rescue and total number of rescue doses per subject were at-risk analyses, that is, subjects who discontinued during the treatment period were included in the periods prior to discontinuation. For example, subjects who discontinued before Hour 6 were included only in 0-6 hour period. Few subjects in either treatment arm discontinued the study early.

Differences between treatment groups in SPID at the six and 12 hour end of dosing intervals using the W2LOCF method are summarized in the table below.

Table 12 Summary of LS Mean SPID at End of Dosing Interval

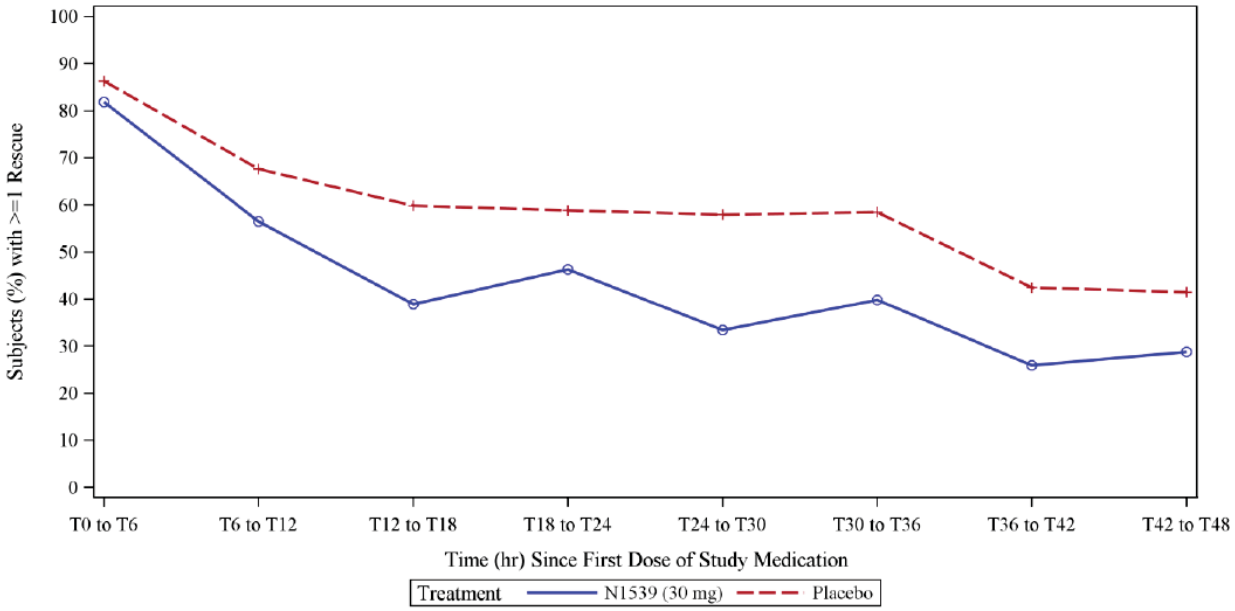
Parameter	N1539 30 mg (N=110)	Placebo (N=109)	P-Value
$SPID_{12-24}$	-2498.3 (123.63)	-2064.7 (124.12)	0.0115
$SPID_{18-24}$	-1204.7 (64.28)	-1078.7 (64.54)	0.1556
$SPID_{36-48}$	-3276.2 (128.54)	-2827.6 (129.05)	0.0119
$SPID_{42-48}$	-1631.9 (65.50)	-1442.8 (65.76)	0.0370

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 45)

The analyses of SPID show that there were no significant differences in PID during the last six hours of the dosing interval as the table above.

The proportion of subjects with ≥ 1 rescue analgesia in 6-hour intervals is displayed in the figure below.

Figure 4 Proportion of Subjects with ≥ 1 Rescue Analgesia in 6-Hour Intervals

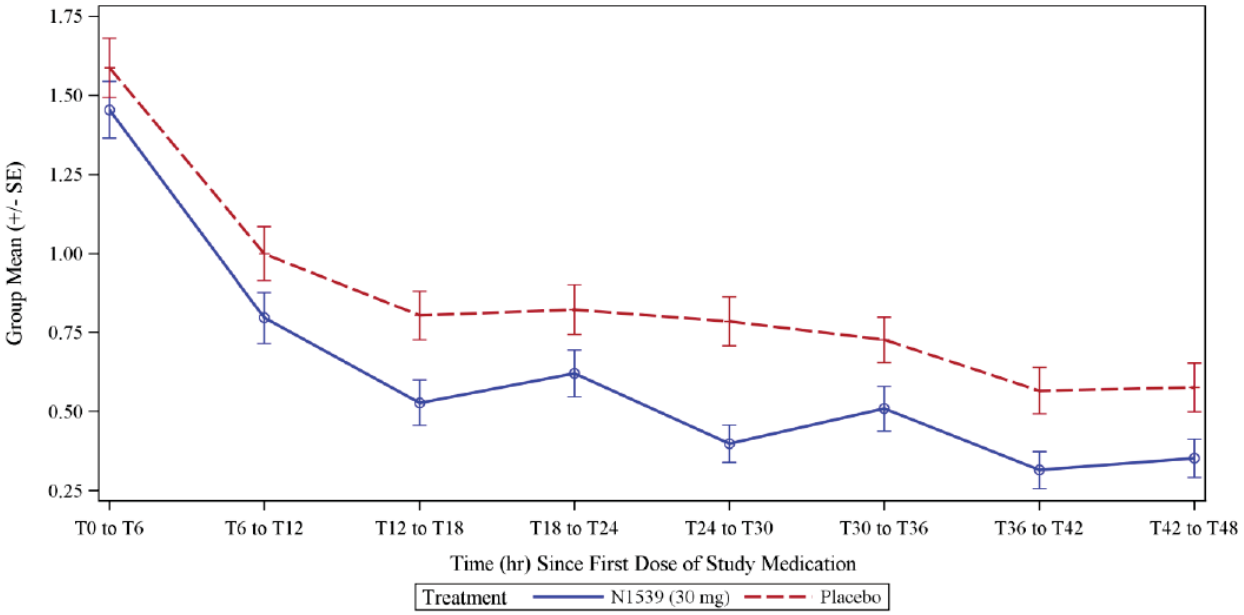


Data reference: Table 14.2.8.1

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 46)

The number of rescue analgesia doses used per subject in 6-hour intervals is displayed in the figure below.

Figure 5 Mean Number of Rescue Analgesia Doses Per Subject in 6-Hour Intervals



Data reference: Table 14.2.8.2

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 46)

Consistent with PID curves, while the proportion of subjects who used rescue analgesia and the number of doses of rescue medication per subject seem to be lower in the N1539 30 mg group as compared to the placebo group for each six-hour interval, there does appear to be a decrease in the magnitude of difference between the groups from Hour 18 to 24 and then again from Hour 30 to 48 as shown in the figures above.

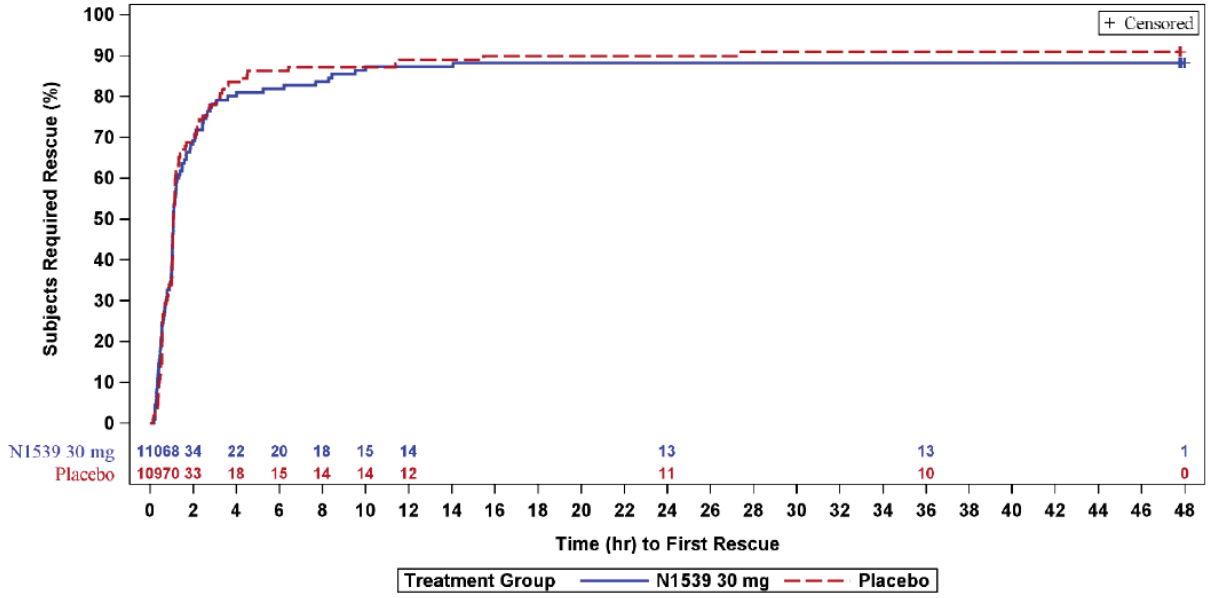
Response Analysis

Four responder categories were defined. A responder was defined as a subject with ≥ 30% improvement or with ≥ 50% improvement (improvement is defined as the percent of overall pain reduction from baseline) over the first six hours or over the first 24 hours after the first dose.

The N1539 30 mg group showed a numerically greater proportion of responders in each category compared with placebo. A significantly higher proportion of subjects reported a ≥ 30% improvement over the first 24 hours following treatment with N1539 30 mg (79 [71.8%]; p=0.0178) versus placebo (62 [56.9%]) using the W2LOCF analysis method. A significant response was not identified for other categories or other imputation methods for SPID.

Rescue Analgesia

Rescue analgesia was available in the form of oral oxycodone 5 mg up to every two hours for subjects with inadequate pain control following randomization. A survival plot of the time to first rescue is provided in the figure below.



Data reference: Appendix 16.2.6, Listing 16.2.10.

Figure 6 Time to First use of Rescue Analgesia for N1539 Compared to Placebo Over the First 48 Hours of Treatment

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 40)

The median time to first rescue for the study drug and placebo were 1.08 hour and 1.09 hour respectively. The proportion of subjects who used ≥1 dose of rescue medication was essentially the same between groups in the first 24 hours (N1539 30 mg: 88%; placebo: 90%). A summary of the time to first rescue and number of subjects requiring rescue is provided in the table below

Table 13 Summary of Time to First Rescue and Number of Subjects Requiring Rescue

Treatment Group	KM Estimates Time to First Rescue – Hr (95% CI)			Number of Subjects (%) Using Rescue		
	25%tile	50% tile	75%tile	Hour 0-24	Hour 24-48	Hour 0-48
N1539 30 mg (N=110)	0.61 (0.47, 0.91)	1.08 (1.03, 1.23)	2.60 (1.70, 6.21)	97 (88.2%)	60 (55.6%)	97 (88.2%)

Placebo (N=109)	0.60 (0.55, 0.87)	1.09 (1.03, 1.17)	2.45 (1.53, 3.63)	98 (89.9%)	81 (75.7%)	99 (90.8%)
Comparisons	log-rank p-value = 0.7572			p=0.6559	p=0.0014	p=0.4994

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 41)

A summary of the number of rescue analgesia doses required per subject is provided in the table below.

Table 14 Summary of the Number of Rescue Analgesia Dosed Requiring Per Subjects

Study Interval / p-value	N1539 30 mg (N=110)	Placebo (N=109)	P-value
Hour 0-24 – LS Mean (SE)	3.66 (0.24)	4.38 (0.24)	0.0275
Hour 24-48 – LS Mean (SE)	1.75 (0.21)	2.72 (0.21)	0.0009
Hour 0-48 – LS Mean (SE)	5.38 (0.41)	7.07 (0.41)	0.0027

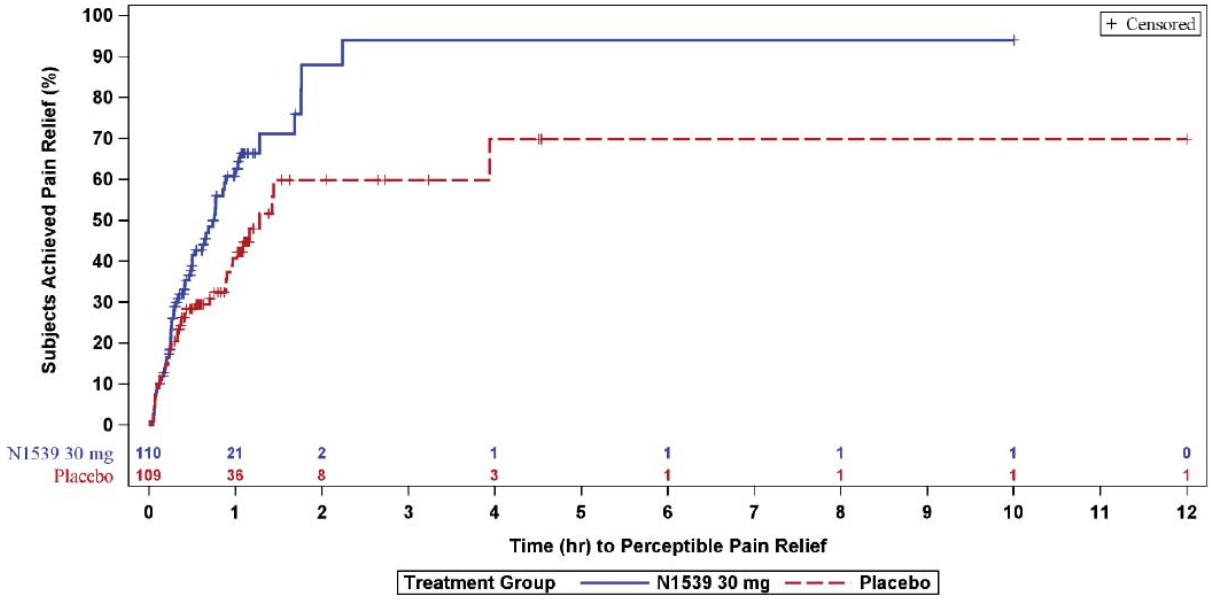
Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 41)

Time to Pain Relief

It is must be noted that the analysis of time to pain relief didn't take rescue medication use into consideration.

The time to perceptible and meaningful pain relief were evaluated using the double-stopwatch Method. There was no significant difference identified in time to meaningful pain relief between the N1539 30 mg group and placebo group. There is no separation between the treatment and placebo group based on the survival plots of the meaningful pain relief as the figures below. A summary of time to pain relief is provided in the table below.

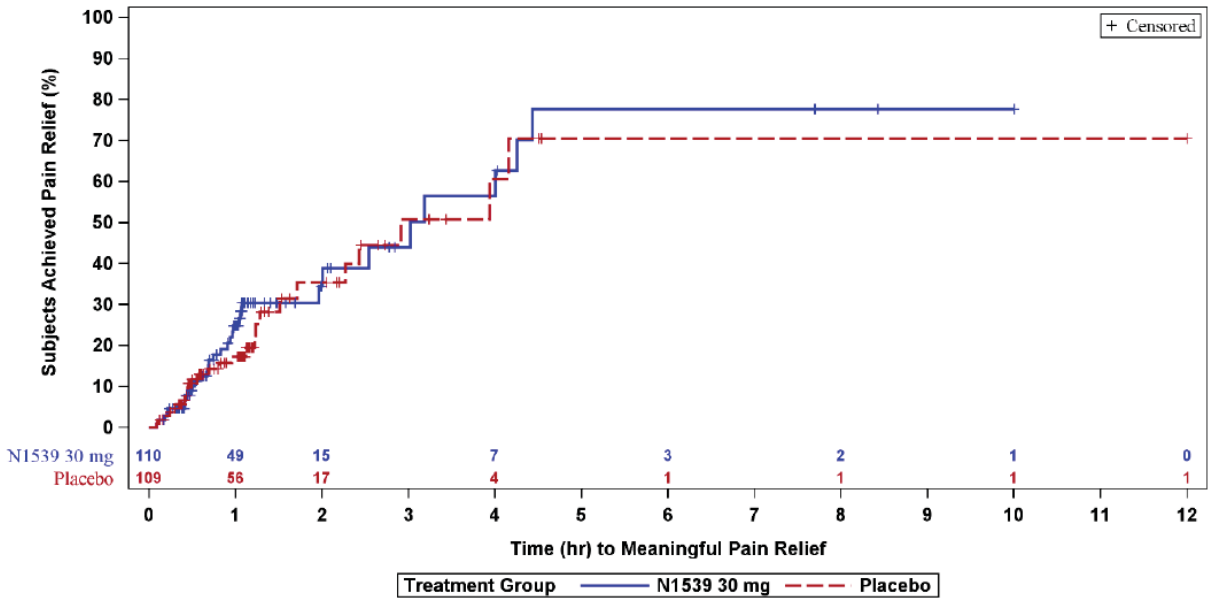
Figure 7 Time to Achieve First Perceptible Pain Relief for N1539 Compared to Placebo Over the First 48 Hours of Treatment



Data reference: Appendix 16.2.6, Listing 16.2.11

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 42)

Figure 8 Time to Achieve Meaningful Pain Relief for N1539 Compared to Placebo Over the First 48 Hours of Treatment



Data reference: Appendix 16.2.6, Listing 16.2.11

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 42)

Table 15 Summary of Time to Pain Relief Analysis

Parameter / Statistic	N1539 30 mg (N=110)	Placebo (N=109)
Time to First Perceptible PR (hr)		
Subjects Achieved Endpoint, n (%)	63 (57.3)	45 (41.3)
25% (95% CI)	0.26 (0.23, 0.41)	0.37 (0.22, 0.88)
50% (95% CI)	0.76 (0.5, 0.89)	1.28 (0.96, NA)
75% (95% CI)	1.69 (1.03, 2.24)	NA (3.94, NA)
Log-Rank Test	0.0050	
Time to Meaningful PR (hr)		
Subjects Achieved Endpoint, n (%)	32 (29.1)	27 (24.8)
25% (95% CI)	1.04 (0.69, 2.01)	1.23 (0.96, 2.27)
50% (95% CI)	3.02 (2.01, 4.43)	2.92 (1.71, NA)

75% (95% CI)	4.43 (3.18, NA)	NA (3.94, NA)
Log-Rank Test	0.5096	

Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 43)

Reviewer's comments:
A meaningful pain relief is typically achieved within the first hour for an IV NSAID analgesic, and that the time to achieve meaningful pain relief for study drug is delayed by that standard.

The mean Time to PR for treatment and placebo was essentially the same (3.0 versus 2.92 for treatment and placebo, respectively). The delayed PR in this studied model suggest that the proposed study drug, given 30 mg IV daily, is not suitable as an analgesic for the management of acute pain. In addition, it must be noted that the meaningful pain relief was achieved after the first rescue (5 mg Oxycodone) given about two hours earlier, which suggests the rescue medication as least partially contributed to the meaningful pain relief achieved.

Patient Global Assessment
A patient global assessment (PGA) of pain control was performed at Hour 24 and 48 using a 5-point scale. No significant difference in PGA was identified at Hour 24, although a statistical improvement in PGA for the N1539 30 mg treatment group was identified at Hour 48 (p=0.0027). Overall, the proportion of subjects reporting good or better (2+) pain control on the PGA was numerically greater for the N1539 30 mg treatment group vs. placebo at Hour 24 (84.3% vs. 67.3%) and Hour 48 (88.8% vs. 83.4%).

Applicant's Efficacy Conclusion
"Treatment with N1539 30 mg demonstrated a statistically significant difference in pain reduction as demonstrated by the SPID24 value versus placebo using the W2LOCF primary analysis. Additionally, statistically significant differences in other evaluated SPID intervals (SPID12, SPID24, and SPID24-48) were also achieved under the primary analysis. Pain reduction in the first 6 hours post-Dose 1 (SPID6) was greater in N1539 30 mg treated subjects but did not reach statistical significance. A significantly higher proportion of subjects reported a ≥30% improvement over the first 24 hours following treatment with N1539 30 mg versus placebo. Time to event analysis yielded a significant result for time to perceptible pain relief, though no significant difference was identified in the time to meaningful pain relief. Subjects in the N1539 30 mg group used a significantly lower number of rescue doses per subject from Hour 0-24, Hour 24-48, and Hour 0-48 compared with placebo. Statistically significant differences were not identified between the treatment groups in the PGA scores at Hour 24, proportion of subjects with a ≥30% improvement at Hour 6 or a ≥50% improvement at Hour 6 or Hour 24, though results numerically favored N1539 30 mg treatment.

Results from various sensitivity analyses supported the primary analysis, suggesting that efficacy data from this study was meaningful suggesting that efficacy data from this study was not affected by missing data or use of rescue medication, and that N1539 30 mg has a superior analgesic effect compared to placebo. Efficacy response at the end of the dosing interval, demonstrated that subjects treated with N1539 30 mg had a greater pain reduction, a lower proportion of subjects requiring rescue, and a lower number of rescue doses per subject compared with placebo treated subjects, suggesting that the drug effect was maintained throughout the 24 hour dosing interval. While a statistically significant difference in pain reduction between treatment groups was not achieved in the last 6 Hours of the dosing interval, the direction of the effect was maintained as the study was not powered to detect a difference from placebo at these time intervals. Within each subgroup, analysis results favored N1539 30 mg treatment over placebo, consistent with the overall population. Study findings support the efficacy of N1539 30 mg administered once daily in the treatment of moderate to severe pain following abdominoplasty surgery."

Reviewer's Efficacy Discussion

The primary endpoint, SPID24, attained the pre-defined level of statistical significance (p =0.0145). However, there are two key deficiencies in the failure of the key secondary endpoints.

The End-of-dosing failure of last six hours of 24-hour dosing interval is demonstrated by minimal difference in the SPID over the last six hours of the dosing interval (SPID18-24) between treatment and control at this surgical models, which suggests the proposed dosing interval is not appropriate. A lack of analgesic efficacy in the last six hours of 24-hour dosing is clinically significant as inadequate pain relief.

The delayed onset suggests the lack of suitability for an acute indication. A short time to first rescue use is clearly demonstrated. The curves for Time to First use of Rescue Analgesia essentially overlap between groups, and the median time to first dose of rescue (oxycodone 5 mg) was one hour for both groups. The meaningful PR for both treatment and placebo is the same (3.0 and 2.9 hours respectively), and delayed. It must be noted that the meaningful pain relief was achieved after the first rescue, which suggests that the meaningful pain relief could have been achieved by the 5-mg oxycodone given earlier.

In addition, frequent rescue even in the treatment arm is required. The numbers of rescue analgesics for the first 24 hours was 3.66 versus 4.38 for treatment and placebo, respectively. With the delayed onset and the end-of-dosing failure, frequent rescue requirement even in the active treatment arm is not unexpected. Although the comparison of the number of rescue analgesics between the treatment and placebo groups reached statistical significance, the fact

that the treatment group used rescue approximately four times over 24 hours raises serious concerns about the clinical relevance of this finding.

The efficacy as an acute analgesic at the proposed dosing interval is not established due end of the dosing failure and the delayed onset in this abdominoplasty model.

Dose/Dose Response

N/A

Durability of Response

N/A

Persistence of Effect

N/A

Additional Analyses Conducted on the Individual Trial

N/A

6.2. REC-15-016

6.2.1. Study Design

Overview and Objective

This was a Phase 3, randomized, multicenter, double-blind, placebo-controlled evaluation of the efficacy and safety of N1539 30 mg in adult subjects undergoing simple unilateral bunionectomy.

The primary objective of this study was to demonstrate the analgesic efficacy of N1539 compared with placebo, using the summed pain intensity difference over the first 48 hours ($SPID_{48}$) in subjects with moderate to severe pain following unilateral bunionectomy.

Secondary objectives of this study included:

- Evaluating the analgesic effects of N1539 versus placebo at various time points using a series of secondary efficacy endpoints for pain intensity, pain relief, and use of rescue medication
- Determine the safety and tolerability of N1539 as evaluated with physical examination,

vital signs, clinical laboratory tests, ECGs, wound evaluation, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

Trial Design

The study was planned to enroll approximately 200 subjects for the intent-to-treat (ITT) analysis set.

Subjects requiring bunionectomy, age 18 to 75 years inclusive, were to be screened for participation at four study sites in the United States. Screening was to occur within 28 days before study drug administration. After signing the informed consent, medical history, physical examination, baseline laboratory testing, 12-lead electrocardiogram (ECG), pregnancy testing, and vital sign measurements were to be completed during the screening visit.

On the day of surgery (Day -1), subjects were to undergo primary unilateral first metatarsal bunionectomy procedure under regional anesthesia. Following surgery, subjects were to be managed using a popliteal block until the morning of Day 1, when the block was to be stopped and subjects were to be evaluated for eligibility for randomization.

Eligible subjects were to be randomized and treated with study drug every 24 hours, and stay at the study site for approximately 48 hours after treatment initiation. After completion of 48 hours of evaluation, subjects could be discharged from the study site. Subjects were eligible to receive a third dose of study drug before discharge at the discretion of the investigator and the subject.

All treated subjects were to be followed through 28 days following the last study dose (LSD). All subjects were to return to the study site seven days post-LSD (LSD+7) and 28 days post-LSD (LSD+28) to complete follow-up study assessments.

Efficacy assessments were to include pain intensity, use of rescue medication, time to pain relief, and Patient Global Assessment (PGA) of pain control. Safety assessments were to include monitoring of AEs, clinical laboratory tests, vital sign measurements, wound evaluation, and ECGs. Whole blood samples were to be collected for pharmacokinetic (PK) analysis and inclusion in a separate population PK analysis.

The following summarizes key activities for each phase of this study: 1) Pretreatment Phase, 2) Treatment Phase, 3) Follow-up.

Pretreatment Phase:

a. Screening Period (Day -28 to Day -2): Subjects were to be consented and screened.

b. Day of Surgery (Day -1):

1) Pre-surgery: Subjects were to be admitted to the study site and reassessed for eligibility for the study. Pre-surgery activities were to be conducted.

2) Surgery: Eligible subjects were to undergo primary, unilateral, first metatarsal bunionectomy. Pre/Intraoperatively, the subject was to have a popliteal block placed. A standard anesthetic regimen was to be followed for all subjects as outlined in the anesthesia protocol.

3) Postoperative Period: Following surgery, subjects were to have the popliteal block maintained and be transferred to the appropriate recovery unit. Treatments allowed during the postoperative period included maintenance of the popliteal block, topical ice, and analgesic administration (ketorolac and/or morphine) as described.

c. Randomization Qualification (Day 1): Following discontinuation of the popliteal block and other postoperative pain management, subjects were to be assessed for randomization to study treatment. Subjects were eligible for randomization if they met all of the postoperative randomization criteria starting after discontinuation of the popliteal block (03:00), and prior to 12:00 on Day 1 (study protocol).

Treatment Phase (Hour 0 through Hour 48)

Once the subject met postoperative randomization eligibility criteria, they were to be randomized in a 1:1 ratio to IV treatment with N1539 30 mg or placebo, administered every 24 hours. Subjects were to be domiciled at the study site throughout the treatment phase.

Randomization and administration of the first dose of study drug was to be within 15 minutes of meeting the qualifying categorical and numeric pain rating scale (NPRS) scores. After randomization, immediately prior to study drug administration, the baseline pain intensity assessment via NPRS was to be completed. Postoperative randomization criteria were to be assessed based on the qualifying NPRS assessment and not the baseline NPRS.

The time of first dose of study drug (Dose 1) was to be recorded as Hour 0. Subjects were to be administered a study dose per their randomization every 24 hours for two doses. Following completion of the Hour 48 study assessments, subjects could receive an additional dose of their randomized treatment prior to discharge, if sufficient pain symptoms were still present, at the discretion of the investigator.

