CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Supplement #:	210-583
Drug Name:	ANJESO (meloxicam) injection, 30 mg/ml
Indication(s):	Management of moderate to severe pain
Applicant:	Recro Pharma Inc.
Date(s):	Letter date: July 26, 2017 PDUFA date: May 26, 2018
Review Priority:	Standard
Biometrics Division:	II
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Keywords:	NDA review, clinical studies

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1. EXECUTIVE SUMMARY

Meloxicam has been approved since 2000 for the relief of the signs and symptoms associated with osteoarthritis, rheumatoid arthritis and juvenile rheumatoid arthritis in patients 2 years or older. The applicant has developed an intravenous (IV) bolus injection formulation (N1539 30 mg) administrated once daily and is seeking an indication for management of moderate to severe pain in adults. To support efficacy, two phase 3 studies were reviewed, Study REC-15-015 in patients with abdominoplasty surgery and Study REC-15-016 in patients with bunionectomy surgery. Both were randomized (R), multicenter (MC), double-blind (DB), placebo-controlled (PC) studies. Patients with inadequately controlled pain symptoms could request rescue analgesia (oral oxycodone 5 mg administered up to every 2 hours).

In Study REC-15-015, the primary efficacy endpoint was defined as the summed pain intensity difference from Hour 0 to Hour 24 ($SPID_{24}$). Based on clinical input, the primary endpoint should evaluate efficacy after at least two doses of study drug, such as a $SPID_{48}$. Therefore, in my review, the efficacy of N1539 30 mg was evaluated by $SPID_{48}$ in both studies. 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 2 hours following this rescue use. The difference between two treatment groups for $SPID_{48}$ was assessed by an analysis of covariance (ANCOVA) model with factors of treatment and investigational site and a covariate of baseline pain intensity score.

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 in most cases, the time to meaningful pain relief was achieved after the first use of rescue analgesics.

Based on my review of the two studies submitted, there is not sufficient evidence that the proposed study drug, N1539 given 30 mg IV daily, is suitable as a standalone analgesic for the management of acute pain.

2. INTRODUCTION

2.1 Overview

Meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), has been approved (Mobic) since 2000 for the relief of the signs and symptoms associated with osteoarthritis, rheumatoid arthritis and juvenile rheumatoid arthritis in patients 2 years or older. Mobic is available as an oral tablet and suspension with a starting daily dose of 7.5 mg and a maximum daily dose of 15 mg. N1539 has been developed to manage moderate to severe acute pain in adults. The applicant claims that

N1539 30 mg, administrated once daily by IV bolus injection over 15 seconds, had a rapid onset of action.

The clinical development program of N1539 has been discussed between the agency and the applicant numerous times under IND 105,172. In the EOP2 meeting held on December 9, 2010, the agency stated that the once daily dosing regimen is unusual for a parenteral analgesia and the primary endpoint should evaluate efficacy after at least two doses of study drug, such as a $SPID_{48}$. Simply demonstrating efficacy throughout a single dosing period is not adequate and the applicant should evaluate pain intensity during the second 12-hour period of the dosing interval. In the second EOP2 meeting dated August 26, 2015, the agency made the following comments:

a. You propose to replace all the pain intensity scores after the first rescue use with the pre-rescue pain score (LOCF) for the primary efficacy analysis. This is not acceptable. Your method is based on an assumption that appears difficult to justify. You may employ this approach as a sensitivity analysis.

b. You may consider the sensitivity analysis you proposed, which carries the prerescue score forward to replace pain intensity scores collected within two hours following each rescue (W2LOCF), as your primary efficacy analysis. Additionally, include a sensitivity analysis that utilizes all pain intensity scores collected before and after each rescue use instead of imputing them.

c. Furthermore, specify how to handle missing data from subjects who discontinue the study early in the efficacy analyses.

In the Pre-NDA meeting dated February 10, 2017, the agency made the following comments:

> We note that your ISE focuses on a pooled analysis of all efficacy data. In the NDA, an ISE is more than just a pooled analysis. It is intended to compare the individual studies including an examination of study-to-study differences in results. You should explore the effect in subsets of the treated population, dose-response information from all sources, any available comparisons with alternative drugs, and any other information, so that the nature of the drug's effectiveness can be as fully defined as possible, and the user of the drug can be given the best possible information on how to use the drug and what results to expect. Refer to the Guidance for Industry *Integrated Summary of Effectiveness*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf for more details.

The current submission contains four phase 1 clinical pharmacology studies, four phase 2 and three phase 3 clinical studies. My review focuses on the two phase 3 studies in patients with abdominoplasty or bunionectomy surgery (Table 1). The phase 3 study (Study REC-15-017) is a safety study in patients with major surgery and is not discussed in my review.