Subjects with inadequately controlled pain symptoms could request rescue analgesia. Subjects were to be encouraged to wait at least one hour after the first study drug

administration before utilizing rescue analgesia, if possible. Pain intensity assessments were to be completed prior to each dose of rescue medication.

Study assessments completed during the treatment phase were to include pain intensity (NPRS), time to pain relief (double stopwatch), PGA of pain control, PK sampling, and vital sign measurement.

Follow-up:

After completing the study assessments through Hour 48, subjects could be discharged from the study site. Subjects were to be provided routine standard of care for pain management after discharge from the study site.

All subjects were asked to return to the study site on LSD+7 and LSD+28 to complete follow-up study assessments.

Study Population
Inclusion Criteria

- Male or female 18 to 75 years of age, inclusive
- Undergoing a primary unilateral first metatarsal bunionectomy repair, without collateral procedures, under regional anesthesia (mayo and popliteal block) not to include base wedge procedure
- Being American Society of Anesthesiology (ASA) physical class 1 or 2
- Female subjects were eligible only if all of the following apply:
    - Not pregnant (female subjects of child bearing potential [FOCBP] must have a negative serum pregnancy tests at screening and negative urine pregnancy test before surgery);
    - Not lactating;
    - Not planning to become pregnant during the study;
    - Commit to the use of an acceptable form of birth control for the duration of the study through LSD+28.
- Body mass index: less than 35 kg/m^2

Postoperative Randomization Criteria

- Report moderate or severe pain on a 4-point categorical pain rating scale (with categories of none, mild, moderate, or severe), AND, a score ≥4 on 11-point NPRS after discontinuation of the popliteal block and before 12:00 on Day 1
- Subject could answer questions and follow commands, and appropriately participate in requisite pain evaluation assessments dictated in the protocol
- The surgical procedure from incision to closure was not longer than 2 hours

- The end of the surgical procedure was not later than approximately 18:00 on Day -1
- The subject had no evidence of respiratory insufficiency, clinically significant hypotension, bradycardia, or any other abnormality, during or following surgery that, in the investigator's opinion, significantly increases the risks of study drug administration
- There were no significant deviations from the surgical protocol, anesthetic protocol, or specified pretreatment analgesic regimen, that would, in the opinion of the investigator, put the subject at risk of participation in the trial, confound the analgesic endpoints of the trial or cause concern regarding the subject's ability to participate in the trial

Exclusion Criteria

- Had a known allergy to meloxicam or any excipient of N1539, aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), or to any peri- or postoperative medications used in this study
- Had an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of > 2X the upper limit of normal (ULN), alkaline phosphatase (AP) >1.5X ULN, or total bilirubin > 1.2X ULN, a prothrombin time (PT) >20% above ULN, or any laboratory abnormality that would place the subject at increased risk for study participation per the judgment of the investigator at screening and/or prior to surgery
- Had a history of or positive test results for HIV, or hepatitis B or C at screening
- Had, as determined by the investigator or the sponsor's medical monitor, a history or clinical manifestations of significant renal, hepatic, cardiovascular, metabolic, neurologic, psychiatric, or other condition that would preclude participation in the study
- Had a history of myocardial infarction or coronary artery bypass graft surgery within the preceding 12 months
- Had a history of migraine (within past 12 months) or frequent headaches (22 events per week requiring analgesics), seizures, or are currently taking anticonvulsants
- Had active or recent (within 6 months) gastrointestinal ulceration or bleeding
- Had a known bleeding disorder or be taking agents affecting coagulation
- Had another painful physical condition that, in the opinion of the investigator, may confound the assessments of postoperative pain
- Had evidence of a clinically significant 12 lead ECG abnormality
- Had a history of alcohol abuse (regularly drinks > 4 units of alcohol per day; 8 oz. beer, 3 oz. wine, 1 oz. spirits) within the past five years or a history of prescription/illicit drug abuse
- Had positive results on the urine drug screen or alcohol breath test indicative of illicit drug

or alcohol abuse at screening, and/or prior to surgery

- Had been receiving or have received chronic opioid therapy defined as greater than 15 morphine equivalents units per day for greater than 3 out of 7 days per week over a 1-month period within 12 months of study treatment initiation
- Used concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs which in the investigator's opinion may exert significant analgesic properties or act synergistically with N1539.

Schedule of events
A summary table of study procedures to be performed, and the assigned time points, is provided for the overall study in the table below.

Table 16 Overview of Study procedures

Procedure; Dose/Hour	Screening	Inpatient					Follow-Up	
		Day -1		Day 1 – Day 3			LSD+7 ± 2	LSD+28 ± 4
		Prior to Surgery	Surgery	Dose 1 / Hour 0	Dose 2 / Hour 24	Hour 48		
Informed Consent	X							
Confinement		←		X		→		
Eligibility Assessment	X	X	X[e]			X		
Demographics and Medical History	X	X						
Physical Examination[f]	X	X				X	X	
Pregnancy Test (FOCBP only)	X[serum]	X[urine]						
Alcohol Breath Test and UDS	X	X						
Clinical Laboratory Tests[a]	X	X				X	X	
HIV and Hepatitis Screening	X							
Vital Signs[b]	X	X		X[d]		X	X	
12 Lead ECG	X	X[c]				X	X	
Bunionectomy Procedure			X					
Study Drug Administration				X	X	X[h]		
Pain Intensity (PI)				X[g]	X[g]	X[g]		
Perceptible and Meaningful PR				X				
PGA of Pain Control					X	X		
PK Sample Collection				X	X			
Wound Evaluation						X	X	X
Prior and Concomitant Medication		←		X		→		
Adverse Event Monitoring				←	X	→		

a Laboratory tests were to include hematology, chemistry, urinalysis, and coagulation tests.
b Vital signs (VS) included: resting blood pressure, resting pulse, and SpO2. Tests were to be obtained after resting (seated/reclined) for ≥ 5 minutes.
c 12-lead ECG was to be done prior to surgery only if screening ECG was done >7 days before surgery
d VS were to be determined at pre dose, then 0.5, 1, 2, 6, and 24 (pre-Dose 2) hours after Dose 1.
e Postoperative randomization criteria were to be assessed on the day after surgery (Day 1), prior to randomization.
f Height, weight and BMI were to be collected at screening only.
g PI scores were to be assessed at the following time points post Dose 1: 0.25, 0.5, 0.75, 1, and 2 hours. Thereafter PI was to be collected every 2 hours until Hour 48.
h Optional dose could be administered after Hour 48 assessments, prior to discharge, at the discretion of the investigator and subject.

Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 17)

Study Endpoints

The primary efficacy endpoint in this study was pain reduction measured by the SPID48.

Statistical Analysis Plan

The Statistical Analysis Plan (SAP) prepared for Study REC-15-016 provides a more technical and detailed elaboration of the principal statistical features stated in the study protocol. The objective of the SAP was to reasonably assure that the statistical methodologies to be used for analysis were complete and accurate.
In the development of the study SAP, the following documents were used:

- Protocol REC-15-016, 11 December 2015
- REC-15-016, eCRF, Final 1.0 27 January, 2016

The principles in the following guidance documents were followed in preparation of the study SAP.

- ICH E3 (1995): Structure and Content of Clinical Study Reports
- ICH E6 (1996): Guideline for Good Clinical Practice
- ICH E9 (1998): Statistical Principles for Clinical Trials

The sample size was selected with an assumption that the effect size for SPID48 is at least 0.40 between N1539 30 mg and placebo. Using a two-group t-test with a 0.05 two-sided significance level, this study would have a greater than 80% power to detect the difference between N1539 and placebo; if the effect size was 0.52 the study power to detect the difference between N1539 and placebo would be at 95%.

Protocol Amendments

No protocol amendments were issued during the study, and no changes to the conduct of the study were implemented. There were two clarification letters issued around elements of the protocol addressing: rescreening of subjects who fell out of window during the screening phase of the study due to administrative scheduling issues, and clarifying scheduling of the Hour 48 wound evaluation.

Changes in the Planned Analysis
Following database lock, and completion of the planned study analyses, the following additional analyses were undertaken.

1. Planned SPID intervals included 6, 12, 24, 48, and 24-48 hours, with SPID48 being the primary endpoint. To examine the analgesic effect of N1539 at the end of dosing, additional SPID intervals, derived by the 2-hour windowed last observation carried forward (W2LOCF) method, were evaluated as ad-hoc. The added SPID in 6-hour intervals included SPID18, SPID30, SPID36, SPID42, SPID12-24, SPID18-24, SPID36-48, and SPID42-48. The same ANCOVA model that included main effect of treatment, investigational site, and baseline PI score was used in each analysis.
2. To further evaluate the end of dosing analgesic effect of N1539, rescue analgesic medication use in 6-hour interval was also evaluated. The analysis included proportion of subjects requiring rescue analgesics and total number of times rescue analgesics used per subjects during the intervals of 0-6, 6-12, 12-18, 18-24, 24-30, 30-36, 36-42, and 42-48 hours after Dose 1. The mean total number of times used analgesic medications and proportion of subjects requiring rescue analgesics in 6-hour interval since Dose 1 were also graphically presented.
3. Investigational site was a statistically significant covariate in the primary analysis of SPID48. Therefore, subgroup analysis of SPID48, derived by W2LOCF method, by investigational site was performed to examine the consistency of treatment effect within each site. The ANCOVA model for this subgroup analysis included main effect of treatment and a covariate of baseline PI score.
4. Subgroup analyses by age, sex, and race were planned; a formal covariate analysis was added to evaluate the effect of each covariate on treatment response. In each analysis the ANCOVA model included main effect of treatment, investigational site, baseline PI score, and the tested covariate age group, sex, or race group, respectively.
5. Race effect on treatment response was statistically significant in the covariate analysis. A subgroup analysis by race group within a site was performed to explore the placebo effect observed within non-white subjects and at Site 2 and to understand the nature of the race effect on treatment response. In this analysis, treatment effect within a race group was evaluated using an ANCOVA model that included main effect of treatment and baseline PI score; a second ANCOVA model that included main effect of treatment, baseline PI score and race group was used to examine the race effect on treatment response within a site.

6.2.2. Study Results

Compliance with Good Clinical Practices

This study was conducted per GCP; US 21 Code of Federal Regulations (CFR) Part 50 (Protection of Human Subjects); US 21 CFR Part 56 (IRBs); US 21 CFR Part 54 (Financial Disclosure); International Conference on Harmonization (ICH) Guidance for Industry, E6 GCP: Consolidated Guidance; the Nuremberg Code; and, where applicable the principles of the

Declaration of Helsinki (Recommendations guiding Medical Doctors in Biomedical Research Involving Human Subjects), and with the NH&MRC National Statement on Ethical Conduct in Human Research (2007).

Financial Disclosure

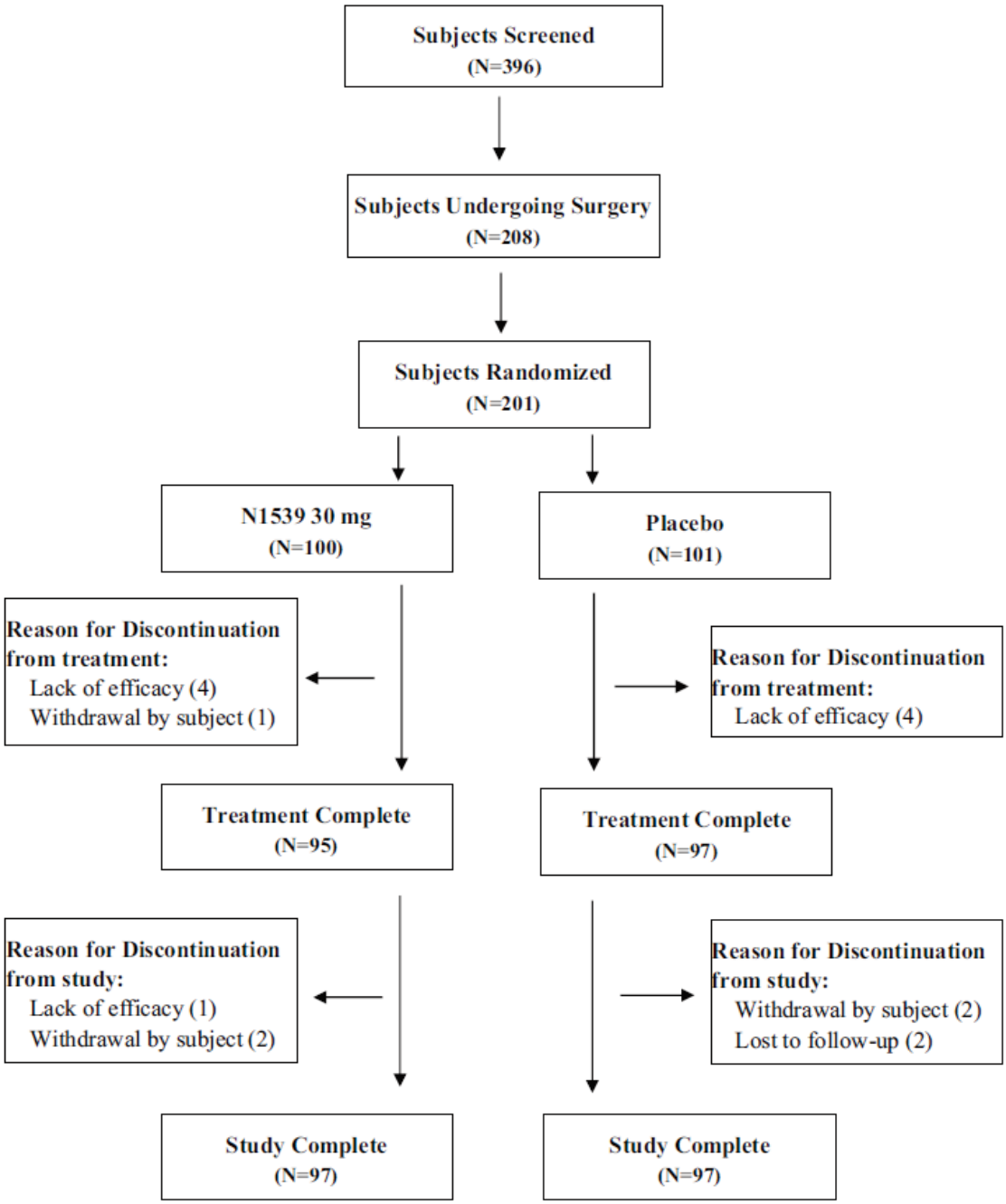
The Applicant's submission included the completed "Certification: Financial Interests and Arrangements of Clinical Investigators" form (Form FDA 3455). The Applicant indicated that the investigators at each site are certified as having no Financial Arrangement as defined in 21 CFR 54.2.

Patient Disposition

A total of 201 subjects completed surgery, met postoperative criteria, and were randomized to treatment. Among the randomized subjects, 191 (95%) completed the 48-hour treatment phase, and 194 (96.5%) completed the LSD+28 follow-up visit. Causes for discontinuing from study drug treatment in the study included: lack of efficacy (eight; four subjects per treatment arm), and subject withdrawal from the study (one; N1539 30 mg).

The disposition of subjects enrolled in this study is depicted as figure below

Table 17 Disposition of Subjects



Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 34)

Protocol Violations/Deviations

Protocol deviations and important protocol deviations were collected during this study. Three major deviations were identified in three subjects: one placebo treated subject missed baseline/pre-dose PI assessment, another placebo treated subject did who not meet randomization criteria was randomized (pain rated as mild prior to randomization), and one N1539 30 mg treated subject had recently started antibiotics that were not discontinued prior to surgery. In the case of the subject with the missed pre-dose PI assessment, the subject was included in the efficacy analysis and the qualifying NPRS score (six out of ten) was used as the baseline for analysis.

Reviewer's comments:
The major protocol deviations are not expected to affect the overall efficacy results.

Table of Demographic Characteristics

A total of 171 female (85.1%) and 30 male subjects were randomized to treatment. Most study subjects were white (64.2%), not Hispanic or Latino (68.2%), and ranged in age from 18 to 72 years (mean ± standard deviation [SD] age 47.6 ± 12.48 years). The overall mean ± SD height and weight were 1.6 ± 0.09 m and 73.7 ± 14.19 kg respectively, with a mean ± SD body mass index (BMI) of 27.6 ± 4.46 kg/m^2. The treatment groups were comparable in demographics and baseline characteristics. A summary of demographic characteristics for each treatment group is provided in the table below.

Table 18 Summary of Demographic Characteristics

Variable	N1539 30 mg (N=100)	Placebo (N=101)	Overall (N=201)
Age (yrs) - mean ± SD	46.7 ± 12.79	48.4 ± 12.17	47.6 ± 12.48
Sex, n (%)			
Male	16 (16.0)	14 (13.9)	30 (14.9)
Female	84 (84.0)	87 (86.1)	171 (85.1)
Race, n (%)			
White	61 (61.0)	68 (67.3)	129 (64.2)
Black or African American	32 (32.0)	26 (25.7)	58 (28.9)
Asian	2 (2.0)	3 (3.0)	5 (2.5)
Native Hawaiian or Other Pacific Islander	2 (2.0)	2 (2.0)	4 (2.0)
Other	3 (3.0)	2 (2.0)	5 (2.5)

Ethnicity, n (%)			
Hispanic or Latino	28 (28.0)	36 (35.6)	64 (31.8)
Not Hispanic or Latino	72 (72.0)	65 (64.4)	137 (68.2)
Baseline Height (m) - mean ± SD	1.6 ± 0.08	1.6 ± 0.09	1.6 ± 0.09
Baseline Weight (kg) - mean ± SD	72.5 ± 14.56	74.9 ± 13.77	73.7 ± 14.19
Baseline BMI (kg/m^2) - mean ± SD	26.9 ± 4.80	28.3 ± 4.02	27.6 ± 4.46
Surgery Duration (hr) - mean ± SD	0.514 ± 0.2397	0.485 ± 0.2001	0.500 ± 0.2206
Bunionectomy Surgery Site: n (%)			
Left Foot	50 (50.0)	52 (51.5)	102 (50.7)
Right Foot	50 (50.0)	49 (48.5)	99 (49.3)
Time (hr) from End of Surgery to First Dose - mean ± SD	18.781 ± 3.3459	18.992 ± 3.2235	18.887 ± 3.2784
Baseline PI (0-10) - mean ± SD	6.7 ± 1.90	7.0 ± 1.82	-

Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 37)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All 201 randomized subjects had at least one medical/surgical history finding prior to receiving study medication. The most common findings included: postmenopausal status, hypertension, female sterilization, bunion operation, headache, and seasonal allergy.

The use of concomitant medications was limited to medications that had been at a stable dose for at least 14 days prior to the scheduled bunionectomy procedure, as well as analgesic medications. Most subjects (99.5%) utilized prior or concomitant medications during their participation in this study. Frequently used types of non-surgical concomitant medications in the study included: analgesics, lipid modifying agents, anti-hypertensives, anti-emetics, antihistamines, and nutritional supplements.

Analgesics including ibuprofen, hydrocodone, oxycodone, acetaminophen, and combination products were utilized in most subjects for rescue analgesia and after completion of the treatment phase for continued postoperative pain management.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Unblinded study personnel were to administer each dose of study medication while the subject was confined at the study site. The exact date and time each dose was administered was to be recorded in the subject's eCRF.

Blinding

All study medication was to be administered by an unblinded staff member who was not to be involved in the collection of safety or efficacy data; both the subject and the investigator/site staff involved with collection of safety and efficacy data were to be blinded to the treatment assignment. Study doses were to be prepared by the designated unblinded and appropriately qualified member(s) of the healthcare team at the research site who was not involved with the collection of safety and efficacy data, for administration per the subject's randomization sequence.

The study blind could be broken only if the safety of a subject was at risk and the treatment plan for that subject depended on which study medication he or she received. If knowledge of the treatment assignment was necessary for the management of a subject's safety, the blind could be broken using the unblinding cards provided per individual treatment randomization numbers. Unless the subject was at immediate risk, the investigator was to make diligent attempts to contact the sponsor before unblinding the subject's treatment assignment.

If a subject's treatment assignment was unblinded without the prior knowledge of the sponsor, the investigator was to notify the sponsor as soon as possible and no later than the

next business morning. All circumstances surrounding a premature unblinding were to be clearly documented.

Prior and Concomitant Therapy

All medications and other treatments taken by subjects within 5 days before dosing and during the study were to be recorded in the eCRF.

All medications that had not been at a stable dose for at least 14 days prior to the scheduled bunionectomy procedure were to be prohibited within five half-lives of the specific prior medication (or, if half-life is unknown, within 48 hours) before the surgical procedure

Prohibited Medications

The following medications were prohibited throughout the study (screening through LSD+28): anticonvulsants, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), neuroleptics, or serotonin-norepinephrine reuptake inhibitors (SNRIs). Selective serotonin reuptake inhibitors were allowed if taken for at least 30 days before the screening period of the study at an unchanged, stable dose. Additionally, gabapentin and pregabalin were not permitted and administration will disqualify the subject from the efficacy evaluation.

No epidural or intrathecal agents were to be used perioperatively, as well as any long-acting local anesthetic agents.

Analgesic medications other than those pre-specified for postoperative use, or for post-randomization rescue use, were prohibited during the treatment period (through Hour 48) including: hydrocodone, codeine, fentanyl, meperidine, tramadol, opioid combinations, acetaminophen, and NSAIDs. Aspirin (acetylsalicylic acid) was prohibited unless taken for cardiac or cardiovascular prophylaxis.

Sedatives (including benzodiazepines) used as minor tranquilizers or hypnotics were not allowed throughout the study unless approved by the investigator and medical monitor.

Rescue

Patients with inadequately controlled pain symptoms could request rescue analgesia (oral oxycodone 5 mg administered up to every two hours). To account for the use of rescue medications, pain intensity (PI) was measured prior to a rescue use and was carried forward to replace PI scores collected within two hours following this rescue use.

Efficacy Results – Primary Endpoint

The mean (SD) baseline pain score was 6.7 (1.90) and 7.0 (1.82) for the N1539 30 mg and placebo groups, respectively. The LS mean (standard error [SE]) of $SPID_{48}$ was -

6956.0 (521.69) for N1539 30 mg and -4829.3 (519.56) for placebo; the difference in $SPID_{48}$ between the treatment groups was statistically significant (p=0.0034), indicating that there was a positive N1539 30 mg treatment effect (i.e. smaller SPID value) on the total pain reduction from baseline during the first 48 hours of treatment using the W2LOCF analysis. A summary of LS Mean $SPID_{48}$ is provided in the table below.

Table 19 Summary of SPID48

Parameter	N1539 30 mg (N=100)	Placebo (N=101)	p-value
Baseline PI (0-10) - mean (SD)	6.7 (1.90)	7.0 (1.82)	-
$SPID_{48}$ - LS Mean (SE)	-6956.0 (521.69)	-4829.3 (519.56)	0.0034

Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 39)

Reviewer's comment: The Applicant's analysis of the primary efficacy endpoint has been confirmed by the Agency's statistical reviewer, Dr. Zhou. Please see Dr. Zhou's review for details.

Sensitivity Analysis

Sensitivity analyses of $SPID_{48}$ using the last observation carried forward (LOCF), baseline observation carried forward (BOCF), and all collected assessments (OBSERVED) methods supported the finding of the primary analysis method, with statistically significant differences in $SPID_{48}$ between treatment groups in each analysis method ($p<0.01$).

Reviewer's comments: Dr. Zhou concurs that sensitivity analyses of SPID48 using the LOCF, BOCF and OBSERVED methods had similar results to the analyses using the W2LOCF method.

Efficacy Results – Secondary and other relevant endpoints

The Sponsor conducted the following secondary efficacy analyses. It must be noted that the Applicant did not account for multiple comparisons in their analyses, therefore the p values reported by the Sponsor are not meaningful. The results of these analyses are useful only in descriptive terms and to show trends.

SPID at Other Intervals

Analysis of SPID at other intervals included $SPID_6$, $SPID_{12}$, $SPID_{24}$, and $SPID_{24-48}$. Under the W2LOCF primary analysis model, subjects treated with N1539 30 mg had greater pain

reduction (i.e., smaller SPID value) than the placebo treated subjects; the differences between N1539 30 mg and placebo at each interval were statistically significant ($p<0.05$).

A summary of LS Mean SPID data at each planned interval is provided in the table below.

Table 20 Summary of LS Mean SPID at Various Intervals

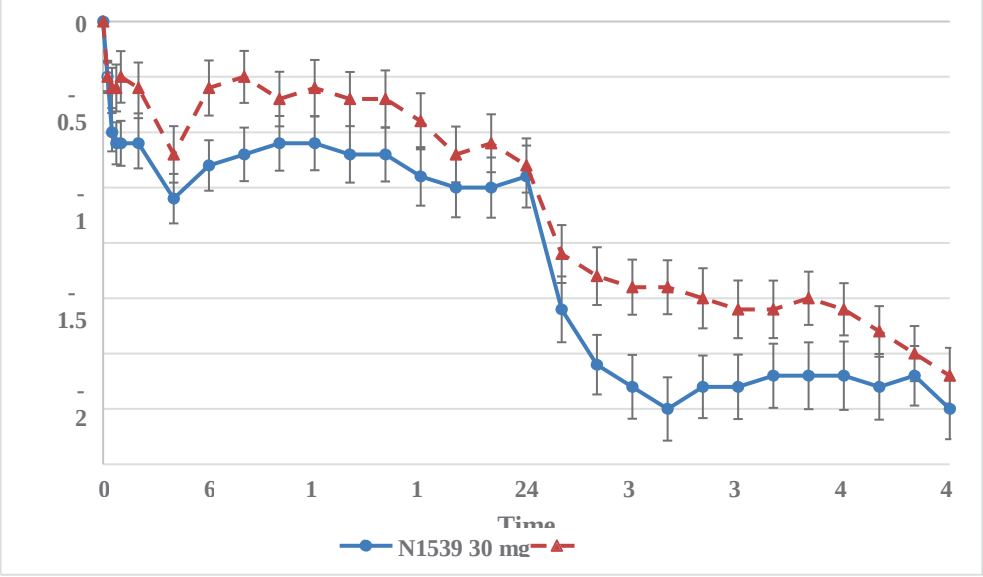
Parameter	N1539 30 mg (N=100)	Placebo (N=101)	p-value
$SPID_6$	-510.78 (66.22)	-288.33 (65.95)	0.0153
$SPID_{12}$	-957.83 (123.30)	-480.15 (122.80)	0.0053
$SPID_{24}$	-2071.0 (247.01)	-1167.9 (246.00)	0.0084
$SPID_{24-48}$	-4885.1 (313.60)	-3661.4 (312.32)	0.0050

Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 40)

Pain Intensity Difference (PID)

PID was calculated from PI scores at each time point, using each planned analysis method. A summary of PID scores using the W2LOCF analysis is depicted over the 48-hour treatment period in the figure below.

Figure 9 Pain intensity Difference for N1539 Compared to Placebo Over the First 48 Hours of Treatment



Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 41)

Reviewer's comments:
The two curves of PID versus time show no difference between active treatment and placebo at last six hours of 24 hours suggests an end-of-dose failure.

End of Dosing Period Efficacy Assessment
At the request of the Division, the Sponsor provided end of dosing period efficacy assessment. To evaluate the efficacy response at the end of the dosing interval, Hours 12-24 and Hours 36-48, the following three efficacy endpoints were evaluated in the same ways as Report-REC-15-015:

- SPIDs derived from W2LOCF, the pre-defined primary analysis method for SPID, during the second 12 hours (SPID12-24, SPID36-48) and last 6 hours (SPID18-24, SPID42-48) of each 24-hour dosing interval, and at increasing intervals (every six hours) throughout the treatment phase (Hour 0-48)
- Proportion of subjects requiring rescue analgesia in each 6-hour interval
- Total number of doses of rescue analgesia per subject in each 6-hour interval

Differences between treatment groups for the end of dose SPID intervals are summarized in the table below using the W2LOCF analysis method. There was not significant in the last 6 hours in both first and second 24-hour dosing.

Table 21 Summary of LS Mean SPID at End of Dosing Interval

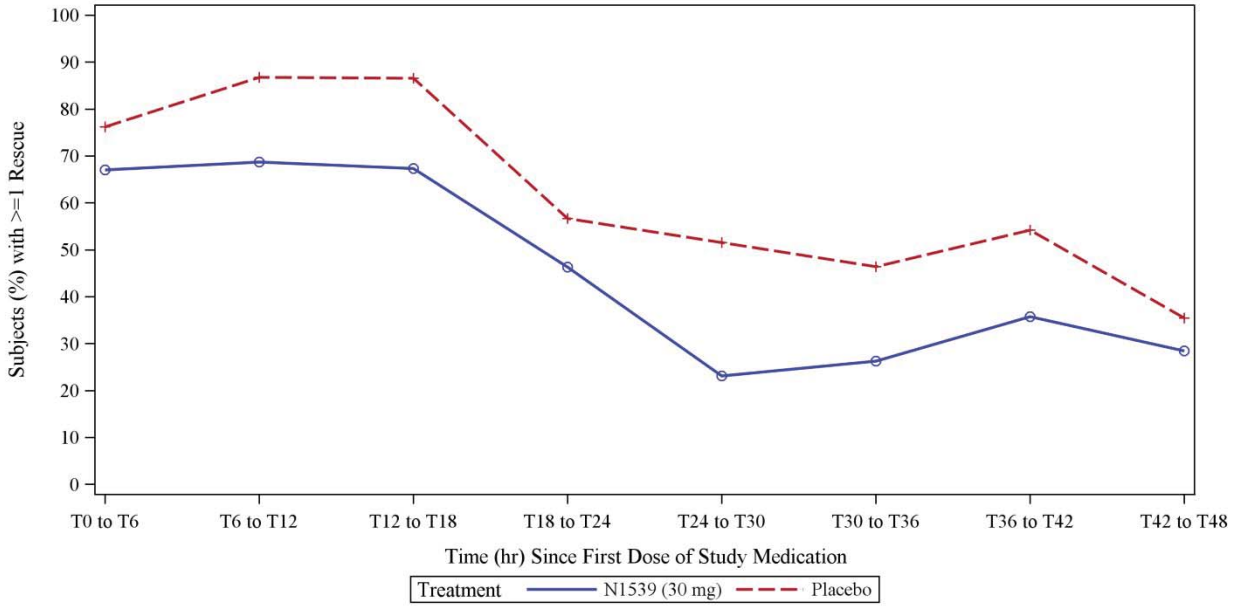
Parameter	N1539 30 mg (N=100)	Placebo (N=101)	p-value
$SPID_{12-24}$	-1113.1 (147.95)	-687.8 (147.35)	0.0376
$SPID_{18-24}$	-582.3 (78.70)	-424.8 (78.38)	0.1466
$SPID_{36-48}$	-2422.4 (159.80)	-1946.3 (159.15)	0.0312
$SPID_{42-48}$	-1226.5 (82.30)	-1054.5 (81.96)	0.1297

Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 47)

Like SPID18-24 and SPID42-48, the magnitude of difference between treatment groups was observed to decrease in the last 6-hours of the dosing interval, rescue use.

The proportion of subjects utilizing rescue and the number of rescue doses per subject, are displayed in 6-hour intervals in table and figure below, respectively.

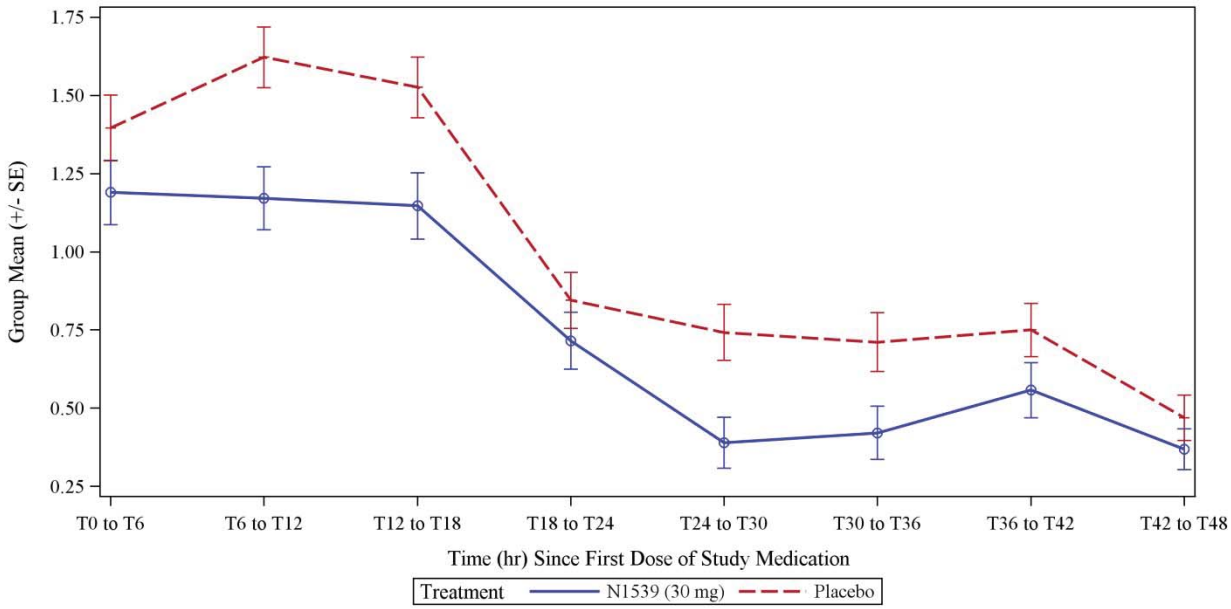
Figure 10 Proportion of Subjects with ≥ 1 Rescue Analgesia in 6-Hour Intervals



Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 48)

The number of rescue analgesia doses used per subject in 6-hour intervals is displayed in the figure below.

Figure 11 Mean Number of Rescue Analgesia Doses Per Subject in 6-Hour Intervals



Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 48)

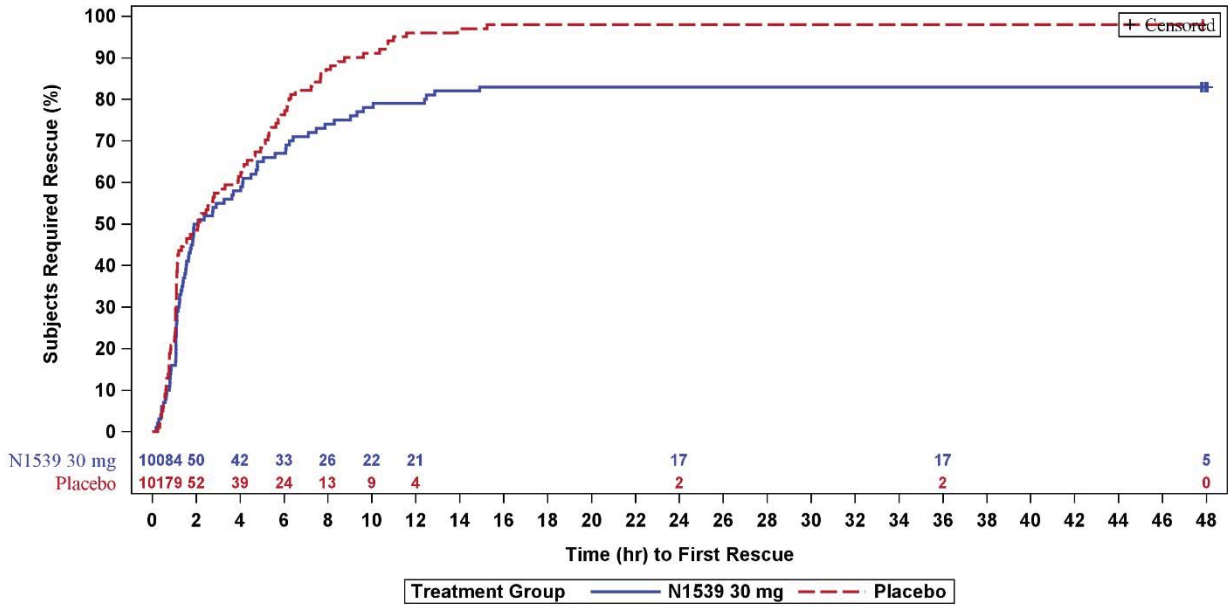
Response Analysis

Response analysis was performed using criteria of ≥ 30% and ≥ 50% improvement (improvement was defined as the percent reduction of PI scores compared to the baseline PI score), over the first six and 24 hours following dosing; analysis was performed using each of the predefined analysis methods of imputation. Under the W2LOCF analysis a significant difference in the proportion of responders was identified using the 30% criteria at Hour 6, and using the 30% and 50% criteria at Hour 24 for N1539 30 mg compared with placebo. Under each analysis, the number of subjects achieving response criteria was numerically greater for N1539 30 mg compared to placebo.

Rescue Analgesia

Rescue analgesia was available in the form of oral oxycodone five mg up to every two hours for subjects with inadequate pain control following study Dose 1. Most subjects used at least one rescue dose within the first 24 hours following Dose 1, and 50% of subjects used their first rescue within the first two hours after Dose 1. The median time to first dose of rescue was approximately two hours in both groups. A survival plot of the time to first rescue is provided in the figure below.

Figure 12 Time to First use of Rescue Analgesia for N1539 Compared to Placebo Over the First 48 Hours of Treatment



Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 40)

A summary of the time to first rescue and number of subjects requiring rescue is provided the table below

Table 22 Summary of Time to First Rescue and Number of Subjects Requiring Rescue

Treatment	KM Estimates Time to First Rescue – Hr (95% CI)			Number of Subjects (%) Using Rescue		
	25%tile	50% tile	75%tile	0-24 Hours	24-48 hours	0-48 hours
N1539 30 mg (N=100)	1.10 (1.06, 1.30)	1.99 (1.53, 4.12)	8.65 (5.06, 14.91)	83 (83.0%)	48 (50.53%)	83 (83.00%)
Placebo (N=101)	1.06 (0.78, 1.11)	2.09 (1.15, 3.31)	5.73 (4.61, 7.23)	99 (98.0%)	71 (73.20%)	99 (98.02%)
Comparisons	log-rank p-value = 0.0076			p=0.0002	p=0.0009	p=0.0002

Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 43)

A summary of number of rescue doses required is summarized in the table below.

Table 23 Summary of the Number of Rescue Analgesia Dosed Requiring Per Subjects

Study Interval	N1539 30 mg (N=100)	Placebo (N=101)	p-value
Hour 0-24 - LS Mean (SE)	3.97 (0.26)	5.06 (0.26)	0.0025
Hour 24-48 - LS Mean (SE)	1.63 (0.25)	2.51 (0.25)	0.0108
Hour 0-48 - LS Mean (SE)	5.45 (0.46)	7.49 (0.46)	0.0014

Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 43)

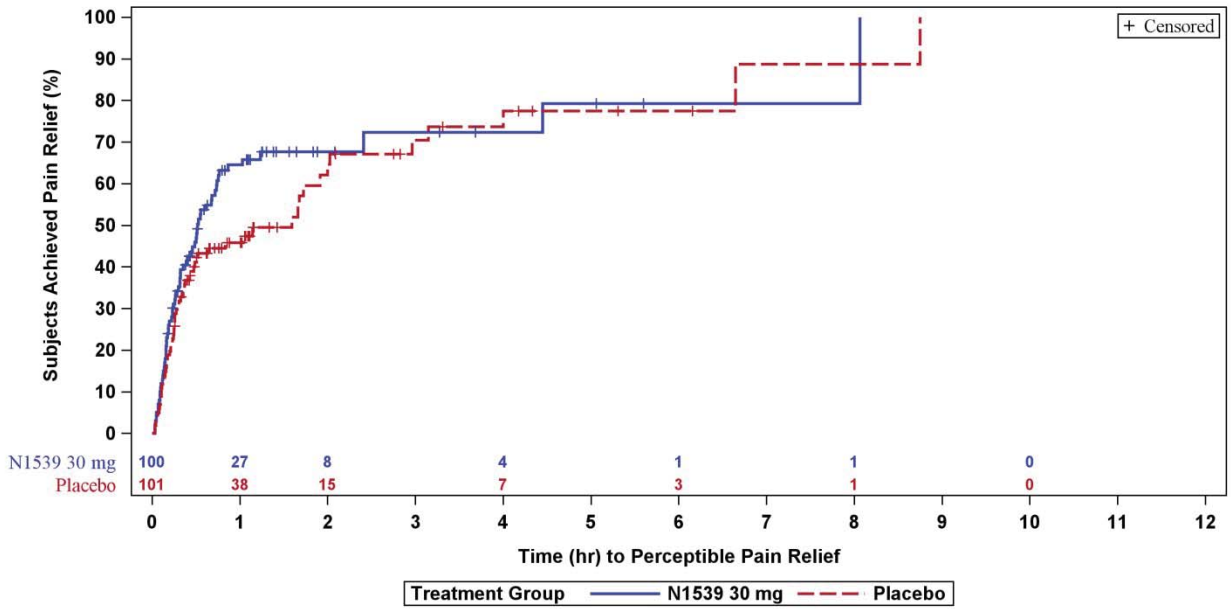
Reviewer's comments:
Similar to comments on REC-15-015 (though less pronounced), there is a delayed onset. The median time to first dose of rescue (oxycodone 5 mg) was approximately two hours for both groups. The number of rescue analgesics for the first 24 hours was 3.97 versus 5.06 for treatment and placebo, respectively. The fact is that even subjects in study arm required close to 20 mg oxycodone over 24 hours, the difference between the two arms is not clinically relevant.

Time to Pain Relief

As commented before, the analysis of time to pain relief didn't take rescue medication use into consideration. the time to pain relief. The time to perceptible and meaningful pain relief were evaluated using the double-stopwatch method. No significant difference was identified for either assessment, although a greater number of subjects receiving N1539 30 mg achieved each level of pain relief compared with placebo. The Kaplan-Meier estimates of median time to pain relief was numerically shorter for subjects receiving N1539 30 mg compared with placebo for both perceptible (0.52 vs. 1.59 hours) and meaningful (2.16 vs. 3.19 hours) pain relief.

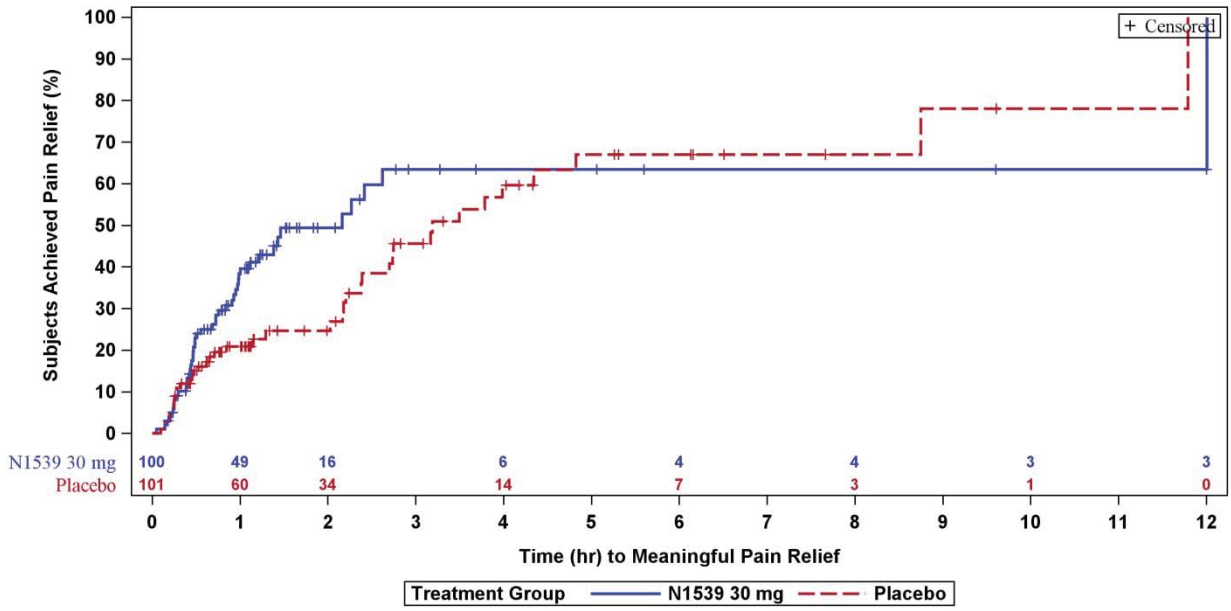
Survival plots of the time to achieve first perceptible and meaningful pain relief are provided in next two figures. A summary of time to pain relief is provided in the table below.

Figure 13 Time to Achieve First Perceptible Pain Relief for N1539 Compared to Placebo Over the First 48 Hours of Treatment



Source: Applicant's submission (Clinical Study Report-REC-15-015, Page 44)

Figure 14 Time to Achieve Meaningful Pain Relief for N1539 Compared to Placebo Over the First 48 Hours of Treatment



Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 44)

Table 24 Summary of Time to Pain Relief Analysis

Parameter / Statistic	N1539 30 mg (N=100)	Placebo (N=101)
Time to First Perceptible PR (hr)		
Subjects Achieved Endpoint, n (%)	66 (66.0)	59 (58.4)
25% tile (95% CI)	0.18 (0.14, 0.27)	0.25 (0.16, 0.35)
50% tile (95% CI)	0.52 (0.35, 0.74)	1.59 (0.48, 2.00)
75% tile (95% CI)	4.45 (1.03, 8.06)	4.00 (2.00, 8.75)
Log-Rank Test	0.1228	-
Time to Meaningful PR (hr)		
Subjects Achieved Endpoint, n (%)	46 (46.0)	40 (39.6)
25% tile (95% CI)	0.56 (0.44, 0.95)	2.03 (0.62, 2.38)
50% tile (95% CI)	2.16 (1.00, 12.01)	3.19 (2.39, 4.82)
75% tile (95% CI)	12.01 (2.62, 12.01)	8.75 (4.35, 11.79)

Log-Rank Test	0.1048	-

Source: Applicant's submission (Clinical Study Report-REC-15-016, Page 45)

Reviewer's comments:
Similar to comments on the REC-15-015 (though less pronounced), there is a delayed onset. The meaningful PR for treatment and placebo were 2.2 and 3.2 hours respectively at the advantage of treatment. However, a delayed PR (2.2 hours) suggests that this product is not suitable for use as an acute analgesic. Again, the meaningful pain relief was achieved AFTER five mg of oxycodone as rescue.

Patient Global Assessment of Pain Control
A patient global assessment (PGA) of pain control was performed at Hour 24 and Hour 48 using a 5-point scale. Differences in PGA response between treatment groups were significant at Hour 48 (p=0.0046), but were not significant at Hour 24. Overall, the proportion of subjects reporting good or better (2+) pain control on the PGA was numerically greater for N1539 30 mg vs. placebo at Hour 24 (57.9% vs. 43.3%) and Hour 48 (84.3% vs. 65.6%).

Applicant's Efficacy Conclusion
"Treatment with N1539 30 mg resulted in clinically and statically significant differences in pain reduction from baseline to placebo over the 48 hour treatment period based on the primary efficacy endpoint, SPID48. Overall, 15 out 19 secondary efficacy endpoints had statistically significant results supporting the efficacy of N1539 30 mg demonstrated in the primary endpoint, including SPID at other intervals, proportion of subjects utilizing rescue and number of rescue does per subjects."

Reviewer's Efficacy Discussion
The primary endpoint, SPID48, attained the pre-defined level of statistical significance (p =0.0034). However, the key secondary endpoints failed in similar ways as REC-15-015.

Similar to REC-15-015, an end-of-dosing failure of last six hours of 24-hour dosing interval is demonstrated by minimal difference in PID (SPID18-24) between active treatment and control, which suggests the proposed dosing interval is not appropriate.

NSAIDs given IV is expected to have a meaningful pain relief within one hour. Similar to REC-15-015 (though less pronounced), delayed onset was demonstrated by short time to first rescue use and frequent rescue medication use, and delayed meaningful RP. Although the curves for time to first use of rescue analgesia did not overlap between groups as in the abdominoplasty study, and the median time to first dose of rescue (oxycodone 5 mg) was two hour for both groups. The meaningful pain relief was achieved after the first rescue. The number of rescue

analgesics for the first 24 hours was 3.97 versus 5.06 for treatment and placebo, respectively. The requirement of close to 20 mg oxycodone over 24 hours makes the difference of rescue requirement in two groups less clinically meaningful.

The efficacy as an acute analgesic at the proposed dosing interval is not established due the end-of-dosing failure and the delayed onset in this bunionectomy model.

Dose/Dose Response

N/A

Durability of Response

N/A

Persistence of Effect

N/A

Additional Analyses Conducted on the Individual Trial

N/A

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The Division commented throughout the development program that a 24-hour primary efficacy endpoint has been used as part of the data to support efficacy for parenteral products in the past. However, the 24-hour period represented multiple doses given the once daily dosing regimen is unusual for a parenteral analgesic. In the five efficacy studies (Phase 2 and Phase 3), the time-weighted SPID was the primary measurement of efficacy. It must be noted that in Study 04, $SPID_{24}$ and $TOTPAR_{24}$ were both incorporated into the primary endpoint.

In the Phase 2 Studies N1539-02 (third molar extraction) and N1539-04 (open abdominal hysterectomy), subjects were treated with a single dose of study drug (during the Study 04 double-blind period), and PI was measured at protocol-defined time points over the subsequent 24-hour period following dosing. Thus, for these two studies SPID24 was the primary efficacy endpoint.

In Phase 2 Study REC-015-014 (bunionectomy), and two key Phase 3 studies REC-015-015 (abdominoplasty), and REC-015-016 (bunionectomy), subjects could receive at least two doses of study drug, and PI was measured at protocol-defined time points throughout the 48-hour period following the first dose. For subjects who underwent bunionectomy surgery (REC-015-014 and REC-015-016), the primary endpoint was SPID48, while for subjects who underwent abdominoplasty (REC-015-015) the primary endpoint was SPID24.

In both key Phase 3 studies (REC-015-015 and REC-015-016), patients with inadequately controlled pain symptoms could request rescue analgesia (oral oxycodone 5 mg administered up to every two hours). To account for the use of rescue medications, pain intensity (PI) was measured prior to a rescue use and was carried forward to replace PI scores collected within two hours following this rescue use as advised by the Agency. The primary endpoints, SPID24 or SPID48, in the two key Phase 3 studies, REC-015-015 (abdominoplasty) and REC-015-016 (bunionectomy), respectively, met the statistical significance. All three Phase 2 studies have a dose-ranging component, the results suggest that the analgesic efficacy is platooned at 30 mg as discussed before.

As shown in the table below and the figure below, N1539 administered at 30 mg was statistically significantly superior to placebo in all five efficacy studies ($p < 0.05$).

Table 25 SPID as Primary Endpoint for Phase 2 and 3 Studies

	REC-15-015[a] Abdominoplasty		REC-15-016[a] Bunionectomy		N1539-02[b] Third Molar Extraction		N1539-04[b] Hysterectomy		REC-15-014[c] Bunionectomy	
	N1539 30 mg N = 110	Placebo N = 109	N1539 30 mg N = 100	Placebo N = 101	N1539 30 mg N = 50	Placebo N = 30	N1539 30 mg N = 60	Placebo N = 60	N1539 30 mg N = 20	Placebo N = 19
Baseline PI Mean (SD)	7.2 (1.6)	7.4 (1.7)	6.7 (1.9)	7.0 (1.8)	77.7 (13.2)	78.0 (13.0)	59.4 (10.0)	57.8 (7.49)	7.7 (2.0)	7.7 (2.2)
Primary SPID Endpoint	$SPID_{24}$	$SPID_{24}$	$SPID_{48}$	$SPID_{48}$	$SPID_{24}$	$SPID_{24}$	$SPID_{24}$	$SPID_{24}$	$SPID_{48}$	$SPID_{48}$
LS Mean	-4262.07	-3535.73	-6956.0	-4829.28	-59101.9	-509.53	-56369.8	3769.62	-9241.89	-1991.34
p-value	0.0145	-	0.0034	-	<0.0001	-	<0.0001	-	0.0007	-
Effect size (95% CI)	0.33 (0.07, 0.60)	-	0.42 (0.14, 0.70)	-	1.53 (1.07, 1.98)	-	2.00 (1.64, 2.36)	-	1.15 (0.51, 1.79)	-

Source: Applicant's submission (ISE, Page 33)

7.1.2. Secondary and Other Endpoints

The key secondary endpoints that were evaluated in the two Phase 3 efficacy studies include SPID at different interval, pain intensity difference, responder analysis, rescue analysis, time to pain relief and patient global. The endpoints selected for secondary analyses are appropriate for the proposed indication as acute analgesic.

The Applicant attempted to pool all Phase 2 and Phase 3 studies in these secondary endpoints. Since the two of the Phase 2 studies (Study 02 and 04) have variety deficiencies as discussed, these kind of pooling is not meaningful. In generally the following secondary endpoints do not favor the study drug as standalone acute analgesic which last 24 hours:

- SPID18-24 (or PID over last six hours)
- Rescue analysis (time to first rescue, and total use of opioid rescue)
- Time to meaningful pain relief

The failure in the key secondary endpoints in the two Phase 3 studies have been fully discussed. The delayed onset in the two Phase 3 studies could not offset by the two Phase 2 studies as one study (dental study, Study 02) is not an adequate for IV NSADIs, and the other (Study 04) is not designed at the same rigidity as a Phase 3 study as fully discussed.

7.1.3. Subpopulations

The Phase 3 studies were not powered for analysis of subgroups. The pooled analyses of the Phase 3 efficacy studies evaluated SPID should be considered descriptive only.

Age
Efficacy parameters were analyzed by age group (< 65 years or ≥ 65 years) for the pooled Phase 3 efficacy studies. It must be noted that only 19/420 subjects were in the ≥ 65 years group. Statistically significant ($p < 0.05$) differences in SPID values between the N1539 and placebo groups were observed for both age subgroups at Hours 24 and 48 in favor of N1539 30 mg.

Sex

A summary of SPID at Hours 24 and 48 is presented by sex for the pooled Phase 3 studies in the table below. While the treatment effect was statistically significant at both 24 and 48

hours for female subjects, the difference in pain reduction was not statistically significant for male subjects at these treatment intervals. However, the SPID24 and SPID48 were numerically smaller.

Table 26 SPID by Gender (Pooled data, Studies 15 and 16)

Parameter	Females		Males	
	N1539 30 mg N = 193	Placebo N = 193	N1539 30 mg N = 17	Placebo N = 17
$SPID_{24}$				
LS mean	-3340.2	-2484.9	-1946.3	-1657.8
Treatment effects p-value	0.0012		0.7481	
$SPID_{48}$				
LS mean	-8945.3	-7082.6	-7580.3	-4897.2
Treatment effects p-value	0.0005		0.1184	

Source: Applicant's submission (ISE, Page 73)

An additional SPID analysis by sex was performed for Study 02, in which approximately one-third of subjects were men by the Applicant as the table below. There were no notable differences in SPID values between the genders.

Table 27 SPID by Gender (Study 02)

	Female		Male	
Parameter	N1539 30 mg N = 36	Placebo N = 17	N1539 30 mg N = 14	Placebo N = 13
$SPID_{0-6}$				
LS Mean Estimate	-19047.3	-239.69	-18609.4	30.11
Effect Size (95% CI)	2.07 (1.49, 2.65)		2.27 (1.50, 3.04)	
P-value[a]	<0.0001		<0.0001	
$SPID_{0-12}$				
LS Mean Estimate	-35851.9	-271.3	-33436.7	591.73
Effect Size (95% CI)	1.93 (1.35, 2.51)		1.95 (1.18, 2.72)	
P-value[a]	<0.0001		<0.0001	

$SPID_{0-24}$				
LS Mean Estimate	-60427.0	-548.2	-56246.3	295.9
Effect Size (95% CI)	1.57 (0.99, 2.15)		1.48 (0.71, 2.25)	
P-value[a]	<0.0001		0.0003	

Source: Applicant's submission (ISE, Page 74)

Race

Efficacy parameters were analyzed by race group (White or non-White) for the pooled Phase 3 studies. Approximately one-third of subjects were in the non-White race group in the Phase 3 studies. Among White subjects, the differences in SPID values between the N1539 30 mg treatment group and placebo group at each treatment interval were statistically significant in favor of N1539 30 mg. In contrast, treatment effect was not statistically significant among non-White subjects at either treatment interval, although the LS mean SPID values were numerically smaller (i.e., greater PI reduction from baseline) for the N1539 30 mg treatment group.

7.1.4. Dose and Dose-Response

The Applicant's recommended dose of N1539 for the management of moderate to severe pain is 30 mg once daily via IV route. Clinical studies evaluated doses of N1539 ranging from 5 to 60 mg in three Phase 2 studies, which have been discussed individually. From those three studies, the choice of 30 mg daily is not unreasonable.

The Sponsor conducted, but terminated a study to evaluate twice daily dosing (once every 12 hours [Q12H]) of N1539 7.5 mg and 15 mg and daily dosing of 30 mg compared to placebo and ketorolac administered once every six hours (Study 05). At the time terminated the study early and efficacy analyses were not performed for the Study 05 CSR, the Sponsor performed ad-hoc efficacy analyses to determine SPID24 and SPID48 as the table below. For both SPID24 and SPID48, the N1539 15 mg Q12H and 30 mg daily doses produced improvements compared to placebo with only the 30-mg daily dose resulting in a statistically significant difference using the W2LOCF method. These results suggest a 15 mg Q12H regimen does may not provide better pain reduction than a 30-mg daily dosing regimen.

In support of dose selection for Phase 3, a population PK/PD model was constructed based on data collected in Studies 01, 02, 03, 04, and 05 that adequately described the observed data and was suitable for simulation of PI and probability of taking rescue medication for clinically relevant doses of N1539. The population PK/PD model was used to simulate PI response and the probability of taking rescue medication for different dose strengths, dosing frequencies, and durations. Please see Clinical Pharmacology review for detail.

Reviewer's comments: The analysis of Study 05 must be met with precaution as the Sponsor acknowledged that the study was terminated early and efficacy analyses were not performed for the Study 05 CSR, the Sponsor performed ad-hoc efficacy analyses to determine SPID24 and SPID48.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The lack of rapid onset of the study drug as evidenced by the early first time to rescue, and delayed meaningful PR, and meaningful pain relief achieved after the first rescue in the both Phase 3 studies have been identified and discussed in the section of key secondary endpoints. It is also noted that the meaningful PR was achieved after the rescue in the both Phase 3 studies. The lack of adequate duration of the study drug with an end-of-dose failure as evidenced by the interval deficiency has been also been discussed in the section of key secondary endpoint. N1539 is intended to be administered as an IV bolus in an acute outpatient or inpatient setting.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

N/A

7.2.2. Other Relevant Benefits

Opioid Consumption
REC-15-017 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial evaluating the safety of N1539 30 mg following major surgery. The primary objective of the study was to evaluate the safety and tolerability of N1539 30 mg compared with placebo.

A total of 721 subjects were enrolled in the study. Subjects were to be randomized within six hours after surgery and were to be treated with at least two doses of study drug. Use of analgesics before, during, and after surgery were not limited (except for the exclusion of use of any other NSAIDs), and the subject was to receive the institutions standard of care pain management.

In addition to standard safety measurements, total opioid consumption was collected throughout the inpatient course. The dose from each identified opioid medication was converted to IV morphine equivalent dose (IVMED) in mg. While use of opioid analgesics was most common, any analgesic was acceptable per the standard of practice for the study site with exception of other NSAIDs usage.

A summary of the total opioid consumption in IVMED for the overall population is provided in the table below.

Table 28 Summary of Total Opioid Use in IV Morphine Equivalent Dose

Interval / Statistic	N1539 30 mg	Placebo
Day 1 (0-24 Hours)		
n	538	183
Mean ± SD	17.0 ± 22.10	21.8 ± 24.70
Median	9.0	14.5
p-value[a]	0.0033	
Day 2 (24-48 Hours)		
n	520	178
Mean ± SD	8.6 ± 19.15	11.3 ± 21.82
Median	0.0	1.3
p-value[a]	0.0775	
Day 3 (48-72 Hours)		
n	274	93
Mean ± SD	4.1 ± 16.60	6.2 ± 21.83
Median	0.0	0.0
p-value[a]	0.2728	
Days 1-2 (0-48 Hours)		
n	538	183
Mean ± SD	25.3 ± 36.96	32.7 ± 41.44
Median	12.3	19.0
p-value[a]	0.0077	
Days 1-3 (0-72 Hours)		
n	538	183
Mean ± SD	27.4 ± 44.67	35.9 ± 52.77
Median	12.5	19.0
p-value[a]	0.0152	
During Treatment		
n	538	183
Mean ± SD	28.8 ± 57.39	37.5 ± 66.06
Median	12.5	19.0

p-value[a]	0.0603	

Source: Applicant's submission (Summary of Clinical Efficacy, Page 85)

Reviewer's comments: REC-15-017 is a safety study, which opioid consumption was descriptively collected. The Study suggests that Mean opioid consumption in the overall population was numerically lower in the N1539 30 mg group compared with placebo at all evaluated intervals. (b) (4)

7.3. Integrated Assessment of Effectiveness

Efficacy Summary
The Applicant has submitted a 505(b)(2) application for an indication of the management of moderate to severe pain with listed drug Mobic, which is approved in 2000 for relief of pain of RA, OA and JRA. The Applicant proposes a dose regimen of 30 mg IV, once-a-day. It must be noted that Mobic, given orally, has a starting daily dose is 7.5 mg, with a maximum daily dose of 15 mg.

From the beginning of the development program, the Division conveyed concern of the proposed dosing internal as a once daily dosing regimen is unusual for a parenteral analgesic. The Division also conveyed that while a 24-hour primary efficacy endpoint has been used as part of the data to support efficacy for parenteral products in the past, the 24-hour period represented multiple doses. Furthermore, the Division unequivocally states that a simply demonstrating efficacy throughout the dosing period is not adequate. The Applicant was asked Specifically evaluate pain intensity during the second 12-hour period of the dosing interval. At the 74-Day inquiry after filing of the NDA, the Applicant was asked to justify the delayed onset as the early Time to first rescue, and the frequent use of rescue.

The N1539 Phase 2/3 clinical program was designed with a primary endpoint that evaluated the effect of N1539 on moderate to severe pain after surgery. The primary endpoint was the time-weighted sum of pain intensity difference (SPID) as compared to placebo. After three Phase 2 dose-ranging studies o from 5 to 60 mg, and a PK/PD modeling, the Sponsor conducted two Phase 3 efficacy studies with 30 mg of study drug for once daily IV dosing.

In the Phase 3 studies, the study drug was used in randomized, double-blind, placebo-

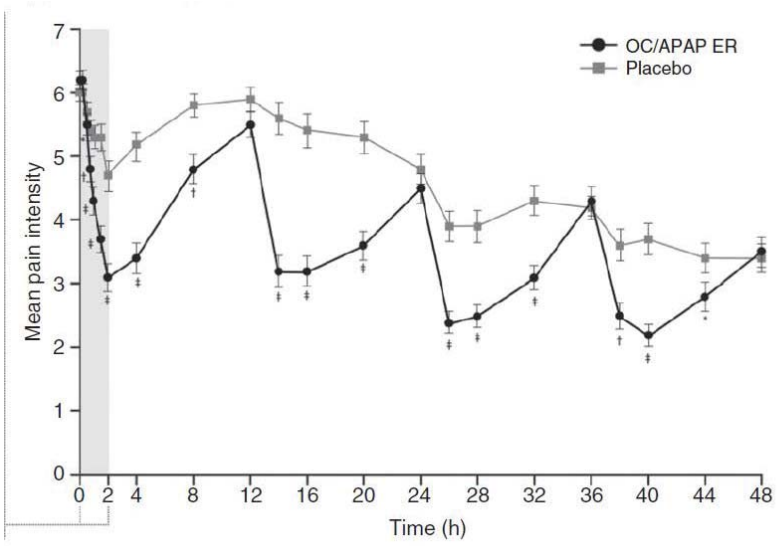
controlled clinical trials in two different pain models (abdominoplasty and bunionectomy). Patients with inadequately controlled pain symptoms could request rescue analgesia (oral oxycodone 5 mg administered up to every two hours). To account for the use of rescue medications, pain intensity (PI) was measured prior to a rescue use and was carried forward to replace PI scores collected within two hours following this rescue use. The once daily dosing of this parenteral analgesic met the primary endpoints, SPID24 and SPID48, in the two surgical models, abdominoplasty and bunionectomy, respectively. However, the efficacy as an acute analgesic is not established due to the failure in the key secondary endpoints:

End-of-dosing failure

The last six hours of 24-hour dosing interval demonstrated no difference in PID (SPID18-24) between active treatment and control at the both surgical models (equally pronounced), which suggests the proposed dosing interval is not appropriate. The Division has repeatedly conveyed to the Sponsor that a once daily IV regimen as acute analgesic is unusual. It is acknowledged that the study is not powered to detect a difference from placebo at these time intervals.

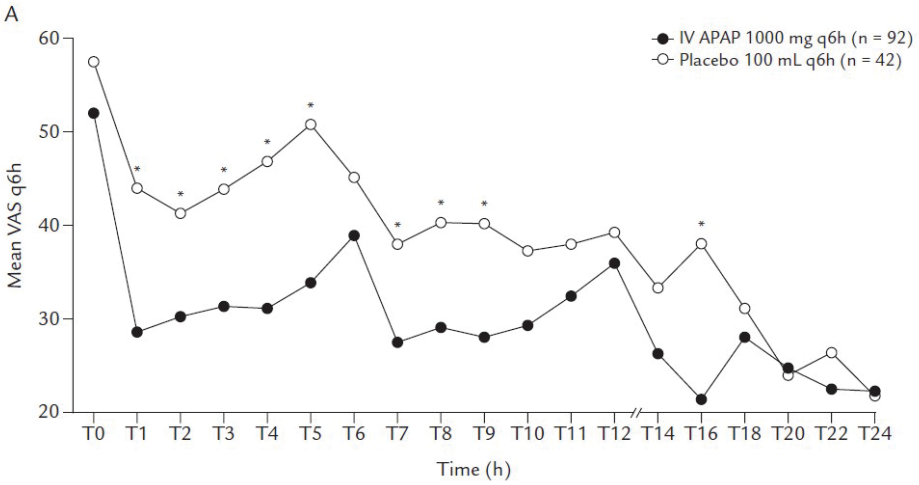
The Sponsor argues that " This reduction of treatment effect at the end of the dosing interval is not unexpected, and similar end of dosing interval effects have been observed with other approved analgesic products." The Sponsor argues that similar end of dosing interval effects that have been observed with other approved analgesic products as Figures below:

Figure 15 Mean Pain Intensity After Oral Administration of Oxycodone/Acetaminophen ER



Source: Applicant's submission (Summary of Clinical Efficacy, Page 93; and Singla, et al, Curr Med Res Opin 2014; 30:349)

Figure 16 Mean VAS Scores After Intravenous Administration of Acetaminophen



Source: Applicant's submission (Summary of Clinical Efficacy, Page 94; and Wininger SJ et al, Clin Ther 2010; 32:2348)

While the analgesic efficacy is waned at the end of the dosing interval, the pain intensity over time curves cited by the Sponsor are different from the figures in the two Phase 3 studies. For most acute analgesic, the dosing frequency is every four to six hours (as the case of IV acetaminophen), it is obvious that the reduction of efficacy at the end of dosing would last much shorter time than the study drug which is given every 24 hours. The lack of analgesic effect over a six-hour long period of 24-hour dosing is clinically significant as adequate pain relief.

Frequent rescue medication use in the study group also supports the finding of the end of dosing failure. The number of rescue analgesics for the first 24 hours was 3.66 versus 4.38 for treatment and placebo, respectively in Study REC-15-015. The number of rescue analgesics for the first 24 hours was 3.97 versus 5.06 for treatment and placebo, respectively, in REC-15-016.

<u>Delayed Onset</u>
A NSAIDS given IV has an expected time to meaningful pain relief less than one hour. A short time to first rescue use, and delayed meaningful pain relief in both surgical modes abdominoplasty is more pronounced than bunionectomy) suggest a delayed onset and that this product is not suitable for use as an acute analgesic.

For Study REC-15-015 (abdominoplasty), the mean times to first rescue were 1.08 hours, and 1.09 hours for study drug and placebo respectively, and the times to meaningful pain relief were 3.02 hours and 2.92 hours respective. For Study REC-15-01616 (bunionectomy), the mean

times to first rescue were 1.99 hours vs. 2.09 hours respectively for study drug and placebo; the times to meaningful pain relief were 2.16 hours, and 3.19 hours respective. For Study REC-15-015, in the active treatment arm, the first rescue was about one hour, and the meaningful pain relief was about three hours. The meaningful pain relief is temporally related to the 5-mg oral oxycodone given two hours earlier. Since the time to meaningful pain relief was measured regardless the first rescue, therefore, it could be argued that the meaningful pain relieve was achieved by the 5 mg Oxycodone given earlier at least in the abdominoplasty study.

In the 74-day letter, the clinical team conveyed Division's concerns of a short time to first rescue use and the frequent rescue medication use and challenging the suitability of study drug as an acute analgesic. I disagree that "In clinical practice, subjects would most likely receive N1539 after surgery and before pain intensity reaches the moderate to severe threshold when it would be more difficult to control and when the need for rescue analgesia would be increased."

Furthermore, while we acknowledge that the Phase 2 studies have more favorable first time to rescue (than the two Phase 3 studies). The Division disagree with the Applicant that the delayed onset in two Phase 3 studies could be potentially offset by the Phase 2 studies. The three Phase 2 studies have the mixed results in term of first rescue, as the bunionectomy study (Study 14) is not different from the two Phase 3 studies. As the Division conveyed at the time when the IND was opened, a dental model is not adequate. While the dental model (Study N1537-02) is the good surgical model to study oral NSAIDs, it is an overtreatment with a IV NSAISs. While open hysterectomy (Study N1537-04) is an adequate surgical model, the study itself is not designed as Phase 3 studies with several deficiencies as discussed before.

As commented earlier in the end-of-dosing failure, frequent rescue medication use in the study group also supports the finding of the delayed onset. i.e. with the delayed onset contributed to the frequent rescue use even in the active treatment arm.

The delayed onset certainly could not be explained by the PK characteristics of the study drug as described in section 4.5, N1530 given 30 mg IV reached Cmax rapidly in minutes. The lack of rapid onset may be related to the selectivity of COX2 inhibition of Meloxicam.

These two deficiencies (end-of-dosing failure and delayed onset, as illustrated in the key secondary endpoints) in the two studied models (abdominoplasty and bunionectomy) suggest that the proposed study drug, given 30 mg IV daily, is not suitable as an analgesic for the management of acute pain at the proposed dosing interval. The two deficiencies identified from clinical perspective are consist with that made by Dr. Zhou, Agency's statistical reviewer:

> *In both studies, there was a statistically significant difference in $SPID_{48}$ between N1539 30 mg and placebo, indicating N1539 30 mg was superior to placebo. However, the*

analyses of pain intensity difference (PID) show that there were no significant differences during the last six hours of the dosing interval. This may indicate end-of-dose failure. Furthermore, in the two studies reviewed, rescue use was about 4 times over the first 24 hours, the median time to the first use of rescue analgesics was within two hours, and the time to meaningful pain relief was achieved after the first use of rescue analgesics.

At last, the Applicant conducted a safety study (Study REC-15-0 17), in addition to standard safety measurements, total opioid consumption was collected descriptively. The dose from each identified opioid medication was converted to IV morphine equivalent dose (IVMED) in mg. The study suggests that mean opioid consumption in the overall population was numerically lower in the N1539 30 mg group compared to placebo. The requirement for making label claim around opioids sparing has been discussed in section 7.2.2.

8. Review of Safety

8.1. Safety Review Approach

The Applicant submitted a total of 11 clinical studies as integrated safety database for N1539 in the management of moderate to severe pain. The safety data from the targeted population (postoperative studies, especially three Phase 3 studies) will be analyzed in detail.

A total of 2075 subjects were evaluated in the 11 studies: 109 subjects were healthy volunteers who were enrolled in the four Phase 1 studies and 1966 were postoperative subjects who were enrolled in the seven Phase 2/3 efficacy and safety studies. Of the 1966 postoperative subjects, 1887 subjects were included for analysis; 1426 were treated with at least dose of N1539 and 517 were treated with at least one dose of placebo and assessed for safety; 56 of 517 placebo subjects also received at least one dose of N1539 in the open-label phase of Study N1539-04. Of note, approximately 10% of subjects in the N1539 30 mg group were considered to have renal impairment (i.e., glomerular filtration rate (GFR) of 60-89 mL/min/1.73 m^2).

The informative safety data come from a total of 1069 surgical subjects who received 30 mg or higher of N1539, in which a total of 903 received 30 mg or higher of N1539 at least two doses.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 11 studies were divided into two populations, those subjects who did not undergo surgery prior to receiving study drug (i.e., healthy volunteers) and those who underwent surgery prior to receiving study drug (i.e., postoperative subjects).

The healthy volunteer population included subjects from the four Phase 1 pharmacokinetic studies (N1539-01, N1539-03, REC-15-018, and REC-15-019). A total of 91 subjects received N1539 at doses ranging from 15 to 180 mg and 18 subjects received placebo as the table below. Six subjects from Cohort 1 in Study REC-15-018 who had mild renal impairment were included in the healthy volunteer category for completeness.

The postoperative subject population included subjects from the seven Phase 2 and Phase 3 studies (Studies N1539-02, N1539-04, N1539-05, REC-15-014, REC-15-015, REC-15-016, and REC-15-017). A total of 1426 subjects received N1539 5, 7.5, 15, 30, and 60 mg and 517 received placebo as the table below. The postoperative subject population was further divided into subgroups as follows:

- Postoperative Phase 3 studies: Studies REC-15-015, REC-15-016, and REC-15-017. 748 subjects received N1539 30 mg and 393 subjects received placebo.
- Postoperative Phase 3 efficacy studies: REC-15-015 and REC-15-016. 210 subjects received N1539 30 mg and 210 subjects received placebo.

Table 29 Safety database for N1539

Safety database for N1539		
Clinical Trial Groups	**N1539 n**	**Placebo n**
Healthy volunteers	91	18
Targeted population	1426	603

Presentation of Safety Data

The safety of N1539 concentrates on the pooled adverse event (AE) data from the seven postoperative studies (N1539-02, N1539-04, N1539-05, REC-15-014, REC-15-015, REC-15-016, and REC-15-017) and the three postoperative Phase 3 studies (REC-15-015, REC-15-016, and REC-15-017). Disposition, demographic, and AE data from the two postoperative Phase 3 efficacy studies (REC-15-015 and REC-15-016) are also pooled.

Because of the differences in data collection time points in the seven postoperative studies for the evaluation of clinical laboratory parameters, vital signs, electrocardiograms (ECG), and investigator determined wound healing, the safety of N1539 focuses on the pooled data from the three postoperative Phase 3 studies where evaluation of these parameters was consistent (REC-15-015, REC-15-016, and REC-15-017).

Extent of Exposure in healthy subjects

In Studies N1539-01, REC-15-018, and REC-15-019, subjects received single doses of N1539 or placebo. In Study N1539-03, subjects received single doses of N1539 30 mg, N1539 60 mg, or placebo on Day 1 and on Day 7 through Day 13 for a maximum total of eight doses. Extent of exposure in healthy volunteers is presented in the table below.

Table 30 Extent of Exposure in Healthy Volunteers

Parameter	Placebo N=18 n (%)	N1539 15 mg N=7 n (%)	N1539 30 mg N=39 n (%)	N1539 60 mg N=15 n (%)	N1539 120 mg N=12 n (%)	N1539 180 mg N=18 n (%)	N1539 Overall N=91 n (%)
Distribution of doses:							
1 dose	14 (77.8)	7 (100.0)	31 (79.5)	7 (46.7)	12 (100.0)	18 (100.0)	75 (82.4)
2 doses	0	0	0	0	0	0	0
3 doses	0	0	0	0	0	0	0
4 doses	0	0	0	0	0	0	0
5 doses	0	0	0	0	0	0	0
6 doses	0	0	0	0	0	0	0
7 doses	0	0	0	0	0	0	0
8 doses	4 (22.2)	0	8 (20.5)	8 (53.3)	0	0	16 (17.6)
Cumulative distribution:							
≥1 dose	18 (100.0)	7 (100.0)	39 (100.0)	15 (100.0)	12 (100.0)	18 (100.0)	91 (100.0)
≥2 dose	4 (22.2)	0	8 (20.5)	8 (53.3)	0	0	16 (17.6)
≥3 dose	4 (22.2)	0	8 (20.5)	8 (53.3)	0	0	16 (17.6)
≥4 dose	4 (22.2)	0	8 (20.5)	8 (53.3)	0	0	16 (17.6)
≥5 dose	4 (22.2)	0	8 (20.5)	8 (53.3)	0	0	16 (17.6)
≥6 dose	4 (22.2)	0	8 (20.5)	8 (53.3)	0	0	16 (17.6)
≥7 dose	4 (22.2)	0	8 (20.5)	8 (53.3)	0	0	16 (17.6)
≥8 dose	4 (22.2)	0	8 (20.5)	8 (53.3)	0	0	16 (17.6)
Data source: ISS Table 3.1							

Source: Applicant's submission (Summary of Clinical Safety, Page 38)

Extent of Exposure in all post-operative studies

In the seven postoperative studies, 1045 subjects received two or more doses of N1539 and 81.6% (743/910) received two or more doses of the proposed 30 mg to-be-marketed formulation.

Table 31 Extent of Exposure in Postoperative Studies

Parameter	Placebo N=517 n (%)	N1539 5-15 mg N=327 n (%)	N1539 30 mg N=910 n (%)	N1539 60 mg N=189 n (%)	N1539 Overall N=1426 n (%)

Distribution:					
1 dose	106 (20.5)	185 (56.6)	96 (10.5)	100 (52.9)	381 (26.7)
2 doses	138 (26.7)	73 (22.3)	344 (37.8)	33 (17.5)	450 (31.6)
3 doses	250 (48.4)	52 (15.9)	424 (46.6)	39 (20.6)	515 (36.1)
4 doses	10 (1.9)	16 (4.9)	38 (4.2)	15 (7.9)	69 (4.8)
5 doses	1 (0.2)	0	3 (0.3)	2 (1.1)	5 (0.4)
6 doses	0	1 (0.3)	1 (0.1)	0	2 (0.1)
7 doses	2 (0.4)	0	4 (0.4)	0	4 (0.3)
8 doses	10 (1.9)	0	0	0	0
Cumulative distribution:					
≥1 dose	517 (100.0)	327 (100.0)	910 (100.0)	189 (100.0)	1426 (100.0)
≥2 doses	411 (79.5)	142 (43.4)	814 (89.5)	89 (47.1)	1045 (73.3)
≥3 doses	273 (52.8)	69 (21.1)	470 (51.6)	56 (29.6)	595 (41.7)
≥4 doses	23 (4.4)	17 (5.2)	46 (5.1)	17 (9.0)	80 (5.6)
≥5 doses	13 (2.5)	1 (0.3)	8 (0.9)	2 (1.1)	11 (0.8)
≥6 doses	12 (2.3)	1 (0.3)	5 (0.5)	0	6 (0.4)
≥7 doses	12 (2.3)	0	4 (0.4)	0	4 (0.3)
≥8 doses	10 (1.9)	0	0	0	0
Data source: ISS Table 3.2.1					

Source: Applicant's submission (Summary of Clinical Safety, Page 45)

Extent of Exposure in all Phase 3 Studies

Subjects in studies REC-15-015 and REC-15-016 were to receive two doses of study drug during the treatment phase with an optional third dose administered prior to discharge at the discretion of the investigator and subject. Subjects in Study REC-15-017, were expected to receive at least two doses of study drug during the treatment phase, with additional doses administered every 24 hours from Hour 0 until discharge, until IV analgesia was no longer clinically appropriate, or until they had received a total of seven doses.

As shown in the table below, most (92.5%, 1055/1141) subjects across the three postoperative studies received two or three doses of study drug.

Table 32 Extent of Exposure in Postoperative Phase 3 Studies

Parameter	Placebo N=393 n (%)	N1539 30 mg N=748 n (%)
Distribution:		
1 dose	11 (2.8)	25 (3.3)
2 doses	127 (32.3)	289 (38.6)
3 doses	243 (61.8)	396 (52.9)
4 doses	10 (2.5)	30 (4.0)
5 doses	1 (0.3)	3 (0.4)
6 doses	0	1 (0.1)
7 doses	1 (0.3)	4 (0.5)

Cumulative distribution:		
≥1 dose	393 (100.0)	748 (100.0)
≥2 doses	382 (97.2)	723 (96.7)
≥3 doses	255 (64.9)	434 (58.0)
≥4 doses	12 (3.1)	38 (5.1)
≥5 doses	2 (0.5)	8 (1.1)
≥6 doses	1 (0.3)	5 (0.7)
≥7 doses	1 (0.3)	4 (0.5)
Data source: ISS Table 3.3.1		

Source: Applicant's submission (Summary of Clinical Safety, Page 82)

Reviewer's comments:
The overall exposure and duration of exposure are adequate.

8.2.2. Relevant characteristics of the safety population:

HEALTHY VOLUNTEERS

Disposition

All randomized subjects received at least one dose of N1539 (N=91) or placebo (N=18) as table below.

Table 33 Subject Disposition in Healthy Volunteers

Parameter	Placebo N=18 n (%)	N1539 15 mg N=7 n (%)	N1539 30 mg N=39 n (%)	N1539 60 mg N=15 n (%)	N1539 120 mg N=12 n (%)	N1539 180 mg N=18 n (%)	N1539 Overall N=91 n (%)
Subjects who completed treatment	18 (100.0)	7 (100.0)	39 (100.0)	15 (100.0)	12 (100.0)	18 (100.0)	91 (100.0)
Subjects who completed study	16 (88.9)	7 (100.0)	39 (100.0)	15 (100.0)	12 (100.0)	12 (66.7)	85 (93.4)
Reasons for not completing the study:							
Forced evacuation of study unit due to Hurricane Matthew	2 (11.0)[a]	0	0	0	0	6 (33.3)	6 (6.6)
Data source: ISS Table 1.1 a One of these subjects was also lost to follow-up.							

Source: Applicant's submission (Summary of Clinical Safety, Page 36)

All subjects completed treatment. In Study REC-15-019, it is interesting to note that eight subjects (six active treatment and two placebo) in Cohort 3 were forced to evacuate the study unit due to an emergency evacuation order issued at the site in preparation for Hurricane Matthew. This evacuation happened before all pharmacokinetic and continuous ECG time point evaluations could be completed after dosing. All subjects, except the one who was lost to follow-up, completed the follow-up safety evaluations.

Demographics and Baseline Characteristics of the Phase 1 Population

Demographic and baseline characteristics of the healthy volunteers in the Phase 1 studies were similar across the N1539 and placebo groups in the table below. Most subjects were white (≥71.4%), male (≥50.0%), and <65 years of age (≥84.6%). The median age of subjects was 30 years in the N1539 group and 29.5 years in the placebo group.

Table 34 Demographics and Baseline Characteristics in Healthy Volunteers

Parameter	Placebo N=18	N1539 15 mg N=7	N1539 30 mg N=39	N1539 60 mg N=15	N1539 120 mg N=12	N1539 180 mg N=18	N1539 Overall N=91
Age (years)							
Mean (SD)	30.7 (7.15)	28.3 (7.61)	37.0 (16.84)	28.6 (7.83)	29.7 (5.94)	31.6 (10.00)	32.9 (13.04)
Median	29.5	24.0	30.0	28.0	29.0	29.0	30.0
Min, Max	19, 45	21, 40	18, 75	19, 45	23, 43	19, 45	18, 75
Age group (years), n (%)							
<65	18 (100.0)	7 (100.0)	33 (84.6)	15 (100.0)	12 (100.0)	18 (100.0)	85 (93.4)
≥65	0	0	6 (15.4)	0	0	0	6 (6.6)
≥75	0	0	1 (2.6)	0	0	0	1 (1.1)
Sex, n (%)							
Male	10 (55.6)	4 (57.1)	24 (61.5)	12 (80.0)	6 (50.0)	9 (50.0)	55 (60.4)
Female	8 (44.4)	3 (42.9)	15 (38.5)	3 (20.0)	6 (50.0)	9 (50.0)	36 (39.6)
Race, n (%)							
White	14 (77.8)	5 (71.4)	33 (84.6)	13 (86.7)	10 (83.3)	17 (94.4)	78 (85.7)
Black/African American	4 (22.2)	2 (28.6)	6 (15.4)	1 (6.7)	2 (16.7)	1 (5.6)	12 (13.2)
American Indian/ Alaska Native	0	0	0	1 (6.7)	0	0	1 (1.1)
BMI (kg/m^2)							
Mean (SD)	24.2 (2.13)	23.1 (2.48)	25.1 (2.56)	23.6 (2.41)	24.0 (2.25)	24.3 (2.03)	24.4 (2.44)
Median	24.6	23.3	26.1	22.6	24.9	24.0	24.6
Min, Max	20, 28	19, 26	20, 31	19, 27	20, 27	20, 28	19, 31

BMI=body mass index
Data source: ISS Table 2.1

Source: Applicant's submission (Summary of Clinical Safety, Page 37)

Postoperative Studies

Disposition

Most subjects in the N1539 (98.0%) and placebo (97.5%) groups completed treatment per protocol. Three (0.2%) subjects in the N1539 group and one (0.2%) subject in the placebo group discontinued treatment due to an AE. Most subjects (≥97.4%) in the N1539 and placebo groups also completed the study as the table below.

Table 35 Subject Disposition in Postoperative Studies

Parameter	Placebo N=517 n (%)	N1539 5-15 mg N=327 n (%)	N1539 30 mg N=910 n (%)	N1539 60 mg N=189 n (%)	N1539 Overall N=1426 n (%)
Subjects who completed treatment	504 (97.5)	326 (99.7)	883 (97.0)	188 (99.5)	1397 (98.0)
Reason for discontinuation of treatment:					
Lack of efficacy[a]	5 (1.0)	0	6 (0.7)	0	6 (0.4)
Adverse event	1 (0.2)	1 (0.3)	2 (0.2)	0	3 (0.2)
Withdrawal by subject	1 (0.2)	0	3 (0.3)	1 (0.5)	4 (0.3)
Physician decision	1 (0.2)	0	0	0	0
Protocol violation	0	0	4 (0.4)	0	4 (0.3)
Noncompliance with study drug	1 (0.2)	0	2 (0.2)	0	2 (0.1)
Other[b]	4 (0.8)	0	10 (1.1)	0	10 (0.7)
Subjects who completed study	504 (97.5)	324 (99.1)	886 (97.4)	189 (100.0)	1399 (98.1)
Reason for discontinuation of study:					
Lack of efficacy	0	0	2 (0.2)	0	2 (0.1)
Adverse event	1 (0.2)	1 (0.3)	0	0	1 (0.1)
Withdrawal by subject	4 (0.8)	1 (0.3)	11 (1.2)	0	12 (0.8)
Lost to follow-up	8 (1.5)	0	10 (1.1)	0	10 (0.7)
Noncompliance/lack of cooperation	0	1 (0.3)	0	0	1 (0.1)
Other[c]	0	0	1 (0.1)	0	1 (0.1)

Data source: ISS Table 1.2.1

a Subjects in Study N1539-02 whose reason for discontinuation was 'other' (rescue medication administered) in the CSR were mapped to 'lack of efficacy'.

b Subjects who did not receive at least 2 doses of study drug due to discharge, IV discontinued, or staff error.

c Subject went to rehabilitation and could not return for visits.

NOTE: Subjects who used rescue medication during the double-blind phase in Study N1539-04 were considered 'discontinued' in the CSR. In the integrated analysis of safety, all subjects were considered as having completed the double-blind phase. The N1539-04 disposition for the integrated safety analysis was based on the double-blind and open label phases.

Source: Applicant's submission (Summary of Clinical Safety, Page 42)

Demographics and Baseline Characteristics of the Postoperative Population

Demographic and baseline characteristics for subjects in the postoperative studies are presented in the table below. Most subjects in treatment groups were white, female, and <65 years of age. The median age of subjects was 47 years in the N1539 group overall and 47 years in the placebo group. Most subjects had no history of hypertension (≥74.5%), diabetes (≥94.6%), or gastrointestinal disorders (≥83.2%). Approximately 10% of subjects in the N1539 30 mg group and 6.8% of subjects in the placebo group were considered high risk (i.e., > 65 years with a GFR of 60-89 mL).

Table 36 Demographics and Baseline Characteristics in Postoperative Studies

Parameter	Placebo N=517	N1539 5-15 mg N=327	N1539 30 mg N=910	N1539 60 mg N=189	N1539 Overall N=1426

Age (years)					
Mean (SD)	46.7 (13.84)	43.0 (11.76)	48.0 (14.59)	40.1 (14.50)	45.8 (14.29)
Median	47.0	46.0	49.0	44.0	47.0
Min, Max	18, 80	18, 65	18, 79	18, 72	18, 79
Age group (years), n (%)					
<65	460 (89.0)	325 (99.4)	781 (85.8)	186 (98.4)	1292 (90.6)
≥65	57 (11.0)	2 (0.6)	129 (14.2)	3 (1.6)	134 (9.4)
≥75	10 (1.9)	0	15 (1.6)	0	15 (1.1)
Sex, n (%)					
Male	115 (22.2)	26 (8.0)	275 (30.2)	18 (9.5)	319 (22.4)
Female	402 (77.8)	301 (92.0)	635 (69.8)	171 (90.5)	1107 (77.6)
Race, n (%)					
White	401 (77.6)	325 (99.4)	737 (81.0)	173 (91.5)	1235 (86.6)
Black/African American	94 (18.2)	0	148 (16.3)	10 (5.3)	158 (11.1)
Asian	9 (1.7)	1 (0.3)	13 (1.4)	1 (0.5)	15 (1.1)
American Indian/Alaska Native	1 (0.2)	0	1 (0.1)	0	1 (0.1)
Native Hawaiian/Other Pacific Islander	3 (0.6)	0	4 (0.4)	2 (1.1)	6 (0.4)
Other	6 (1.2)	1 (0.3)	6 (0.7)	2 (1.1)	9 (0.6)
Multiple	3 (0.6)	0	1 (0.1)	1 (0.5)	2 (0.1)
Body mass index (kg/m^2)					
Mean (SD)	27.9 (4.33)	25.6 (3.19)	28.4 (4.81)	26.4 (3.42)	27.6 (4.53)
Median	27.8	25.1	28.2	26.4	27.3
Min, Max	18, 40	19, 32	18, 42	19, 34	18, 42
Positive history for, n (%):					
Hypertension	107 (20.7)	14 (4.3)	232 (25.5)	9 (4.8)	255 (17.9)
Diabetes	21 (4.1)	2 (0.6)	49 (5.4)	1 (0.5)	52 (3.6)
Gastrointestinal conditions[a]	66 (12.8)	4 (1.2)	153 (16.8)	4 (2.1)	161 (11.3)
Risk group, n (%)					
High risk[b]	35 (6.8)	0	95 (10.4)	1 (0.5)	96 (6.7)
Not high risk	482 (93.2)	327 (100.0)	815 (89.6)	188 (99.5)	1330 (93.3)
Investigational site country, n (%)					
USA	438 (84.7)	61 (18.7)	802 (88.1)	70 (37.0)	933 (65.4)
Canada	3 (0.6)	0	5 (0.5)	0	5 (0.4)
Australia/New Zealand	12 (2.3)	0	31 (3.4)	0	31 (2.2)
Georgia	23 (4.4)	80 (24.5)	27 (3.0)	45 (23.8)	152 (10.7)
Serbia	16 (3.1)	82 (25.1)	28 (3.1)	30 (15.9)	140 (9.8)
Poland	25 (4.8)	104 (31.8)	17 (1.9)	44 (23.3)	165 (11.6)

Data source: ISS Table 2.2.1
a Gastrointestinal history of interest included prior or concomitant gastroesophageal reflux disease, gastrointestinal ulcer, and/or bleeding within the gastrointestinal track.
b High risk was defined as age > 65 years with a GFR of 60-89 mL/min/1.73 m^2, as calculated using the MDRD equation.

Source: Applicant's submission (Summary of Clinical Safety, Page 43)

Surgical characteristics of subjects in the postoperative studies are presented in the table below. In treatment groups, 67% (1304/1943) of subjects had other surgical procedures performed and 33% (639/1943) had orthopedic surgical procedures. The median duration (~1 hour) of surgery was similar in treatment groups. The mean time from the end of surgery to the first dose of study drug was longer in subjects who had bunionectomy surgery and open abdominal surgery. This difference was due to the management of postoperative pain after each surgery.

Subjects who underwent bunionectomy received a popliteal sciatic nerve block that started

when surgery ended on Day -1 and continued until the day after surgery. Thus, these subjects were ineligible for study drug randomization until discontinuation of the nerve block on Day 1, when pain was rated as moderate or severe on a 4-point categorical pain rating scale and pain intensity (PI) was ≥4 on 11-point NPRS.

Subjects who underwent open abdominal hysterectomy were not randomized to treatment until the day after surgery when IV patient-controlled analgesia (morphine) was discontinued.

Table 37 Surgical Characteristics in Postoperative Studies

	Placebo N=517	N1539 5-15 mg N=327	N1539 30 mg N=910	N1539 60 mg N=189	N1539 Overall N=1426
Subjects who had orthopedic surgery, n (%):	216 (41.8)	0	403 (44.3)	20 (10.6)	423 (29.7)
Bunionectomy	133 (25.7)	0	160 (17.6)	20 (10.6)	180 (12.6)
Complex foot	19 (3.7)	0	52 (5.7)	0	52 (3.6)
Complex shoulder surgery	2 (0.4)	0	6 (0.7)	0	6 (0.4)
Orthopedic trauma	1 (0.2)	0	0	0	0
Spinal	3 (0.6)	0	10 (1.1)	0	10 (0.7)
Total ankle replacement	0	0	1 (0.1)	0	1 (0.1)
Total hip replacement	18 (3.5)	0	50 (5.5)	0	50 (3.5)
Total shoulder replacement	1 (0.2)	0	7 (0.8)	0	7 (0.5)
Total knee replacement	39 (7.5)	0	117 (12.9)	0	117 (8.2)
Subjects who had other surgeries, n (%):	301 (58.2)	327 (100.0)	507 (55.7)	169 (89.4)	1003 (70.3)
Abdominoplasty	120 (23.2)	0	142 (15.6)	0	142 (10.0)
Cholecystectomy	1 (0.2)	4 (1.2)	6 (0.7)	0	10 (0.7)
Gastrointestinal	13 (2.5)	0	26 (2.9)	0	26 (1.8)
Gynecological	21 (4.1)	0	68 (7.5)	0	68 (4.8)
Head and neck	0	0	1 (0.1)	0	1 (0.1)
Hysterectomy	64 (12.4)	266 (81.3)	72 (7.9)	119 (63.0)	457 (32.0)
Inguinal hernia	10 (1.9)	7 (2.1)	14 (1.5)	0	21 (1.5)
Soft tissue	42 (8.1)	0	128 (14.1)	0	128 (9.0)
Third molar extraction	30 (5.8)	50 (15.3)	50 (5.5)	50 (26.5)	150 (10.5)
Surgery duration (hours)					
Mean (SD)	1.069 (0.76)	1.086 (0.66)	1.164 (0.89)	0.986 (0.72)	1.122 (0.82)
Median	0.917	1.000	1.000	0.833	1.000
Min, Max	0.10, 7.78	0.10, 3.25	0.10, 9.95	0.10, 3.67	0.10, 9.95
Time from end of surgery to first dose (hours)					
Mean (SD)	8.020 (9.02)	18.100 (7.77)	5.383 (7.56)	16.338 (8.55)	9.751 (9.69)
Median	2.133	21.217	1.653	19.667	3.217
Min, Max	0.08, 27.74	0.23, 26.80	0.01, 26.13	1.13, 27.72	0.01, 27.72
Data source: ISS Table 2.2.1					

Source: Applicant's submission (Summary of Clinical Safety, Page 44)

Postoperative Phase 3 Studies

Disposition

Most of subjects in the N1539 (96.9%) and placebo (96.5%) groups completed treatment per protocol. Two (0.3%) subjects in the N1539 30 mg group and one subject (0.3%) in the placebo group discontinued treatment due to an AE. Most subjects (~97%) in both treatment groups

also completed the study as the table below.

Table 38 Subject Disposition in Postoperative Phase 3 Studies

Parameter	Placebo N=393 n (%)	N1539 30 mg N=748 n (%)
Subjects who completed treatment	381 (96.9)	722 (96.5)
Reason for discontinuation of treatment:		
Lack of efficacy	5 (1.3)	6 (0.8)
Adverse event	1 (0.3)	2 (0.3)
Withdrawal by subject	1 (0.3)	2 (0.3)
Protocol violation	0	4 (0.5)
Non-compliance with study drug	1 (0.3)	2 (0.3)
Other[a]	4 (1.0)	10 (1.3)
Subjects who completed study	382 (97.2)	727 (97.2)
Reason for discontinuation of study:		
Lack of efficacy	0	2 (0.3)
Withdrawal by subject	4 (1.0)	8 (1.1)
Lost to follow-up	7 (1.8)	10 (1.3)
Other[b]	0	1 (0.1)

Data source: ISS Table 1.3.1
a Subjects who did not receive at least 2 doses of study drug due to discharge, IV discontinued, or staff error.
b Subject who went to rehabilitation and could not return for visits.

Source: Applicant's submission (Summary of Clinical Safety, Page 78)

Demographics and Baseline Characteristics of Postoperative Phase 3 Population

Demographic and baseline characteristics for subjects in the postoperative Phase 3 studies are presented in the table below. Baseline characteristics were similar between the two treatment groups. Most subjects in each treatment group were white, female, and <65 years of age. The median age of subjects was 50 years in the N1539 30 mg group and 48 years in the placebo group.

Most subjects in treatment groups had no history of hypertension (≥70.3%), diabetes (≥94.0%), or gastrointestinal disorders (≥79.9%). Most (≥87.3%) subjects were not considered high risk (i.e., > 65 years with a GFR of 60-89 mL). Most subjects did not use antihypertensive (≥67.8%) or antithrombotic (≥67.5%) medications. These Phase 3 studies were conducted in the United States (n=1090), Canada (n=8), and Australia and New Zealand combined (n=43).

Table 39 Demographics and Baseline Characteristics in Postoperative Phase 3 Studies

Parameter	Placebo N=393	N1539 30 mg N=748

Age (years)		
Mean (SD)	48.5 (13.28)	50.0 (13.78)
Median	48.0	50.0
Min, Max	21, 80	18, 79
Age group (years), n (%)		
<65	339 (86.3)	620 (82.9)
≥65	54 (13.7)	128 (17.1)
≥75	10 (2.5)	15 (2.0)
Sex, n (%)		
Male	87 (22.1)	240 (32.1)
Female	306 (77.9)	508 (67.9)
Race, n (%)		
White	292 (74.3)	589 (78.7)
Black/African American	83 (21.1)	137 (18.3)
Asian	9 (2.3)	12 (1.6)
American Indian/Alaska Native	1 (0.3)	1 (0.1)
Native Hawaiian/Other Pacific Islander	2 (0.5)	4 (0.5)
Other	3 (0.8)	4 (0.5)
Multiple	3 (0.8)	1 (0.1)
Body mass index (kg/m^2)		
Mean (SD)	28.3 (4.33)	28.7 (4.86)
Median	27.9	28.5
Min, Max	18, 40	18, 42
Positive history for, n (%)		
Hypertension	96 (24.4)	222 (29.7)
Diabetes	19 (4.8)	45 (6.0)
Gastrointestinal conditions[a]	62 (15.8)	150 (20.1)
Risk group, n (%)		
High risk[b]	33 (8.4)	95 (12.7)
Not high risk	360 (91.6)	653 (87.3)

Data source: ISS Table 2.3.1
a Gastrointestinal history of interest included prior or concomitant gastrointestinal esophageal reflux disease, gastrointestinal ulcer, and/or bleeding within the gastrointestinal track
b High risk was defined as age > 65 years with a GFR of 60-89 mL/min/1.73 m^2, as calculated using the MDRD equation

Source: Applicant's submission (Summary of Clinical Safety, Page 80)

Surgical characteristics of subjects in the three Phase 3 postoperative studies are presented in the table below. In Study REC-15-015, all subjects underwent abdominoplasty, while subjects in Study REC-15-016 underwent bunionectomy surgery. In Study REC-15-017 subjects underwent a major surgical procedure. The median duration (~1 hour) of surgery was similar between treatment groups. The mean time from the end of surgery to the first dose of study drug was longer in subjects who had bunionectomy surgery (18.9 hours) compared to subjects who had abdominoplasty (0.85 hours) and other major surgeries (1.7 hours). This difference was due to the management of postoperative pain after bunionectomy surgery. Subjects who underwent bunionectomy received a popliteal sciatic nerve block that started when surgery ended on Day -1 and continued until the day after surgery. Thus, these subjects were ineligible for study drug randomization until discontinuation of the nerve block on Day 1, when pain was rated as moderate

or severe on a 4-point categorical pain rating scale and pain intensity (PI) was ≥4 on 11-point NPRS.

Table 40 Surgical Characteristics in Postoperative Phase 3 Studies

Parameter	Placebo N=393	N1539 30 mg N=748
Subjects who had orthopedic surgery, n (%):	197 (50.1)	383 (51.2)
Bunionectomy	114 (29.0)	140 (18.7)
Complex foot	19 (4.8)	52 (7.0)
Complex shoulder	2 (0.5)	6 (0.8)
Orthopedic trauma	1 (0.3)	0
Spinal	3 (0.8)	10 (1.3)
Total ankle replacement	0	1 (0.1)
Total hip replacement	18 (4.6)	50 (6.7)
Total shoulder replacement	1 (0.3)	7 (0.9)
Total knee replacement	39 (9.9)	117 (15.6)
Subjects who had other surgeries, n (%):	196 (49.9)	365 (48.8)
Abdominoplasty	120 (30.5)	142 (19.0)
Gastrointestinal	13 (3.3)	26 (3.5)
Gynecological	21 (5.3)	68 (9.1)
Head and neck	0	1 (0.1)
Soft tissue	42 (10.7)	128 (17.1)
Surgery duration (hours)		
Mean (SD)	1.123 (0.78)	1.209 (0.92)
Median	0.983	1.033
Min, Max	0.23, 7.78	0.20, 9.95
Time from end of surgery to first dose (hours)[a]		
Mean (SD)	5.926 (7.92)	3.838 (6.10)
Median	1.589	1.441
Min, Max	0.08, 27.74	0.01, 25.28

Data source: ISS Table 2.3.1
a Represents the average between the surgical types.

Source: Applicant's submission (Summary of Clinical Safety, Page 81)

8.2.3. Adequacy of the safety database:

The safety data from the 1045 subjects who received two or more doses of N1539 including the 743 who received two or more doses of N1539 30 mg, the proposed to-be-marketed dose. The safety population is an adequate representation of the treatment population of subjects with acute pain.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Data integrity and submission quality were adequate for this review.

8.3.2. Categorization of Adverse Events

The safety assessments in the N1539 clinical development program include physical examinations, vital signs, pulse oximetry, 12-lead ECGs, clinical laboratory tests (chemistry, hematology, and urinalysis), pregnancy tests, and AEs.

Adverse Events were coded by system organ class and preferred term based on the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary.

8.3.3. Routine Clinical Tests

Laboratory values, including chemistry, hematology, urinalysis, and coagulation tests, were collected at various time points during the postoperative studies.

8.4. Safety Results

8.4.1. Deaths

Postoperative subjects
One subject who received placebo in Study REC-15-016 died. This subject withdrew from the study on LSD+8 for personal reasons. The death was considered unrelated to study drug. A narrative for this subject is provided by the Applicant as follows:

A sudden death was experienced by Subject (b) (6), a 39–year old Caucasian female of Hispanic or Latino descent, after their participation in this study. The subject had an unremarkable medical history, including no history of drug abuse and had two negative urine drug screens prior to surgery. The subject underwent distal first metatarsal osteotomy of the right foot on (b) (6). The subject was randomized to treatment with placebo on (b) (6) and received three study doses prior to discharge on (b) (6). The subject returned and completed part of the last study day (LSD)+7 visit assessments on (b) (6) before leaving the site to deal with a personal issue. On (b) (6), the subject contacted the site to withdraw from participation in the study. The subject did not return for LSD+28 assessments. On (b) (6), the clinical site was made aware that the subject had died on (b) (6), 55 days following the last dose of study medication. Autopsy reported the cause of death as due to "complications of the toxic effects of methamphetamine". The investigator considered the AE to be of severe intensity and not related to study medication. The outcome of the event was reported as fatal. The sponsor considered the AE to be not related to study medication and assessed the event as not expected. The sponsor did not break the blind early and an expedited report was not issued.

Reviewer's comment: I agree with the Applicant that this death was unrelated to study drug.

Healthy Subjects
No subject in the Phase 1 studies died.

8.4.2. Serious Adverse Events

Postoperative subjects (Phase 2 and 3 studies)
Fifteen subjects (15/517, 2.9%) in the placebo group (including the subject who died, all in three Phase 3 studies), five subjects (5/327, 1.5%) in the N1539 5-15 mg group, and 15 subjects (15/910, 1.6%) in the N1539 30 mg group had SAEs during the conduct of the clinical studies. No subject in the N1539 60 mg group had an SAE.

Subject with SAEs are listed by study, subject number, and treatment group in the table below, which includes the Applicant's causality assessment. Narratives for all subjects with SAEs were submitted by the Sponsor and reviewed and are not reproduced here.

Table 41 SAEs in Postoperative Studies (Phase 2 and Phase 3 studies)

Study/ Subject No. Dose Surgery Type	Age (years)/ Sex/ Race	Preferred Term/ Verbatim Term	Onset Day/ Stop Day	Severity/ Relationship to Study Drug	Action Taken with Study Drug/ Other Actions Taken	Outcome	Narrative Location
N1539							
N1539-04 (b) (6) N1539 5 mg Open abdominal hysterectomy	43 Female White	Vaginal haemorrhage/ Vaginal spotting	10/13	Mild Unrelated	None/ None	Resolved/Recovered	Appendix A of the ISS
N1539-04 (b) (6) N1539 7.5 mg Open abdominal hysterectomy	47 Female White	Postprocedural haematoma/ Postoperative wound haematoma	3/15	Mild Unrelated	None/ Concomitant treatment given	Resolved/Recovered	Appendix A of the ISS
N1539-04 (b) (6) N1539 5 mg Open abdominal hysterectomy	46 Female White	Ileus/Ileus	6/12	Severe Unrelated	None/ Multiple medications were administered	Resolved/Recovered	Appendix A of the ISS
N1539-04 (b) (6) N1539 15 mg Open abdominal hysterectomy	65 Female White	Wound dehiscence/ Wound dehiscence	8/15	Mild Unrelated	None/ Re-suturing of wound	Resolved/Recovered	Appendix A of the ISS
N1539-04 (b) (6) N1539 15 mg Open abdominal hysterectomy	45 Female White	Wound infection/ Wound infection	5/18	Mild Unrelated	None/ Concomitant treatment given	Resolved/Recovered	Appendix A of the ISS

N1539							
REC-15-015 (b) (6) N1539 30 mg Abdominoplasty	54 Male Black/African American	Postprocedural haemorrhage/ Post procedural hemorrhage	2/101	Moderate/ Unrelated	Dose not changed/ A total of 6 units of packed red cells administered. Subject retuned to OR for ligation of active vessel bleed.	Resolved/Recovered	Appendix A of the ISS
REC-15-017 (b) (6) N1539 30 mg Total knee replacement	63 Male Black/African American	Anaemia/ Postoperative anemia	4/5	Moderate Unrelated	Not applicable/ Concomitant medication given.	Resolved/Recovered	Appendix A of the ISS
		Acute kidney injury/ Acute renal failure	18/20	Moderate Unrelated	Not applicable/ Concomitant medication given	Resolved/Recovered	
REC-15-017 (b) (6) N1539 30 mg Total knee replacement	64 Male White	Tendon injury/ Retinacular tear of left knee	15/16	Severe Unrelated	Not applicable/ Surgical repair of the tear.	Resolved/Recovered	Appendix A of the ISS
REC-15-017 (b) (6) N1539 30 mg Gynecological/Genitourinary Abdominal (hysterectomy/salpingectomy)	41 Female White	Intestinal perforation/ Bowel perforation	5/6	Severe Unrelated	Not applicable/ Concomitant medication given. The subject underwent laparotomy exploratory with ileocecectomy, and protective loop ostomy.	Resolved/Recovered	Appendix A of the ISS

Study/ Subject No. Dose Surgery Type	Age (years)/ Sex/ Race	Preferred Term/ Verbatim Term	Onset Day/ Stop Day	Severity/ Relationship to Study Drug	Action Taken with Study Drug/ Other Actions Taken	Outcome	Narrative Location
N1539							
REC-15-017 (b) (6) N1539 30 mg Gynecological/Genitourinary	57 Female White	Pneumonia/ Right upper lobe pneumonia	5/6	Mild Unrelated	Not applicable/ Concomitant medication given.	Resolved/Recovered	ISS M5.3.5.3 Appendix A
REC-15-017 (b) (6) N1539 30 mg Abdominal	51 Male White	Omental infarction/ Infarcted omentum	5/5	Moderate Unrelated	Not applicable/ Concomitant medication given. Prolonged hospitalization requiring the subject to return to the OR.	Resolved/Recovered	ISS M5.3.5.3 Appendix A
REC-15-017 (b) (6) N1539 30 mg Abdominal	56 Female White	Small intestinal obstruction/ Small bowel obstruction	9/17	Moderate Unrelated	Not applicable/ Placement of nasogastric.	Resolved/Recovered	ISS M5.3.5.3 Appendix A
REC-15-017 (b) (6) N1539 30 mg Abdominal (repair hernia incisional with biologic and prosthetic mesh)	67 Male White	Small intestinal obstruction/ Small bowel obstruction	5/11	Moderate Unrelated	Not applicable/ Decompression colonoscopy.	Resolved/Recovered	ISS M5.3.5.3 Appendix A
		Post procedural pulmonary embolism/ Postoperative pulmonary embolus	5/-	Moderate Unrelated	Not applicable/ Concomitant medication given.	Not resolved/ Not recovered. Mechanical ventilation.	
		Respiratory distress/ Respiratory distress syndrome	5/13	Severe Unrelated	Not applicable/ Other.	Recovered/Resolved with sequela. Mechanical ventilation.	
		Acute kidney injury/	21/-	Moderate Unrelated	Not applicable/	Not recovered/Not resolved	

N1539							
		Acute kidney injury/ Acute renal failure	21/-	Moderate Unrelated	Not applicable/ Concomitant medication given.	Not recovered/Not resolved	
REC-15-017 (b) (6) N1539 30 mg Gynecological/Genitourinary	38 Female Black/African American	Postoperative ileus/ Postoperative ileus	7/9	Mild Unrelated	Not applicable/ Concomitant medication given.	Recovered/Resolved	Appendix A of the ISS
REC-15-017 (b) (6) N1539 30 mg Total knee replacement	56 Female White	Hypervolaemia/ Hypervolemia	5/7	Severe Unrelated	Not applicable/ Oxygen administered.	Recovered/Resolved	Appendix A of the ISS
REC-15-017 (b) (6) N1539 30 mg Abdominal	64 Male White	Incision site infection/ Small infection at the bottom of the wound	8/23	Mild Unrelated	Not applicable/ Abscess drained.	Recovered/Resolved	Appendix A of the ISS
		Septic shock/ Septic shock on double J	20/34	Severe Unrelated	Not applicable/ Concomitant medication given.	Recovered/Resolved	
REC-15-017 (b) (6) N1539 30 mg Total knee replacement	77 Female/ Black/African American	Post procedural pulmonary embolism/ Postoperative pulmonary embolism	13/24	Mild Unrelated	Not applicable/ Concomitant medication given.	Recovered/Resolved	Appendix A of the ISS

N1539							
REC-15-017 (b) (6) N1539 30 mg Total knee replacement	47 Male White	Diverticulitis/ Acute sigmoid diverticulitis	28/42	Moderate Unrelated	Not applicable/ Concomitant medication given.	Recovered/Resolved	Appendix A of the ISS
		Mesenteric abscess/ Mesenteric abscess *(Bacteroides fragilis, Pseudomonas aeruginosa)*	28/123	Moderate Unrelated	Not applicable/ Concomitant medication given. Aspiration and partial bowel resection.	Recovered/Resolved	
REC-15-017 (b) (6) N1539 30 mg Total knee replacement	49 Female White	Femoral neck fracture/ Surgical perforation of femur	2/2	Severe Unrelated	Not applicable/ Surgical revision required.	Recovered/Resolved	Appendix A of the ISS
REC-15-017 (b) (6) N1539 30 mg Total knee replacement	65 Female White	Post procedural pulmonary embolism/ Post procedure pulmonary embolism	3/-	Severe Unrelated	Drug withdrawn/ Concomitant medication given. General internal medicine and family doctor were to continue to monitor.	Not recovered/ Not resolved	Appendix A of the ISS

Study/ Subject No. Dose Surgery Type	Age (years)/ Sex/ Race	Preferred Term/ Verbatim Term	Onset Day/ Stop Day	Severity/ Relationship to Study Drug	Action Taken with Study Drug/ Other Actions Taken	Outcome	Narrative Location
Placebo							
REC-15-015 (b) (6) Placebo Abdominoplasty	31 Female Black/African American	Post procedural haemorrhage/ Post procedural bleeding	1/4	Severe Possibly related	Drug withdrawn. Subject received 3 units of packed red blood cells over a 2-day period.	Recovered/Resolved	ISS M5.3.5.3 Appendix A
REC-15-015 (b) (6) Placebo Abdominoplasty	33 Female Black/African American	Post procedural pulmonary embolism/ Pulmonary emboli	2/-	Moderate Possibly related	Drug withdrawn.	Unknown	ISS M5.3.5.3 Appendix A
REC-15-015 (b) (6) Placebo Abdominoplasty	52 Female Black/African American	Postoperative wound infection/ Postoperative wound infection	33/84	Mild Unrelated	Dose not changed/ Medication required.	Recovered/Resolved	ISS M5.3.5.3 Appendix A
REC-15-016 (b) (6) Placebo Bunionectomy	39 Female White	Sudden death/ Sudden death	58/58	Severe/ Unrelated	Dose not changed.	Fatal	ISS M5.3.5.3 Appendix A
REC-15-016 (b) (6) Placebo Bunionectomy	48 Female White	Fracture/ Fractured osteotomy site	18/73	Moderate Unrelated	Dose not changed/ Surgery.	Recovered/Resolved	ISS M5.3.5.3 Appendix A
REC-15-017 (b) (6) Placebo Total knee replacement	60 Female White	Respiratory arrest/ Respiratory arrest	1/2	Moderate Unrelated	Not applicable/ Concomitant medication given.	Recovered/Resolved	ISS M5.3.5.3 Appendix A
REC-15-017 (b) (6) Placebo Total knee replacement	72 Male White	Coronary artery disease/ Myocardial ischemia secondary to coronary artery disease	3/4	Mild Unrelated	Not applicable/ Concomitant medication given.	Recovered/Resolved	ISS M5.3.5.3 Appendix A

Study/ Subject No. Dose Surgery Type	Age (years)/ Sex/ Race	Preferred Term/ Verbatim Term	Onset Day/ Stop Day	Severity/ Relationship to Study Drug	Action Taken with Study Drug/ Other Actions Taken	Outcome	Narrative Location
Placebo							
REC-15-017 (b) (6) Placebo Total knee replacement	66 Male White	Dizziness/ Dizziness	4/5	Mild Unrelated	Not applicable/ None	Recovered/Resolved	ISS M5.3.5.3 Appendix A
REC-15-017 (b) (6) Placebo Gynecological/Genitourinary	44 Female Black/African American	Postoperative abscess/ Vaginal cuff abscess	20/22	Mild Unrelated	Not applicable/ Concomitant medication given	Recovered/Resolved	ISS M5.3.5.3 Appendix A
REC-15-017 (b) (6) Placebo Abdominal	37 Female White	Nausea/ Nausea	43/-	Severe Unrelated	Not applicable/ Concomitant medication given	Not recovered/ Not resolved	ISS M5.3.5.3 Appendix A
		Hepatocellular injury/ Hepatocellular dysfunction	43/-	Severe Unrelated	Not applicable/ Follow-up with hepatologist.	Not recovered/ Not resolved	
		Liver function test abnormal/ Elevated liver function tests (LFTs)	43/-	Severe Unrelated	Not applicable/ Follow-up with hepatologist.	Not recovered/ Not resolved	ISS M5.3.5.3 Appendix A
REC-15-017 (b) (6) Placebo Gynecological/Genitourinary	52 Female Black/African American	Postoperative ileus/ Postoperative ileus	7/9	Mild Unrelated	Not applicable/ Concomitant medication given	Recovered/Resolved	ISS M5.3.5.3 Appendix A
REC-15-017 (b) (6) Placebo Total knee replacement	67 Male Black/African American	Dyspnoea/ Short of breath	8/9	Mild Unrelated	Not applicable/ Concomitant medication given. Hospitalized.	Recovered/Resolved	ISS M5.3.5.3 Appendix A
REC-15-017 (b) (6) Placebo Abdominal	43 Female White	Abdominal abscess/ Right upper quadrant abscess	5/11	Severe Unrelated	Not applicable/ Concomitant medication given	Recovered/Resolved	ISS M5.3.5.3 Appendix A

Study/ Subject No. Dose Surgery Type	Age (years)/ Sex/ Race	Preferred Term/ Verbatim Term	Onset Day/ Stop Day	Severity/ Relationship to Study Drug	Action Taken with Study Drug/ Other Actions Taken	Outcome	Narrative Location
Placebo							
REC-15-017 (b) (6) Placebo Abdominal	75 Male White	Incisional hernia/ Ruptured incisional hernia	4/11	Severe Unrelated	Not applicable/ Hospitalized.	Recovered/Resolved	ISS M5.3.5.3 Appendix A
REC-15-017 (b) (6) Placebo Abdominal	41 Female Black/African American	Jejunal stenosis/ Mild stenosis of gastrojejunal anastomosis	7/35	Moderate/ Possibly related	Not applicable/ None	Recovered/Resolved	ISS M5.3.5.3 Appendix A
		Anastomotic ulcer/ Gastrojejunal ulcer without hemorrhage or perforation	19/35	Moderate/ Possibly related	Not applicable/ Concomitant medication given	Recovered/Resolved	

Source: Applicant's submission (Summary of Clinical Safety, Pages 51-58)

Reviewer's comments:
It is interesting to note that all SAEs at the placebo group happen in the three Phase 3 studies (i.e., none in the three Phase 2 studied). The Applicant's assignment of severity as moderate in the case of respiratory arrest (Study 017, Pt (b) (6) in placebo group) is unacceptable, all SAEs must be considered serious. The narrative suggests that this 60-year-old women, s/p total knee replacement, developed cyanosis after hydromorphone, she received CPR, and received naloxone and fully recovered.

Postoperative subjects (Phase 3 studies)
Fifteen (3.8%) subjects in the placebo group and 15 (2.0%) subjects in the N1539 30 mg group had SAEs. Each subject reported the event only once. SAEs in the three postoperative studies are presented in the table below.

Table 42 SAEs in Postoperative Phase 3 Studies

Parameter	Placebo N=393	N1539 30 mg N=748
Subjects with ≥1 SAE, n (%)	15 (3.8)	15 (2.0)
Number of reported SAEs	18	21
Blood and lymphatic system disorders, n (%)		
Anemia	0	1 (0.1)
Cardiac disorders, n (%)		
Coronary artery disease	1 (0.3)	0
Gastrointestinal disorders, n (%)		
Intestinal perforation	0	1 (0.1)
Jejunal stenosis	1 (0.3)	0
Nausea	1 (0.3)	0
Omental infarction	0	1 (0.1)
Small bowel obstruction	0	2 (0.3)
General disorders and administration site conditions, n (%)		
Sudden death	1 (0.3)	0
Hepatobiliary disorders, n (%)		
Hepatocellular injury	1 (0.3)	0
Infections and infestations, n (%)		
Abdominal abscess	1 (0.3)	0
Diverticulitis	0	1 (0.1)
Incision site infection	0	1 (0.1)
Mesenteric abscess	0	1 (0.1)
Pneumonia	0	1 (0.1)
Postoperative abscess	1 (0.3)	0
Postoperative wound infection	1 (0.3)	0
Septic shock	0	1 (0.1)

Injury, poisoning and procedural complications, n (%)		
Anastomotic ulcer	1 (0.3)	0
Femoral neck fracture	0	1 (0.1)
Fracture	1 (0.3)	0
Incisional hernia	1 (0.3)	0
Post procedural hemorrhage	1 (0.3)	1 (0.1)
Post procedural pulmonary embolism	1 (0.3)	3 (0.4)
Postoperative ileus	1 (0.3)	1 (0.1)
Tendon injury	0	1 (0.1)
Investigations, n (%)		
Liver function test abnormal	1 (0.3)	0
Metabolic and nutrition disorders, n (%)		
Hypervolaemia	0	1 (0.1)
Nervous system disorders, n (%)		
Dizziness	1 (0.3)	0
Renal and urinary disorders, n (%)		
Acute kidney injury	0	2 (0.3)
Respiratory, thoracic and mediastinal disorders, n (%)		
Dyspnoea	1 (0.3)	0
Respiratory arrest	1 (0.3)	0
Respiratory distress	0	1 (0.1)
Data source: ISS Table 9.3.1.		

Source: Applicant's submission (Summary of Clinical Safety, Page 86)

Healthy Subjects
No subject in the Phase 1 studies has an SAE.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Postoperative subjects (Phase 2 and 3 studies)
The TEAEs that led to discontinuation of treatment or study are presented in the table below. The percentage of subjects who discontinued study drug and/or the study was low and similar between the N1539 30 mg group and the placebo group. Narratives for subjects who discontinued treatment or study due to an AE were submitted by the Sponsor, which did not provide additional valuable information, therefore, not reproduced here.

Table 43 TEAEs Leading to Discontinuation in Postoperative Studies (Phase 2 and Phase 3 studies)

Parameter	Placebo N=517	N1539 5-15 mg N=327	N1539 30 mg N=910	N1539 60 mg N=189
Subjects with ≥1 TEAE leading to discontinuation of treatment or study, n (%)	3 (0.6)	1 (0.3)	2 (0.2)	0
Number of reported TEAEs	4	1	2	0
General disorders/administration site conditions, n (%)				
Localized oedema	0	0	1 (0.1)	0

Injury, poisoning and procedural complications, n (%)				
Anaemia postoperative	1 (0.2)	0	0	0
Drug toxicity[a]	1 (0.2)	0	0	0
Post procedural haemorrhage[b]	1 (0.2)	0	0	0
Post procedural pulmonary embolism[b]	1 (0.2)	0	1 (0.1)	0
Skin and subcutaneous tissue disorders, n (%)				
Rash maculo-papular	0	1 (0.3)	0	0
Data source: ISS Table 10.2.1 a Due to morphine rescue medication. b Serious adverse events.				

Source: Applicant's submission (Summary of Clinical Safety, Page 59)

Postoperative subjects (Phase 3 studies)

Two (0.5%) subjects in the placebo group and two (0.3%) subjects in the N1539 30 mg group had discontinuations due to TEAEs as the table below. Narratives for subjects who discontinued treatment or study due to a TEAE were submitted by the Sponsor, but not reproduced here.

Table 44 TEAEs Leading to Discontinuation in Postoperative Phase 3 Studies

Parameter	Placebo N=393	N1539 30 mg N=748
Subjects with ≥1 TEAEs leading to discontinuation of treatment or study, n (%)	2 (0.5)	2 (0.3)
Number of reported TEAEs	3	2
General disorders and administration site conditions, n (%)		
Localized edema	0	1 (0.1)
Injury, poisoning and procedural complications, n (%)		
Anemia postoperative	1 (0.3)	0
Post procedural hemorrhage[a]	1 (0.3)	0
Post procedural pulmonary embolism[a]	1 (0.3)	1 (0.1)
Data source: ISS Table 10.3.1 a Serious adverse event.		

Source: Applicant's submission (Summary of Clinical Safety, Page 87)

Healthy Subjects

No subject in the Phase 1 studies had discontinued due to an AE.

8.4.4. Significant Adverse Events

As presented in the next section (8.4.4)

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Postoperative subjects (Phase 2 and 3 studies)
The most commonly reported TEAEs (those occurring in ≥3% in any treatment group) are presented in the table below.

The most commonly reported TEAEs in treatment groups were nausea, headache, vomiting, and dizziness. Most TEAEs were reported at similar rates in the N1539 treatment groups compared to the placebo group.

Table 45 TEAEs (Occurring in ≥3% of Subjects) in Postoperative Studies (Phase 2 and 3 studies)

	Placebo N=517	N1539 5-15 mg N=327	N1539 30 mg N=910	N1539 60 mg N=189
Subjects with ≥1 TEAE, n (%)	296 (57.3)	121 (37.0)	497 (54.6)	59 (31.2)
Number of reported TEAEs	666	198	1078	99
Blood and lymphatic system disorders, n (%)				
Anemia	6 (1.2)	26 (8.0)	19 (2.1)	18 (9.5)
Gastrointestinal disorders, n (%)				
Constipation	25 (4.8)	8 (2.4)	61 (6.7)	2 (1.1)
Nausea	131 (25.3)	14 (4.3)	189 (20.8)	11 (5.8)
Vomiting	38 (7.4)	9 (2.8)	42 (4.6)	3 (1.6)
Nervous system disorders, n (%)				
Dizziness	25 (4.8)	0	32 (3.5)	2 (1.1)
Headache	54 (10.4)	5 (1.5)	51 (5.6)	3 (1.6)
Psychiatric disorders, n (%)				
Insomnia	11 (2.1)	14 (4.3)	13 (1.4)	6 (3.2)
Renal and urinary disorders, n (%)				
Ketonuria[a]	5 (1.0)	23 (7.0)	6 (0.7)	10 (5.3)
Skin and subcutaneous tissue disorders, n (%)				
Pruritus	15 (2.9)	0	31 (3.4)	2 (1.1)

Data source: ISS Table 6.2.1

a Ketonuria was reported by one site in Study N1539-04 where NSAIDs were not typically the first line of treatment for postoperative pain management; rather, parenteral paracetamol (acetaminophen) was used. According to the investigator, the occurrence of ketonuria in this study was more frequent than he typically had seen, and, therefore, he chose to report these as AEs that may be related to treatment with N1539 and morphine. There were no reports of ketonuria from the other sites in this study.

Source: Applicant's submission (Summary of Clinical Safety, Page 47)

A summary of TEAEs occurring in ≥ 1% or 2% N1539 30 mg of treated subjects in REC-15-015, REC-15-016, respectively, is provided in the tables below. Similar to all postoperative studies as summarized before, the overall incidence of TEAEs and incidence of individual events was generally similar between treatments, with fewer N1539 30 mg treated subjects experiencing

an AE in these two Phase 3 studies. The most frequently reported TEAEs included nausea, headache, vomiting, and pruritus, with similar incidence between treatments.

Table 46 TEAE Occurring in ≥1% of N1539 Treated Subjects (REC-15-015)

Preferred Term	Total Events	N1539 30 mg (N=110)		Placebo (N=109)	
		Events	n (%)	Events	n (%)
Nausea	74	32	30 (27.3)	42	41 (37.6)
Headache	32	13	13 (11.8)	19	18 (16.5)
Vomiting	15	5	5 (4.5)	10	10 (9.2)
Dizziness	14	4	4 (3.6)	10	10 (9.2)
Decreased appetite	5	2	2 (1.8)	3	3 (2.8)
Alanine aminotransferase increased	4	2	2 (1.8)	2	2 (1.8)
Constipation	4	2	2 (1.8)	2	2 (1.8)
Hypotension	4	2	2 (1.8)	2	2 (1.8)
Aspartate aminotransferase increased	3	2	2 (1.8)	1	1 (0.9)
Hyperhidrosis	3	2	2 (1.8)	1	1 (0.9)
Pruritus generalised	3	2	2 (1.8)	1	1 (0.9)
Induration	2	2	2 (1.8)	0	0
Injection site pain	2	2	2 (1.8)	0	0
Tachycardia	2	2	2 (1.8)	0	0

Source: REC-15-015 Study Report (Page 55)

Table 47 TEAE Occurring in ≥1% of N1539 Treated Subjects (REC-15-016)

Preferred Term	Total Events	N1539 30 mg (N=100)		Placebo (N=101)	
		Events	n (%)	Events	n (%)
Nausea	61	30	20 (20.0)	31	26 (25.7)
Headache	22	8	8 (8.0)	14	12 (11.9)
Vomiting	14	3	3 (3.0)	11	9 (8.9)
Pruritus	11	8	8 (8.0)	3	3 (3.0)
Decreased appetite	10	2	2 (2.0)	8	7 (6.9)

Constipation	9	4	4 (4.0)	5	5 (5.0)
Dizziness	7	3	3 (3.0)	4	4 (4.0)
Flushing	7	4	3 (3.0)	3	1 (1.0)
Skin abrasion	5	2	2 (2.0)	3	2 (2.0)
Somnolence	5	3	3 (3.0)	2	2 (2.0)
Hyperhidrosis	3	2	2 (2.0)	1	1 (1.0)
Blister	2	2	2 (2.0)	0	0
Cellulitis	2	2	2 (2.0)	0	0
Diarrhoea	2	2	2 (2.0)	0	0
Oedema peripheral	2	2	2 (2.0)	0	0
Pruritus generalised	2	2	2 (2.0)	0	0

Source: REC-15-016 Study Report (Page 60)

Two TEAEs (i.e., anemia and ketonuria) occurred in the N1539 5-15 mg and N1539 60 mg groups, and the Applicant provided further discussion.

In Study N1539-04, investigators were instructed to report a hemoglobin value after surgery that was less than 8.0 g/dL as an AE. Additionally, any hemoglobin value after surgery that was between 8.0 g/dL and 9.9 g/dL and had decreased by at least 0.5 g/dL from screening was also considered an AE.

Because of this protocol mandate, 33.3% (2/6) of the anemias reported in the placebo group, 100.0% (26/26) in the N1539 5-15 mg group, 5.3% (1/19) in the N1539 30 mg group, and 100% (18/18) in the N1539 60 mg group were from subjects treated during the double-blind and open-label phases in Study N1539-04.

Ketonuria was reported by one site in Study N1539-04 as the table below. Per the investigator, the occurrence of ketonuria in this study was more frequent than he typically had seen, and, he therefore chose to report these findings as AEs possibly related to treatment with N1539 and morphine.

Table 48 TEAE of Ketonuria Reported in Study N1539-04

	Placebo N=64	**N1539 5-15 mg N=211**	**N1539 30 mg N=60**	**N1539 60 mg N=89**
Ketonuria, n (%)	5 (7.8)	23 (10.9)	6 (10.0)	10 (11.2)
Data source: Study N1539-04 CSR Table 14.3.2.1.1				

Source: Applicant's submission (Summary of Clinical Safety, Page 48)

In the seven postoperative studies, 100.0% (5/5) of the ketonuria reported in the placebo group, 100% (23/23) in the N1539 5-15 mg group, 100.0% (6/6) in the N1539 30 mg group, and 100% (10/10) in the N1539 60 mg group were from subjects treated during the double-blind and open-label phases of Study N1539-04.

Reviewer's comments:
The higher rates of anemia and ketonuria were reported in one single study (Study N1539-04), which is not replicated in other post-operative studies.

Postoperative subjects (Phase 3 studies)
The most commonly reported TEAEs (those occurring in ≥3% in the N1539 30 mg treatment group) are presented in the table below.

Table 49 Summary of TEAEs in Postoperative Phase 3 Studies

	Placebo N=393	**N1539 30 mg N=748**
Subjects with ≥1 TEAE, n (%)	253 (64.4)	441 (59.0)
Number of reported TEAEs	569	934
Maximum severity of TEAE, n (%)		
Mild	207 (52.7)	359 (48.0)
Moderate	100 (25.4)	173 (23.1)
Severe	12 (3.1)	17 (2.3)
Subjects with ≥1 treatment-related TEAE[a], n (%)	145 (36.9)	195 (26.1)
Number of reported treatment-related TEAEs	255	330
Deaths, n (%)	1 (0.3)	0
Subjects with SAE[b], n (%)	15 (3.8)	15 (2.0)
Number of SAEs	18	21
Subjects with TEAEs leading to discontinuation of treatment or study, n (%)	2 (0.5) 3	2 (0.3) 2
Number of TEAEs per subject		
Mean (SD)	1.4 (1.73)	1.2 (1.69)
Median	1	1
Min, Max	0, 15	0, 16

Data source: ISS Table 4.3.1, ISS Table 8.3.1, and ISS Table 10.3.1.
a Includes TEAEs possibly, probably, and definitely related.
b Includes the SAE with an outcome of death.

Source: Applicant's submission (Summary of Clinical Safety, Page 83)

The percentage of subjects reporting TEAEs was comparable between the N1539 30 mg group (59.0%) and the placebo group (64.4%). The most commonly reported TEAEs across treatment

groups was nausea. TEAEs of nausea, vomiting, dizziness, and headache were reported less frequently in the N1539 30 group compared with the placebo group.

Healthy Subjects
Treatment-emergent and treatment-related TEAEs are presented in the table below.

Table 50 TEAEs (Occurring in ≥2 Subjects) in Healthy Volunteers

Parameter	Placebo N=18 n (%)	N1539 15 mg N=7 n (%)	N1539 30 mg N=39 n (%)	N1539 60 mg N=15 n (%)	N1539 120 mg N=12 n (%)	N1539 180 mg N=18 n (%)
Subjects with ≥1 TEAE	3 (16.7)	1 (14.3)	9 (23.1)	6 (40.0)	2 (16.7)	2 (11.1)
Gastrointestinal disorders						
Diarrhoea	0	0	0	2 (13.3)	0	0
Nausea	0	0	2 (5.1)	2 (13.3)	0	0
Nervous system disorders						
Dizziness	0	0	0	0	0	2 (11.1)
Headache	0	1 (14.3)	0	2 (13.3)	0	0
Somnolence	0	0	2 (5.1)	0	0	0
Skin and subcutaneous tissue disorders						
Dermatitis contact	0	0	3 (7.7)	0	0	0
Vascular disorders						
Presyncope	0	0	0	2 (13.3)	0	0
Data source: ISS Table 6.1						

Source: Applicant's submission (Summary of Clinical Safety, Page 40)

There seemed to be no increase in the percentage of subjects reporting a specific TEAE as the dose of N1539 increased from 15 mg to 180 mg. The two reports of somnolence in the N1539 30 mg group and one report of pre-syncope in the N1539 60 mg group occurred within the first 60 minutes of study drug administration.

8.4.6. Laboratory Findings

Laboratory values, including chemistry, hematology, urinalysis, and coagulation tests, were collected at various time points during the postoperative studies. Because of the differences in data collection time points the clinical laboratory evaluation presented in this section focuses on the pooled Phase 3 studies (REC-15-015, REC-15-016, and REC-15-017).

Selected laboratory assessments, including parameters related to renal and hepatic function as well as bleeding risk, were analyzed by evaluating the incidence of potentially clinically significant shifts from baseline at subsequent assessment time points in individual subjects.

Hematology
In the pooled postoperative Phase 3 studies, there were no differences between the treatment groups in the percentage of subjects with potentially clinically significant hematology

laboratory parameters of special interest with two exceptions. However, in the Phase 3 studies, a higher percentage of subjects in the N1539 30 mg group had hemoglobin and hematocrit values that shifted from normal at baseline to low during the study compared to subjects in the placebo group.

The percentage of subjects with potentially clinically significant hemoglobin and hematocrit values was higher in the N1539 30 mg group compared to the placebo group, although only one report of 'hematocrit decreased' in each treatment group and one report of 'hemoglobin decreased' in each treatment group were deemed clinically significant by the investigator and reported as an AE as the table below. The incidence of clinically significant hematology parameters that were reported as AEs was similar between treatment groups in the pooled postoperative Phase 3 studies.

Most events of anemia (i.e., anemia and anemia postoperative) were transient and mild or moderate in intensity. Most subjects were either prescribed medications such as ferrous sulfate to treat their anemia or received no treatment. Five subjects (one placebo and four N1539 30 mg) required blood transfusions. One placebo subject (01-064) suffered a 'postprocedural hemorrhage' that led to severe anemia and was considered a SAE. The narrative for this subject was summarized in section Anemia.

Reviewer's comments:
Since bleeding rates increased in the treatment arm (see 8.5.1), a decrease in Hematology and hematocrit were observed accordingly more pronounced in the study group. The concomitant administration of prophylactic anticoagulant therapy post-surgery may contribute to increased bleeding rate.

Chemistry
In the pooled postoperative Phase 3 studies, there were no differences between the treatment groups in the percentage of subjects with potentially clinically significant chemistry laboratory parameters of special interest with one exception. However, in the Phase 3 studies, a higher percentage of subjects in the N1539 30 mg group had albumin values that shifted from normal at baseline to low during the study compared to subjects in the placebo group.

The percentage of subjects with potentially clinically significant albumin values in the Phase 3 studies was higher in the N1539 30 mg group compared to the placebo group, although only one report of 'blood albumin decreased' in the N1539 30 mg group was deemed clinically significant by the investigator and reported as an AE. This event was considered mild in intensity.

The incidence of clinically significant chemistry parameters that were reported as AEs generally similar between treatment groups in the pooled postoperative Phase 3 studies. All events

were mild or moderate in intensity, except for one report of 'liver function test abnormal' in one placebo subject (0.3%) and two reports of 'liver function test abnormal' in two N1539 30 mg subjects (0.3%) that were reported as severe. All events occurred only once. The narratives of three subjects with severe events are provided by the Applicant as follows:

N1539 30 mg: Subject (b) (6), a 69-year-old white male, with a relevant medical history of hemorrhagic diathesis, coronary artery disease, myocardial infarction, thalassemia alpha, and hypertension, underwent a total knee replacement on (b) (6). The subject's liver function test values were within the normal range at screening and one day after surgery. At visit LSD+7, his ALT, AST, and bilirubin values were above the normal range. An unscheduled visit for laboratory retesting approximately one week later ((b) (6)) showed these liver function test values trending toward normal. During a second unscheduled visit (Feb 2, 2017), all liver function test values had returned to within the normal range. This AE was considered severe in intensity and possibly related to study drug.

N1539 30 mg: Subject (b) (6), a 66-year-old white female, with no relevant medical history underwent a total knee replacement on (b) (6). The subject's liver function test values were within the normal range at screening and one day after surgery. At visit LSD+7, her ALT and AST values were above the normal range. An unscheduled visit for laboratory retesting approximately two weeks later ((b) (6)) showed these liver function test values trending toward or within the normal range. During a second unscheduled visit (Feb 23, 2017), all liver function test values had returned to within the normal range. This AE was considered severe in intensity and possibly related to study drug.

Placebo: Subject (b) (6), a 37-year-old white female, with no relevant medical history underwent laparoscopic cholecystectomy surgery on (b) (6). The subject's liver function test values were within the normal range at screening. At the inpatient treatment visit ((b) (6)) and LSD+1 ((b) (6)), her ALT and AST values were above the normal range. During LSD+7 visit ((b) (6)), all liver function test values had returned to within the normal range. This AE was considered severe in intensity and not related to study drug.

Reviewer's comments: There do not appear to be any consistent electrolytes abnormalities related to study drug administration.

Coagulation Laboratory Parameters
In the pooled Phase 3 studies, there were no notable differences between the treatment groups in the percentage of subjects with potentially clinically significant coagulation laboratory parameters of special interest.

8.4.7. Vital Signs

Vital signs were collected at various time points in the seven postoperative studies. Analyses were performed to determine the number of subjects meeting criteria for potentially clinically significant changes (PCSCs) in blood pressure at any time during the study. Clinically meaningful changes in vital signs, as determined by the investigator, were to be captured as AEs.

In the pooled postoperative Phase 3 studies, there were no notable differences between the treatment groups in the percentage of subjects with PCSCs systolic and diastolic blood pressure. In both treatment groups, decreases in both systolic and diastolic blood pressure tended to be more common than did increases in blood pressure parameters.

All events were mild or moderate in intensity, except for one report of severe 'oxygen saturation decreased' in one N1539 30 mg subject who had an SAE of post procedural pulmonary embolism' and a TEAE of 'atelectasis' and one report of severe 'respiratory distress' in one N1539 30 mg subject who had a SAE of 'post procedural pulmonary embolism'. All TEAEs for these two subjects were considered unrelated to study drug. These two subjects are discussed as below.

Subject (b) (6), a 65-year-old white female underwent a total knee replacement on (b) (6), (b) (6) and received N1539 30 mg on (b) (6). On (b) (6), she was diagnosed with a pulmonary embolism, tachypnea, and oxygen saturation decreased. Each of these events were unrelated to study drug. The pulmonary embolism was a SAE.

Subject (b) (6) in the N1539 30 mg group in Study REC-15-017 had SAEs of small bowel obstruction, pulmonary embolism, respiratory distress for which he was on mechanical ventilation, and acute renal failure. He was hospitalized in the intensive care unit for more than two months related to multiple medical complications requiring repeated surgical procedures, prolonged antibiotic therapy, and cardiorespiratory support.

Reviewer's comments: There do not appear to be any consistent vital abnormalities related to study drug administration. The first case of pulmonary embolism is the common postoperative complication, and the second case developed a series of postoperative complications of small bowel obstruction, pulmonary embolism, respiratory distress.

8.4.8. Electrocardiograms (ECGs)

Postoperative three Phase 3 Studies
The incidence of abnormal ECG findings was similar between the treatment groups at baseline, during treatment, and during the study. Most subjects in both treatment group had ECG findings that were not clinically significant. The incidence of clinically significant electrocardiogram parameters that were reported as AEs was similar in both treatment groups in the pooled Phase 3 studies. All events occurred only once and all were mild in intensity. None

were deemed related to study drug.

8.4.9. QT

Study REC-15-019
Study REC-15-019 was a Phase 1, randomized, double-blind, placebo-controlled evaluation of the effect of single ascending doses of N1539 on QTc intervals in healthy male and female subjects. The study enrolled a total of 56 subjects, with 48 subjects completing the study. Eligible subjects (18 to 45 years) were randomly assigned to a study arm, N1539 or placebo, during the treatment period. Enrollment was to occur in three gender balanced cohorts of 16 subjects (12 subjects randomized to N1539 and four subjects to placebo; eight males and eight females in each cohort). The planned cohorts included:

Table 51 Dosing Cohorts in Study REC-15-019

Cohort Number	N1539 Dose	Number of Subjects (Active:Placebo)
1	30 mg	16 (12:4)
2	120 mg	16 (12:4)
3	180 mg	16 (12:4)

Source: Applicant's submission (Summary of Clinical Safety, Page 107)

While administered as a single dose, exposures in this study at 120 mg and 180 mg doses of N1539 demonstrated a meaningful exposure multiple (>6 fold) compared to the 30 mg anticipated clinical dose, while maintaining a tolerability profile comparable to placebo. Results showed that therapeutic and supra-therapeutic doses of N1539 up to 180 mg did not affect cardiac repolarization in the form of prolonged QTcF interval, or in other measures including heart rate, PR, and QRS.

An Interdisciplinary Review Team for QT Studies Consultation provided a Concentration-QT Study Review, which concurs that N1539 does not prolong the QTc interval and the discussion as follows:

> *This conclusion is based on the concentration-QTc analysis and central tendency analysis of data collected in Study Rec- 15-019, which showed that 1) for the highest dose of 180 mg the upper bound of the 2-sided 90% confidence interval for ΔΔQTcF was less than 10 ms (Table 1 and Table 2), and 2) there was no statistically significant relationship between ΔQTcF and ANJESO concentrations. The study used placebo control, but there was no positive control*
> *(moxifloxacin) for assay sensitivity. The highest dose studied provides at least 2-fold exposure margin over anticipated highest clinically relevant exposure scenario with*

therapeutic dose and it is therefore appropriate to waive the requirement for inclusion of a positive control per ICH E14 Q&A (R3), Section 5.1.

Reviewer's comments
I agree that based on the dedicated QTc study, therapeutic and supra-therapeutic doses of N1539 up to 180 mg did not prolonged QTc interval as concurred by Agency's QT team. Please also see Clinical Pharmacology review for detail on this topic.

8.4.10. Immunogenicity

N/A

8.5. Analysis of Submission-Specific Safety Issues

Sponsor-defined Adverse event of special interest (AEOSI) included selected events related to concerns associated with NSAIDs, including bleeding, cardiovascular, hepatic, injection site reactions, renal, thrombotic, and wound healing events. Most individual AEOSI events occurred at similar rates between the N1539 30 mg group and the placebo group and most events were reported only once by a subject. AEOSI occurring in >1 subject in any treatment group are provided in the table below.

Table 52 Commonly Occurring (>1 Subject) AEOSI in Postoperative Studies

	Placebo N=517 n (%)	N1539 5-15 mg N=327 n (%)	N1539 30 mg N=910 n (%)	N1539 60 mg N=189 n (%)
Subjects with ≥1 AEOSI	67 (13.0)	41 (12.5)	131 (14.4)	27 (14.3)
Bleeding	11 (2.1)	30 (9.2)	33 (3.6)	19 (10.1)
Anemia	6 (1.2)	26 (8.0)	19 (2.1)	18 (9.5)
Anemia postoperative	1 (0.2)	0	4 (0.4)	0
Ecchymosis	0	0	3 (0.3)	0
Post procedural hematoma	0	2 (0.6)	0	1 (0.5)
Wound hematoma[a]	0	0	3 (0.3)	0
Cardiovascular	6 (1.2)	0	6 (0.7)	2 (1.1)
Electrocardiogram abnormal	0	0	0	2 (1.1)
Hypertension	4 (0.8)	0	5 (0.5)	0
Hepatic	28 (5.4)	8 (2.4)	42 (4.6)	5 (2.6)
Alanine aminotransferase increased	13 (2.5)	5 (1.5)	16 (1.8)	5 (2.6)
Aspartate aminotransferase increased	9 (1.7)	4 (1.2)	9 (1.0)	4 (2.1)
Blood alkaline phosphatase increased	6 (1.2)	2 (0.6)	3 (0.3)	1 (0.5)
Gamma-glutamyl transferase increased	8 (1.5)	0	21 (2.3)	0
Hepatic enzyme increased	5 (1.0)	0	1 (0.1)	0
Hyperbilirubinemia	1 (0.2)	3 (0.9)	0	0
Liver function test abnormal	3 (0.6)	0	5 (0.5)	0
Transaminases increased	0	0	2 (0.2)	0

Injection site reactions	6 (1.2)	0	12 (1.3)	0
Infusion site pain	0	0	2 (0.2)	0
Infusion site phlebitis	0	0	2 (0.2)	0
Infusion site pruritus	0	0	2 (0.2)	0
Infusion site thrombosis	0	0	2 (0.2)	0
Injection site erythema	2 (0.4)	0	0	0
Injection site pain	3 (0.6)	0	3 (0.3)	0
Renal	2 (0.4)	0	8 (0.9)	0
Acute kidney injury	0	0	3 (0.3)	0
Blood creatinine increased	2 (0.4)	0	1 (0.1)	0
Blood urea increased	1 (0.2)	0	2 (0.2)	0
Urine output decreased	0	0	2 (0.2)	0
Thrombotic	1 (0.2)	0	4 (0.4)	0
Post procedural pulmonary embolism	1 (0.2)	0	3 (0.3)	0
Wound healing	17 (3.3)	4 (1.2)	44 (4.8)	3 (1.6)
Cellulitis	0	0	7 (0.8)	1 (0.5)
Incision site cellulitis	3 (0.6)	0	1 (0.1)	0
Incision site erythema	2 (0.4)	0	3 (0.3)	0
Incision site infection	1 (0.2)	0	5 (0.5)	0
Incision site oedema	0	0	3 (0.3)	0
Incision site rash	0	0	2 (0.2)	0
Induration	0	0	3 (0.3)	0
Postoperative wound infection	1 (0.2)	0	2 (0.2)	1 (0.5)
Procedural complication	1 (0.2)	0	2 (0.2)	0
Seroma	3 (0.6)	0	3 (0.3)	0
Wound dehiscence	2 (0.4)	1 (0.3)	4 (0.4)	0
Wound haematoma[a]	0	0	3 (0.3)	0
Wound infection	2 (0.4)	3 (0.9)	0	0

Data source: ISS Table 11.2.1
a Subjects with wound haematoma are counted once in the 'bleeding' and once in the 'wound healing' categories.
Narratives for all subjects with an AEOSI can be found in ISS M5.3.5.3 Appendix A.

Source: Applicant's submission (Summary of Clinical Safety, Page 60)

There are several SAEs such as hemorrhage, acute renal failure, pulmonary embolism which are identified as adverse effect of special interest as discussed below.

8.5.1. Bleeding Events

NSAIDs reversibly inhibit platelet cyclooxygenase which can cause prolongation of bleeding time due to impairment of thromboxane-dependent platelet aggregation. In view of this class effect, the Applicant searched all seven postoperative studies. The bleeding events occurred in 2.1% of placebo subjects and 3.6% of N1539 30 mg subjects overall. The incidence of bleeding events in the N1539 5-15 mg group and the N1539 60 mg group was notably higher (9.2% and 10.1%, respectively) and was largely driven by Study N1539-04, where investigators were instructed to report any hemoglobin value that was less than 8.0 g/dL after surgery as an AE irrespective of clinical significance as discussed in section 8.4.5. Additionally, any hemoglobin value after surgery that was between 8.0 g/dL and 9.9 g/dL and had decreased by at least 0.5 g/dL from screening was also considered an AE and reported as such. Based on this protocol mandate,

anemia was reported in Study N1539-04 as shown in the table below. All reports of anemia during the double-blind and open-label phases of Study N1539-04 were mild or moderate in intensity.

Table 53 TEAE of Anemia Reported in Study N1539-04

	Placebo N=64	N1539 5-15 mg N=266	N1539 30 mg N=72	N1539 60 mg N=119
Anemia, n (%)	2 (3.1)	26 (9.8)	1 (1.4%)	18 (15.1)
Data source: Study N1539-04 CSR Table 14.3.2.1.2				

Source: Applicant's submission (Summary of Clinical Safety, Page 61)

Reviewer's comments:
Higher rates of bleeding events were observed in the study drug as compared to placebo that were associated with a dose dependent trend in the rates between 30 to 60 mg, which may due to the concomitant administration of prophylactic anticoagulant therapy post-surgery. The prophylactic anticoagulant therapy to prevent life threatening thromboembolic events is recommended for post-surgical patients particularly following major orthopedic procedures.

8.5.2. Anemia

Related to section above (8.5.1), the Applicant searched the safety database in the seven postoperative studies. Most events of anemia (i.e., anemia and anemia postoperative) were transient and mild or moderate in intensity. Most subjects were either prescribed medications such as ferrous sulfate to treat their anemia or received no treatment. Five subjects (one placebo and four N1539 30 mg) required blood transfusions. One placebo subject suffered a 'post procedural hemorrhage' that led to severe anemia. The four subjects in the N1539 30 mg group had hemoglobin and hematocrit values that were below the normal range prior to surgery and decreased further after surgery. These five subjects are discussed below.

Subject (b) (6): This was a 31-year-old Black female who received placebo in Study REC-15-015. At screening and prior randomization, her hemoglobin and hematocrit values were within the normal range. Following abdominoplasty surgery on (b) (6), she developed severe anemia after a post procedural hemorrhage. She received three units of packed red blood cells over a two-day period ((b) (6)). The event of anemia was considered by the investigator to be severe in intensity and possibly related to study drug.

Subject (b) (6): This was a 64-year-old white male who received N1539 30 mg in Study REC-15-017. At screening and prior randomization, his hemoglobin and hematocrit values were below the normal range. After spinal surgery, his hemoglobin and hematocrit values decreased further. He received one unit of pack red blood cells on (b) (6) and another unit on (b) (6)

(b) (6). This event of anemia was considered by the investigator to be mild in intensity and not related to study drug.

Subject (b) (6): This subject was a 41-year-old white female who received N1539 30 mg in Study REC-15-017. This subject had a medical history significant for uterine leiomyoma with heavy uterine bleeding since December of 2015. Prior to randomization, her hemoglobin and hematocrit values were below the normal range. After abdominal hysterectomy and salpingectomy on (b) (6). She received two units of packed red blood cells on (b) (6) 7, (b) (6). This event of anemia was considered by the investigator to be mild in intensity and not related to study drug. On (b) (6), she was diagnosed with a bowel perforation, which was considered a SAE.

Subject (b) (6): This was a 63-year-old black male who received four doses of N1539 30 mg in Study REC-15-017. This subject had a medical history significant for congestive heart failure, myocardial infarction, diabetes, and hypertension. Prior to randomization, his hemoglobin and hematocrit values were below the normal range. After a total knee replacement on (b) (6), his hemoglobin and hematocrit values decreased further. He received one unit of packed red blood cells on (b) (6) and two more units on (b) (6) 16. This event of anemia was considered by the investigator to be a SAE that was moderate in intensity, and not related to study drug.

Subject (b) (6): This was a 37-year-old white female who received N1539 30 mg in Study REC-15-017. This subject had medical history significant for anemia. Prior to randomization, her hemoglobin and hematocrit values were below the normal range. She underwent gynecological/genitourinary surgery on (b) (6). One day after her last dose of study drug her hemoglobin was within the low end of the normal range, while her hematocrit value remained below the normal range. She received two units of packed red blood cells on (b) (6) (b) (6) and on LSD+7 her hemoglobin and hematocrit values were within the normal range. This event of anemia was considered by the investigator to be moderate in intensity and not related to study drug.

Reviewer's comments:
Since higher rates of bleeding events were observed in the study drug as compared to placebo that were associated with a dose dependent trend in the rates between 30 to 60 mg, as discussed before, accordingly, a decrease in hematocrit were observed more pronounced in the study group.

8.5.3. Hematoma

Related to the section 8.5.1, the Applicant searched the safety database in the seven postoperative studies. Hematoma (i.e., post procedural hematoma or wound hematoma)

was reported for six subjects (0.7%) who received N1539 and no subjects who received placebo. These events were mild or moderate in severity and all events resolved.

As defined by protocol, the three subjects in Study REC-15-017 underwent wound evaluations approximately seven days after their last dose of study drug. Two of these subjects had a hematoma score of none and the third subject had a hematoma score of minimal and not clinically significant; thereby making it unlikely that these three events were drug related.

8.5.4. Hemorrhage

Related to section 8.5.1, the Applicant searched the safety database in the seven postoperative studies. The hemorrhagic events (i.e., incision site hemorrhage; post procedural hemorrhage; rectal hemorrhage; and vaginal hemorrhage) were reported for three (0.6%) subjects who received placebo, three who received N1539 30 mg (0.3%), and one who received N1539 60 mg (0.3%). Three of these events of were SAEs.

- Subject (b) (6) who received N1539 5 mg in Study N1539-04 had mild vaginal spotting and was admitted to the hospital for further examination. She was discharged with the assessment that this type and amount of vaginal spotting is often seen after a vaginal hysterectomy and was not clinically significant.
- Subject (b) (6) who received N1539 30 mg in Study REC-15-015 required surgical intervention for ligation of an active vessel bleed and received a total of six units of packed red cells.
- Subject (b) (6) who received placebo in Study REC-15-015 required surgical intervention evacuation of a hematoma and clipping of an active vessel bleed. The subject received a total of three units of packed red cells.

8.5.5. Ecchymosis

Three subjects (0.3%) in the N1539 30 mg group and no subjects in the placebo group reported events of ecchymosis. All events were mild and none required additional treatment. Subject (b) (6) underwent bunionectomy in Study REC-15-014 and reported 'ecchymosis right hallux' on (b) (6), six days after her last dose of N1539 30 mg ((b) (6)). She received a total of two doses. Two events occurred in two subjects who underwent abdominal surgery in Study REC-15-017:

- Subject (b) (6) had 'ecchymosis' that started on (b) (6), which was the day of surgery, and resolved on (b) (6). He received a total of two doses.
- Subject (b) (6) had 'excessive ecchymosis' that started on (b) (6), two days after his last dose, and resolved on (b) (6). He received a total of three doses.

8.5.6. Cardiovascular Events

NSAIDs has a boxed warning regarding an increase in risk for serious cardiovascular thrombotic events, myocardial infarction and stroke associated with the use of these drugs. In view of this, the Applicant conducted an analysis of major adverse cardiac events contained in the safety database. In the seven postoperative studies, cardiovascular events occurred in 1.2% of placebo subjects, 0.7% of N1539 30 mg subjects, 1.1% of N1539 60 mg subjects overall. No subject in the N1539 5-15 mg group had cardiovascular events.

Hypertension, which was reported at similar rates in the placebo (0.8%) and N1539 30 mg (0.5%) was the most commonly reported cardiovascular event. All but one of these subjects had a medical history significant for hypertension.

There were four reports of electrocardiogram abnormalities that occurred randomly across the treatment groups. Everyone were considered mild and none required treatment.

One subject in the placebo group had 'myocardial ischemia secondary to coronary artery disease' that prolonged his hospitalization and was considered an SAE.

8.5.7. Injection Site Reactions

A search of the safety database for toxicity related to N1539s route of administration (i.e., IV bolus) was conducted by the Applicant. In the seven postoperative studies, injection site reactions occurred at similar rates between the placebo (1.2%) and the N1539 30 mg (1.3%) groups. No subjects in the N1539 5-15 mg or N1539 60 mg groups had injection site reactions.

The most commonly reported event associated with the injection site was infusion/injection site pain, which occurred in 0.6% of placebo subjects (3/517) and 0.5% of N1539 30 mg subjects (5/910). All events associated with the injection site were mild or moderate in intensity and all resolved.

Phlebitis (injection site phlebitis, vessel puncture site phlebitis, and infusion site phlebitis) was reported at similar rates in the placebo group (0.2%, 1/517) and the N1539 30 mg group (0.3%, 3/910). All events of phlebitis were associated with the injection site and all were mild in intensity and resolved without treatment.

Other events associated with the injection site including infusion site thrombosis, injection site erythema, injection site induration, infusion site pruritus, and injection site infection were reported at similar rates in the placebo group (0.8%, 4/517) and the N1539 30 mg group (0.4%, 4/910). These events were mild in intensity except for one report of infusion site thrombosis in one N1539 30 mg subject that was moderate. All events resolved.

8.5.8. Hepatic Events

Since class labeling for NSAIDs includes a warning regarding hepatic toxicity, the Applicant searched the safety database for hepatobiliary events in order to determine if there was an increase in risk for hepatic toxicity to occur in post-surgical patients treated with N1539. In the seven postoperative studies, hepatic events occurred in 5.4% of placebo subjects, 4.6% of N1539 30 mg subjects, 2.4% of N1539 5-15 mg subjects and 2.6% of N1539 60 mg subjects. Most individual hepatic events occurred at similar or lower rates in the N1539 30 mg group compared to the placebo group. Two events (i.e., transaminases increased and gamma-glutamyl transferase increased) were reported at higher rates in the N1539 30 group compared to the placebo group as follows:

'Transaminases increased' was reported in two subjects in the N1539 30 mg (0.2%) group and no subjects in the placebo group. These events were transient and nonspecific and not considered clinically meaningful.

'Gamma-glutamyl transferase (GGT) increased' was reported at a higher rate in the N1539 30 mg group compared to the placebo group (2.3% versus 1.5%). When multiple liver function abnormalities were identified in a subject's clinical labs, a general AE of 'liver function test abnormal' or 'hepatic enzymes increased' was recorded. When liver function test values were examined for the eight placebo subjects and the six N1539 30 mg subjects who had an AEOSI of 'hepatic enzyme increased' or 'liver function test abnormal', GGT values were found to be increased above the normal range for seven of the eight placebo subjects and all six of the N1539 30 mg subjects on the same day that the events 'hepatic enzyme increased' and 'liver function test abnormal' were recorded. Thus, across the seven postoperative studies, 2.9% (15/517) placebo subjects and 3.0% (27/910) N1539 30 mg subjects had elevated GGT values at some point during the study.

All hepatic events were mild or moderate in intensity except for 'liver function test abnormal' in one placebo subject and two N1539 30 mg subjects that were reported as severe events.

Reviewer's comments:
The three cases of LFTs abnormality have been described and discussed in section Laboratory Findings.

8.5.9. Renal Events

Renal toxicity associated with NSAIDs occurs via a reduction in prostaglandin synthesis that can result in a hemodynamically-mediated decrease in function that may result in acute renal failure in patients with underlying risk factors such as volume depletion. The induction of anesthesia is also considered to be a low-to-moderate risk factor for NSAID induced renal

toxicity. In view of this, the Applicant searched the safety database for renal-related events in order to determine if there was an increase in risk for renal toxicity to occur in post-surgical patients treated with the N1539. In the seven postoperative studies, the incidence of renal events was higher in the N1539 group (0.9%) than the placebo group (0.4%). No subjects in the N1539 5-15 mg group or the N1539 60 mg group had a renal event. All renal events were mild in intensity except for two reports of acute renal injury (i.e., acute renal failure) that were considered moderate. These two subjects are discussed below.

Subject (b) (6): This subject was a 63-year-old black male who received four doses of N1539 30 mg in Study REC-15-017. This subject had a medical history significant for congestive heart failure, myocardial infarction, diabetes, and hypertension. Prior to randomization, his creatinine value was elevated above the normal range, which was outside the protocol permitted range and a major protocol violation, and his urine was 2+ for protein. He received IV furosemide 10 mg on (b) (6) for fluid volume overload. This event of acute renal failure was considered by the investigator to be a SAE that was moderate in intensity and not related to study drug. This subject also had an event of anemia as described before.

Subject 1 (b) (6) in the N1539 30 mg group in Study REC-15-017 had SAEs of small bowel obstruction, pulmonary embolism, respiratory distress for which he was on mechanical ventilation, and acute renal failure. He was hospitalized in the intensive care unit for more than two months related to multiple medical complications requiring repeated surgical procedures, prolonged antibiotic therapy, and cardiorespiratory support.

Subject (b) (6) in the N1539 30 mg group in Study REC-15-017 had an acute kidney injury that was mild in intensity and resolved the next day without treatment.

Reviewer's comment:
As a NSAIDs given IV in postoperative subjects, not surprisingly, overall renal events were higher in the study drug 30 mg (0.9%) that placebo (0.4%). There are two case of acute renal injury, which were not attributed to the study drug by the Investigator. It must be noted one of the two case was a protocol violation as renal function was outside the accepted range. There is also a free-standing discussion on this topic in 8.7.

8.5.10. Thrombotic Events

The Applicant searched safety database in the seven postoperative studies, the incidence of thrombotic events was similar between the placebo (0.2%) and N1539 30 mg (0.4%) groups. No subjects in the N1539 5-15 mg group or the N1539 60 mg group had thrombotic events.

All events were mild or moderate in intensity except for 'post procedural pulmonary embolism' that was reported as severe in Subject (b) (6) who received N1539 30 mg in Study REC-15-017.

These events were SAEs except for the event of deep vein thrombosis in Subject (b) (6)0 in Study REC-17-017.

8.5.11. Gastrointestinal Events

NSAIDs class labeling includes warning on the occurrence of serous and potentially fatal GI reaction. While the Applicant did not provide a free-standing search on this topic, no SAEs attributed to N1539, and the overall GI AEs were similar between N1539 and placebo group as reviewed in 8.4.2.

8.5.12. Wound Healing

Investigator Satisfaction with Surgical Wound Healing
In the Phase 3 studies, investigators provided a wound healing satisfaction score using an 11-point numeric rating scale in which a score of 0 was 'completely unsatisfied' and a score of 10 was 'completely satisfied'.

As shown in the table below, investigator satisfaction assessments were similar between N1539 30 mg and placebo in the pooled Phase 3 studies at each postoperative evaluation. Mean assessment scores of 9.4 out of 10 suggest that investigators were consistently satisfied with overall wound healing.

Table 54 Investigator Satisfaction with Wound Healing in Postoperative Phase 3 Studies

Time Point	Placebo N=393	N1539 30 mg N=748
Satisfaction score (Scale: 0-10)		
Hour 48[a]		
n	202	202
Mean (SD)	9.4 (0.84)	9.4 (0.94)
Median	10.0	10.0
Min, Max	5, 10	5, 10
LSD+1		
n	181	531
Mean (SD)	9.4 (0.97)	9.5 (0.88)
Median	10.0	10.0
Min, Max	5, 10	0, 10
LSD+7		
n	381	726
Mean (SD)	9.5 (0.96)	9.4 (1.12)
Median	10.0	10.0
Min, Max	2, 10	0, 10

LSD+28[a]		
n	201	198
Mean (SD)	9.6 (0.88)	9.7 (0.75)
Median	10.0	10.0
Min, Max	3, 10	5, 10

LSD=last dose day
Data source: ISS Table 18.3.1
a Studies REC-15-015 and REC-15-016 only.

Source: Applicant's submission (Summary of Clinical Safety, Page 110)

Clinically Significant Wound Assessments

Investigators in the Phase 3 studies rated the symptoms and severity of erythema, drainage, edema, induration, and hematoma using a 5-point Likert scale as described in the table below. Wound assessment parameters rated with a score greater than 0 were required to be assessed by the investigator for clinical significance. If considered clinically significant, an AE was recorded.

Most subjects in N1539 30 mg group (56.1%, 420/748) and the placebo group (60.1%, 236/393) had wound finding events that were not considered clinically significant by the investigator.

Among individual wound parameter evaluations (erythema, drainage, edema, induration, hematoma), the distribution of assessment ratings was generally similar between N1539 30 mg and placebo.

Table 55 Wound Healing Assessment in Postoperative Phase 3 Studies

Parameter	**Placebo N=393 n (%)**	**N1539 30 mg N=748 n (%)**
Abnormal wound healing, not clinically significant:		
Any time during the study	236 (60.1)	420 (56.1)
Abnormal wound healing, clinically significant:		
Any time during the study	9 (2.3)	16 (2.1)
Erythema		
LSD+7		
0=none	281 (73.2)	554 (76.0)
1=very slight	82 (21.4)	143 (19.6)
2=slight	17 (4.4)	20 (2.7)
3=moderate	4 (1.0)	12 (1.6)
4=severe	0	0
LSD+28[a]		
0=none	177 (87.6)	174 (87.4)
1=very slight	21 (10.4)	21 (10.6)
2=slight	3 (1.5)	4 (2.0)
3=moderate	1 (0.5)	0
4=severe	0	0

Drainage		
LSD+7		
0=none	343 (89.3)	664 (91.1)
1=serous	24 (6.3)	28 (3.8)
2=serosanguinous	13 (3.4)	28 (3.8)
3=bloody	3 (0.8)	7 (1.0)
4=purulent	1 (0.3)	2 (0.3)
LSD+28[a]		
0=none	196 (97.0)	194 (97.5)
1=serous	4 (2.0)	4 (2.0)
2=serosanguinous	0	1 (0.5)
3=bloody	2 (1.0)	0
4=purulent	0	0
Edema		
LSD+7		
0=none	212 (55.2)	457 (62.7)
1=very slight	124 (32.3)	184 (25.2)
2=slight	37 (9.6)	65 (8.9)
3=moderate	9 (2.3)	23 (3.2)
4=severe	2 (0.5)	0
LSD+28[a]		
0=none	145 (71.8)	147 (73.9)
1=very slight	42 (20.8)	38 (19.1)
2=slight	12 (5.9)	12 (6.0)
3=moderate	3 (1.5)	2 (1.0)
4=severe	0	0

Parameter	**Placebo N=393 n (%)**	**N1539 30 mg N=748 n (%)**
Induration, n (%)		
LSD+7		
0=none	293 (76.3)	588 (80.7)
1=minimal	80 (20.8)	114 (15.6)
2=mild	8 (2.1)	14 (1.9)
3=moderat	3 (0.8)	13 (1.8)
e 4=severe	0	0
LSD+28[a]		
0=none	169 (83.7)	172 (86.4)
1=minimal	28 (13.9)	24 (12.1)
2=mild	4 (2.0)	1 (0.5)
3=moderat	1 (0.5)	2 (1.0)

Hematoma, n (%)		
LSD+7		
0=none	364 (94.8)	679 (93.1)
1=minimal	16 (4.2)	36 (4.9)
2=mild	3 (0.8)	11 (1.5)
3=moderat	1 (0.3)	3 (0.4)
e 4=severe	0	0
LSD+28[a]		
0=none	200 (99.0)	198 (99.5)
1=minimal	1 (0.5)	1 (0.5)
2=mild	1 (0.5)	0
3=moderat	0	0

LSD=last dose day
Data source: ISS Table 18.3.1
a Studies REC-15-015 and REC-15-016 only.

Source: Applicant's submission (Summary of Clinical Safety, Page 11-112)

Reviewer's comment:
Overall, incidence was similar between N1539 30 mg (2.1%, 16/748) and placebo (2.3%, 9/393). A total of 25 subjects had clinically significant observations at some time during the study. Clinically significant wound healing event and other relevant TEAEs are presented by study, treatment group, and subject number for these 25 subjects in were summarized by the Sponsor, but not reproduced in the review.

8.5.13. Opioid Consumption

This topic has been discussed in section 7.2.2. Briefly, analysis was performed on the collected concomitant medications administered during the REC-15-017 study to evaluate the opioid requirements of subjects in the study due to the potential correlation of opioid use with certain AEs and adverse outcomes. The dose from each identified opioid medication was converted to IV Morphine Equivalent Dose (IVMED) in mg. Mean opioid consumption in the overall population was numerically lower in the N1539 30 mg group compared with placebo at all evaluated intervals as in the section 7.2.2. The subjects in the N1539 30 mg group seem to have less nausea, vomiting, pruritus, and dizziness numerically compared to subjects in the placebo group as the Figure below.

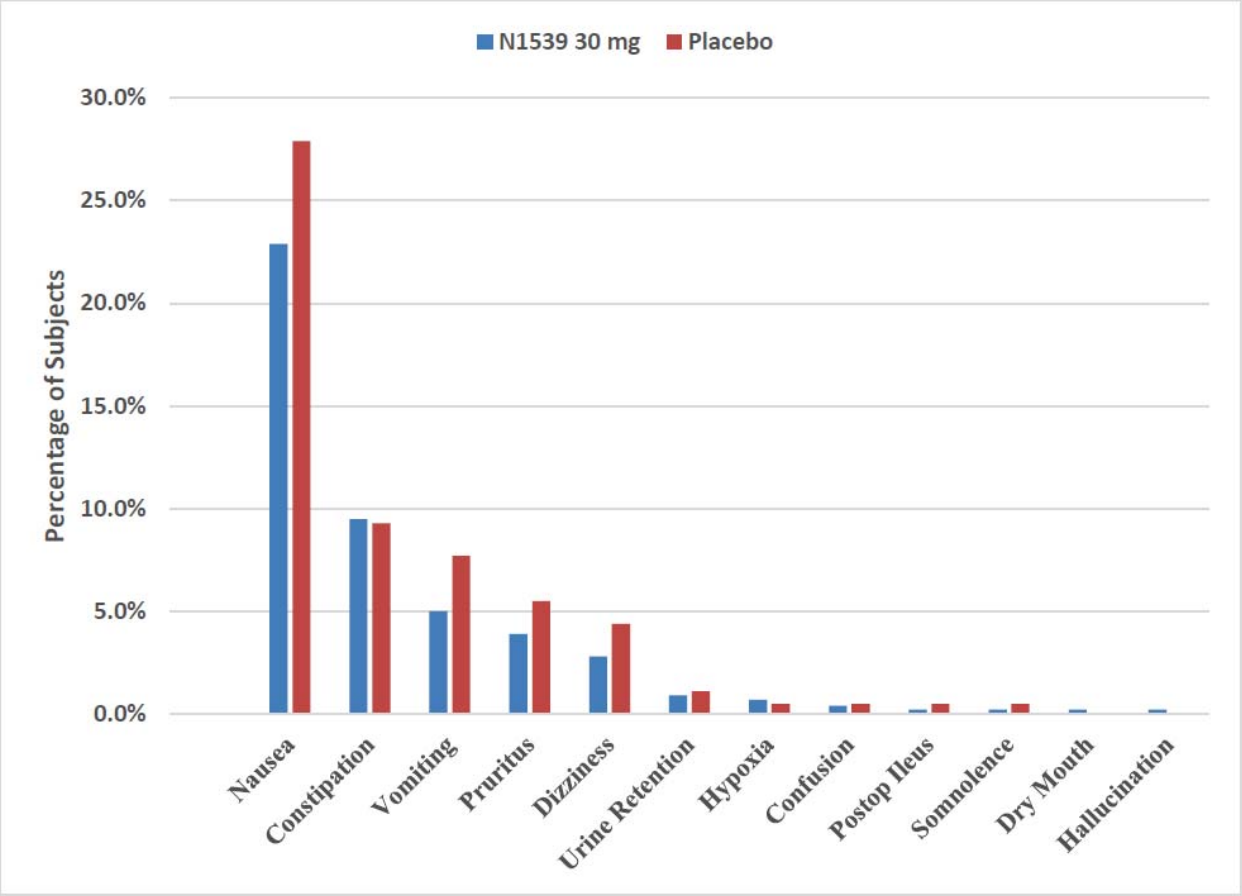


Figure 17 TEAEs Commonly Associated with Opioid Use in Study REC-15-017

Source: Applicant's submission (Summary of Clinical Safety, Page 15)

Reviewer's comments: Study REC-15-017 is a safety study, which opioid consumption was descriptively collected. The Study suggests that mean opioid consumption in the overall population was mildly reduced in the N1539 30 mg group compared with placebo. The study also suggests that TEAEs commonly associated with opioid were also mild decreased in the N1539 30 mg group compared to subjects in the placebo group. (b) (6)

8.6. Safety Analyses by Demographic Subgroups

Most (90.2%, 1752/1943) subjects in the postoperative studies were <65 years of age. The most commonly occurring TEAEs in the <65-year-old group was like that observed in the postoperative studies overall. There were too few subjects who were ≥65 years of age in these studies to make a comprehensive comparison between age groups. However, TEAEs within

each age group generally occurred at similar or lower rates in the N1539 30 mg group compared to the placebo group. Overall, incidences of TEAEs seem to be similar by age group.

There were too few men who received N1539 5-15 mg or N1539 60 mg to make a comparison between men and women across these treatment groups. In the comparison of genders who received N1539 30 mg, men tended to report more constipation, while women tended to report more nausea and vomiting. TEAEs within each sex group generally occurred at similar rates in the N1539 30 mg group compared to the placebo group. Overall, incidences of TEAEs seem to be similar by sex group.

There were too few non-white subjects who received N1539 5-15 mg or N1539 60 mg to make a meaningful comparison between white and non-white subjects across these treatment groups. TEAEs within each race group generally occurred at similar rates in the N1539 30 mg group compared to the placebo group. Overall, incidences of TEAEs seem to be similar by race group.

8.7. Specific Safety Studies/Clinical Trials

Renal Impairment

TEAEs within each renal function group (Subjects aged 65 to 80 years with impaired renal function (GFR 60-89 mL/min/1.73 m2) vs subjects aged 18 to 55 years with normal renal function (GFR ≥ 90 mL/min/1.73 m2) generally occurred at similar rates in the N1539 30 mg group compared to the placebo group. Except for constipation which occurred at a higher rate among subjects in the N1539 30 mg group with renal impairment compared to subjects in the N1539 30 mg group with normal renal function, there were no notable differences in TEAEs between subjects with impaired renal function and those with normal renal function who received N1539 30 mg in the table below.

Table 56 TEAEs (Occurring in ≥3% of Subjects) Subset by Renal Function

	Normal Renal Function				Impaired Renal Function			
	Placebo N=482	**N1539 5-15 mg N=327**	**N1539 30 mg N=815**	**N1539 60 mg N=188**	**Placebo N=35**	**N1539 5-15 mg N=0**	**N1539 30 mg N=95**	**N1539 60 mg N=1**
Subjects with ≥1 TEAE, n (%)	269 (55.8)	121 (37.0)	436 (53.5)	58 (30.9)	27 (77.1)	0	61 (64.2)	1 (100.0)
N of TEAEs	590	198	945	94	76	0	133	5
TEAEs, n (%)								
Nausea	121 (25.1)	14 (4.3)	171 (21.0)	10 (5.3)	10 (28.6)	0	18 (18.9)	1 (100.0)
Headache	53 (11.0)	5 (1.5)	48 (5.9)	2 (1.1)	1 (2.9)	0	3 (3.2)	1 (100.0)
Vomiting	35 (7.3)	9 (2.8)	37 (4.5)	3 (1.6)	3 (8.6)	0	5 (5.3)	0
Constipation	21 (4.4)	8 (2.4)	45 (5.5)	2 (1.1)	4 (11.4)	0	16 (16.8)	0
Anaemia	4 (0.8)	26 (8.0)	14 (1.7)	18 (9.6)	2 (5.7)	0	5 (5.3)	0
Dizziness	24 (5.0)	0	31 (3.8)	2 (1.1)	1 (2.9)	0	1 (1.1)	0
Pruritus	13 (2.7)	0	27 (3.3)	2 (1.1)	2 (5.7)	0	4 (4.2)	0
Insomnia	8 (1.7)	14 (4.3)	11 (1.3)	6 (3.2)	3 (8.6)	0	2 (2.1)	0

Ketonuria[a]	5 (1.0)	23 (7.0)	6 (0.7)	10 (5.3)	0	0	0	0

Data source: ISS Table 5.2.6
Renal impairment = subjects who were > 65 years with a GFR of 60-89 mL/min/1.73 m^2, as calculated using the MDRD equation.
a Ketonuria was reported by one site in Study N1539-04 where NSAIDs were not typically the first line of treatment for postoperative pain management (refer to Section 31.4.2for details).

Source: Applicant's submission (Summary of Clinical Safety, Page 135)

To further investigate the potential risks of N1539 in subjects with impaired renal function, a Phase 1 study was conducted to evaluate the pharmacokinetics and safety of N1539 30 mg administered as an IV bolus over 15-30 seconds in older subjects with impaired renal function compared to healthy controls (Study REC-15-018). Study REC-15-018 was a Phase 1, single-center, open-label evaluation of the pharmacokinetics and safety, of single doses of N1539 in older subjects with impaired renal function compared with healthy controls. The study enrolled 12 subjects. Eligible subjects were assigned to a study cohort based on their age and renal function. Renal function was to be assessed using the MDRD equation for estimation of the GFR. Enrolled subjects were matched between cohorts per gender and BMI (±20%). Subjects were assigned to cohorts as follows:

- Cohort 1 (n=6; 3 males, 3 females): subjects aged 65 to 80 years with impaired renal function (GFR 60-89 mL/min/1.73 m^2)
- Cohort 2 (n=6; 3 males, 3 females): subjects aged 18 to 55 years with normal renal function (GFR ≥ 90 mL/min/1.73 m^2)

Findings from this study showed that meloxicam plasma concentrations and PK parameters were generally similar between subject cohorts. Please see Clinical Pharmacology review for detail.

There was no incidence of death, SAEs, or discontinuations due to an AE during the study. The incidence of AEs is 33.3% of subjects with any event with no subject experiencing more than one event. AEs were generally mild or moderate in intensity, and consistent with the AE profile of N1539/meloxicam in previous studies. There were no clinically significant vital sign or ECG findings, and only one clinically significant laboratory assessment change.

Reviewer's comments:
I agree that overall, the incidences of TEAEs seem to be similar in subjects with impaired renal function who were treated with N1539 30 mg compared with placebo or subjects with normal renal function. Please also see Clinical Pharmacology review.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

See Pharmacology and Toxicology review.

8.8.2. Human Reproduction and Pregnancy

There have been no adequate and well-controlled studies of study drug in pregnant women.

8.8.3. Pediatrics and Assessment of Effects on Growth

No event of pediatric exposure was reported in the submission. Study drug was not studied in subjects younger than 18 years of age.

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

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

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

This drug is not currently marketed.

8.9.2. Expectations on Safety in the Postmarket Setting

The safety in the postmarket setting is expected to be similar to that of an NSAID, particularly one that is administered IV over a short duration.

8.9.3. Additional Safety Issues From Other Disciplines

None

8.10. Integrated Assessment of Safety

Safety Summary
The clinical development program included 11 studies, which includes 91 healthy subjects enrolled in the four Phase 1 studies and 1426 post-operative subjects in seven Phase 2 and 3 studies exposed to at least one dose of study drug. The safety database has 1045 subjects who received two or more doses of study drug including the 748 who received two or more doses at the proposed to-be-marketed dose of 30 mg of the study drug. The most informative data (748 subjects received study, and 391 receiving placebo) came from the two efficacy studies (REC-15-015, REC-15-016), and a double-blind safety study (REC-15-017).

There is no death or SAE in the healthy subjects. There is one death in the placebo group, none in the study drug group in the post-operative population. The SAEs happened to 15 subjects (15/517, 2.9%) in the placebo group, five subjects (5/327, 1.5%) in the N1539 5 to 15 mg group,

and 15 (15/910, 1.6%) in the N1539 30 mg group, none in the 60-mg group. In the post-operative population, the most commonly reported TEAEs were nausea, headache, vomiting, and dizziness.

Review of adverse events of special interest did not identify any potential safety issues related to the IV route of administration of the study drug. Higher rates of bleeding events were observed in the study drug as compared to placebo that were associated with a dose dependent trend in the rates between 30 to 60 mg, which may due to the concomitant administration of prophylactic anticoagulant therapy post-surgery. Accordingly, a decrease in hematocrit were observed. Overall renal events were higher in the study drug 30 mg (0.9%) that placebo (0.4%). There are two case of acute renal injury which are moderate in the active treatment arm. A similar rates of wound healing events were observed in the study drug as compared to placebo

The safety database contained an acceptable number of subjects (95) with mild renal impairment treated with the study drug. Overall, the drug's safety profile except constipation was similar in this subpopulation to what was observed in nonimpaired patients.

In conclusion, the overall safety profile of N1539 is consistent with what has been observed in patients treated with NSAIDs as a class, particularly one that is administered IV over a short duration.

9. Advisory Committee Meeting and Other External Consultations

Advisory Committee meeting is not expected for this product.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

While the labeling review is ongoing, there are two comments could be made:

Applicant claims (b) (6) in section 14, the Clinical Studies, the requirements (b) (6) has been discussed throughout the review and will be conveyed to the Applicant.

There are references to (b) (6) other listed drugs in the annotated draft labeling: (b) (6) of the annotated draft labeling. If referring (b) (6) were intended, then, the Applicant will be required to provide a patent certification as well as scientific bridges.

10.2. Nonprescription Drug Labeling

N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

N/A

12. Postmarketing Requirements and Commitments

In order to comply with the Pediatric Research Equity Act (PREA), the Applicant submitted a pediatric study plan. Deferral of pediatric studies was requested because the drug is ready for approval for use in adults before the pediatric studies are complete. The Agency and the Applicant agreed on the Pediatric Study Plan on June 29, 2016. A summary of planned clinical studies is presented in the outline and the tables below:

Table 57 Planned Pediatric Studies

Planned Pediatric Clinical Studies			
Age Group	Type of Study	Comments	Deferral Request Planned for the study (Y/N)
2 to <17 years	Safety and PK	(b) (4)	Y
1 to <2 years	Safety, Efficacy, and PK		Y
Birth to <1 year	Waiver requested		N

Source: Agreed upon iPSP

A partial waiver is granted for the birth to < 1 year pediatric age group by PeRC during iPSP, which is based on that there is evidence strongly suggesting that the drug or biological product would be unsafe in that age group. The agreed upon iPSP was reviewed further by the Agency's Pediatric Review Committee (PeRC) on April 11, which provided the following additional recommendations to be conveyed to the Applicant at the CR letter:

- Provide a timeline for juvenile toxicology study
- Start study in birth to < 1 year pediatric age study immediately after completing the juvenile toxicology study without waiting for the completing study in the 2 to <17 years age group

13. Appendices

13.1. References

N/A

13.2. Financial Disclosure

The Applicant's submission included the completed "Certification: Financial Interests and Arrangements of Clinical Investigators" form (Form FDA 3455). The Applicant indicated that the investigators at each site are certified as having no Financial Arrangement as defined in 21 CFR 54.2.

The table below are lists of clinical investigators in three Phase 3 studies.

Table 58 List of Investigators for Study REC-15-015

Site ID	Name Investigator	Address	Phone Number
01	Paulette Saddler, MD	Lotus Clinical Research, LLC 100 W. California Blvd #25 Pasadena, CA USA 91105	626-397-2390
01	Sonia Singla, DO	Lotus Clinical Research, LLC 100 W. California Blvd #25 Pasadena, CA USA 91105	626-397-2390
02	Harold Minkowitz, MD	Research Concepts GP LLC 5108 Valerie Street Bellaire, TX USA 77401	713-480-3028
03	David Leiman, MD	Hermann Drive Surgical Hospital 2001 Hermann Drive Houston, TX USA 77004	713-894-4840
04	Barr Loring Baynton, MD	Endeavor Clinical Trials, P.A. 8042 Wurzbach Road, Suite 420 San Antonio, TX USA 78229	210-949-0807

Source: Applicant's submission (Administrative Information)

Table 59 List of Investigators for Study REC-15-016

Site ID	Principal Investigator	Address	Phone Number

01	Fardin Hakakian, DPM	Lotus Clinical Research, LLC 100 W. California Blvd #25 Pasadena, CA USA 91105	626-397-3410
02	Ira Gottlieb, DPM	Chesapeake Research Group, LLC 8028 Ritchie Highway Suites 100 – 106 Pasadena, Maryland USA 21122	410-761-0118
03	Richard A. Pollak, DPM	Endeavor Clinical Trials, P.A. 8042 Wurzbach Road, Suite 420 San Antonio, TX USA 78229	210-949-0807
04	John C. Zimmerman, DPM	9300 Stockdale Highway Suite 400 Bakersfield, CA USA 93311	661-663-3096

Source: Applicant's submission (Administrative Information)

Table 60 List of Investigators for Study REC-15-017

Site ID	Principal Investigator	Address	Phone Number
01	Timothy I. Melson, MD	Shoals Medical Trials Inc. 1300 S. Montgomery Ave. Sheffield, AL 35660	256-386-4001
04	Harold Sydney Minkowitz, MD	First Surgical Hospital 4801 Bissonnet Street Bellaire, TX 77401	713-480-3028
05	David G. Leiman, MD	Hermann Drive Surgical Hospital 2001 Hermann Dr. Houston, TX 77004	713-367-8548
06	Sander R. Binderow, MD	Atlanta Colon and Rectal Surgery 5667 Peachtree Dunwoody Road Suite 330 Atlanta, GA 30342	404-252-5669
07	Peter Kroll, MD	Comprehensive Research Institute, LLC 353 New Shackle Island Road Suite B-122 Hendersonville, TN 37075	615-824-2014
09	W. Andrew Tyndall, MD, PhD	University Orthopedics Center 3000 Fairway Drive Altoona, PA 16602	814-949-4050

10	Sabry Ayad, MD	Cleveland Clinic Fairview Hospital 18101 Lorain Ave. Cleveland, OH 44111	216-476-7052
11	Sergio D. Bergese, MD	The Ohio State University, Wexner Medical Center N-411 Doan Hall 410 West 10th Avenue Columbus, OH 43210	614-293-3559
13	John C. Zimmerman, DPM	Trovare Clinical Research, Inc. 9300 Stockdale Highway, Suite 400 Bakersfield, CA 93311	661-663-3096
15	Keith A. Candiotti, MD	University of Miami Jackson Memorial Hospital 1611 NW 12th Avenue Miami, FL 33136	305-585-7677
16	Nicholas Bonfillio, MD	Great Falls Clinic Specialty Center 3000 15th Ave. South Great Falls, Montana 59405	406-771-3282

Site ID	**Principal Investigator**	**Address**	**Phone Number**
17	Jorge E. Marcet, MD	Tampa General Hospital 1 Tampa General Circle Suite F-145 Tampa, FL 33606	813-844-4545
18	Henry A. Frazer, PharmD	Drug Research and Analysis Corp. 1758 Park Place, Suite 200 Montgomery, AL 36106	334-265-2700
19	Christopher R. Duggar, MD	Drug Research and Analysis Corp. 1758 Park Place, Suite 200 Montgomery, AL 36106	334-265-2700
20	David L. Boyer, MD	Shoals Clinical Research Associates 205 Marengo Street Florence, AL 35630	256-768-8021
21	Adam C. Young, MD	Rush University Medical Center 1653 W. Congress Parkway Jelke 1489 Chicago, IL 60612	312-942-0040

22	Philippe Richebe, MD, PhD	Maisonneuve Rosemont Hospital 5415 Boulevard de l'Assomption Montreal, Quebec H1T 2M4 Canada	514-252-3426
23	Richard Brull, MD	Toronto Western Hospital 399 Bathurst Street Suite 2MC405 Toronto, Ontario M5T 2S8 Canada	416-603-5118
24	Richard D. Berkowitz, MD	Phoenix Clinical Research, LLC 7171 N. University Drive Suite 100 Tamarac, FL 33321	754-205-5001
25	Joseph S. Gimbel, MD	Arizona Research Center 2525 West Greenway Road Suite 114 Phoenix, Arizona 85023	602-863-6363
27	Kipling P. Sharpe, MD	Orthopaedic Specialists of North America, PLLC – DBA – OrthoArizona 1760 East Pecos Road, #207 Gilbert, AZ 85295	480-889-1211
Site ID	**Principal Investigator**	**Address**	**Phone Number**
29	Vishal Uppal, MD	Department of Anesthesia 5th Floor, Halifax Infirmary Site Room 5452, 1796 Summer Street Halifax, NS B3H 3A7 Canada	902-473-2331
30	Anthony R. Houston, MD	Peninsula Specialist Centre Suite 11 Corner George & Florence Streets Kippa-Ring, QLD 4021 Australia	+61738895577
32	Mary Jane Fitzpatrick, MD	Sports Medicine Professionals 21 Erin Street Richmond, VIC 3121 Australia	+61394296444
33	John S. A. Currie, MD	Clinical Trials New Zealand Ltd 32 Kahikatea Drive Hamilton 3206 New Zealand	+6478430105

35	Timothy G. Short, MD	Auckand City Hospital Dept. Anesthesia & Perioperative Medicine, Level 8 Support Building Park Rd. Grafton Auckland 1023 New Zealand	+6493074949
36	Simon J. Carson, MD	Southern Clinical Trials 3 Strickland Street Christchurch 8024 New Zealand	+6433371979
37	Michael Von Papen, MD	Gold Coast Private Hospital 14 Hill Street Southport, QLD 4215 Australia	+61755631360
38	Ross Crawford, MD	Holy Spirit Northside Private Hospital 627 Rode Road Chermside, QLD 4032 Australia	+61731394481
40	Jaideep Mehta, MD, MBA	The University of Texas (UT Health) 6431 Fannin St., MSB 5.020 Houston, TX 77030	713-500-6200
Site ID	**Principal Investigator**	**Address**	**Phone Number**
41	Stephen F. Richardson, MD (formerly Devin Bradley Despain, D.O.)	Jean Brown Research 1045 E 3900 South, Suite 100 Salt Lake City, UT 84124	801-261-2000
42	Peter J. Winkle, MD, FACP, FACG, CP	Anaheim Clinical Trials, LLC 1085 N. Harbor Blvd. Anaheim, CA 92801	714-774-7777
43	John A. C. Murdoch, MD	Kingston General Hospital 76 Stuart Street, Victory 2 Kingston, Ontario k7L 2V7 Canada	613-548-7827
44	Barr Loring Baynton, MD	Endeavor Clinical Trials, PA 8042 Wurzbach Suite 420 San Antonio, TX 78258	210-949-0807
46	Shanker Lakshman, MD	Lotus Clinical Research, LLC 100 W. California Blvd., Unit 25 Pasadena, CA 91105	626-568-8727

Source: Applicant's submission (Administrative Information)

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 56		
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)

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