Table 1: Summary of trials to be assessed in the statistical review

Trial ID	Design	DB Treatment/ Sample Size	Primary Efficacy Endpoint
REC-15-015	R, DB, MC, PC	N1539 30 mg: 110 Placebo: 109	$SPID_{24}$
REC-15-016	R, DB, MC, PC	N1539 30 mg: 100 Placebo: 101	$SPID_{48}$

2.2 Data Sources

All data were supplied electronically as SAS transport files. The clinical study report is located at the following location in the CDER electronic document room (EDR):

\\Cdsesub1\EVSPROD\NDA210583\0001

The datasets, define files and programs are located in EDR at:

\\Cdsesub1\EVSPROD\NDA210583\0001\m5\datasets

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The electronic datasets and define files submitted by the applicant were of acceptable quality, and were sufficient for validating study results.

3.2 Evaluation of Efficacy

3.2.1 Study REC-15-015

Study Design and Endpoints

Study REC-15-015 was a phase 3, MC, R, DB, PC study in patients with moderate to severe pain following abdominoplasty surgery. The study was conducted at four centers in the United States from January 2016 until October 2016. The study consisted of three phases: pretreatment, treatment and follow-up phase (28 days after the last study dose). Following surgery, IV fentanyl was used to maintain analgesia. Patients were evaluated for eligibility for randomization within 3 hours of the end of surgery. After a 1:1 randomization, patients took study drug every 24 hours and stayed at the study site for at least 48 hours after treatment initiation. Patients were eligible to receive a third dose of study drug before discharge at the discretion of the investigator. Patients with inadequately controlled pain symptoms could request rescue analgesia (oral oxycodone 5 mg administered up to every 2 hours). Patients were encouraged to wait at least one hour after the first dose of study drug before requesting rescue analgesia.

PI scores were assessed using an 11-point numeric pain rating scale at scheduled times during the 48-hour period (Hour 0, 0.25, 0.5, 0.75, 1, 2, 4, 6 and every 2 hours until 48 hours). There was a ±5 minute window allowed for the collection of each PI assessment in the first 6 hours, then a ±15 minute window for subsequent PI assessments. PI was also assessed within 5 minutes prior to administration of each dose of rescue analgesia, and at time of early discontinuation.

The primary objective of the study was to demonstrate the analgesic efficacy of N1539 30 mg compared with placebo in patients with moderate to severe pain following abdominoplasty surgery. The primary efficacy endpoint was the summed pain intensity difference from 0 to 24

hours after the first dosing of study drug ($SPID_{24}$). Secondary efficacy endpoints included SPID at various other time points (such as $SPID_6$, $SPID_{12}$, $SPID_{48}$, and $SPID_{24-48}$), time to perceptible and meaningful pain relief as measured by the two stopwatch technique, proportion of patients with improvement ≥ 30% and ≥ 50% within 6 hours following the study dose, the patient global assessment of pain control at 24 and 48 hours, time to administration of the first dose of rescue analgesia and frequency of rescue analgesia used during 0-24, 24-48 and 0-48 hours.

Statistical Methodologies

The primary efficacy analysis population consisted of all randomized patients. The difference between two treatment groups for all SPIDs was assessed by an ANCOVA model with factors of treatment and investigational site and a covariate of baseline pain intensity score. The PI score obtained prior to use of rescue was carried forward to replace PI scores collected within 2 hours following this rescue use (W2LOCF). To investigate the robustness of the primary analysis to different methods of handling rescue use, a number of sensitivity analyses were performed:

- PI score collected prior to the first use of rescue medication was carried forward to replace all PI scores following the first rescue use (LOCF);

- Baseline PI score was carried forward to replace all PI scores collected after the first use of rescue medication (BOCF);

- All PI scores, scheduled, pre-rescue and pre-early termination of pain assessment were analyzed without imputations (OBSERVED).

The LOCF method was used to impute missing PI scores. Although it is a single imputation method which is not recommended by the National Academy of Science (NAS) report on missing data, I am not concerned about it in this study as very few patients (2%) didn't complete the 48-hour pain assessment.

For all time to event endpoints (time to the first dose of rescue medication, time to perceptible pain relief and time to meaningful pain relief), patients without the event were censored at time of last evaluation (PI assessment at 48 hours or time of early discontinuation). A Kaplan-Meier (KM) survival curve was graphically displayed for each treatment group and the log-rank test was utilized to compare two survival curves. To further explore the usage of rescue medication, the frequency of rescue analgesia required per patient was calculated for different time intervals, 0-24, 24-48 and 0-48 hours. I also present the percentages of patients with different frequencies of rescue use for each treatment group.

Patient Disposition, Demographic and Baseline Characteristics

The disposition of all randomized patients is shown in Table 2. A total of 219 patients were randomized and 214 (98%) patients completed the 48-hour pain assessment. There were two (2%) patients in the N1539 30 mg treatment group and three (3%) patients in the placebo group who didn't complete the 48-hour pain assessment.

Table 2: Patient disposition in Study REC-15-015 – Number (%) of Patients

	N1539 30 mg n (%)	Placebo n (%)	Overall n (%)
Patients randomized	110	109	219
Patients treated with >= 1 dose of study drug	110 (100)	109 (100)	219 (100)
Patients completed treatment	108 (98.2)	107 (98.2)	215 (98.2)
Patients completed 48-hour pain assessment	108 (98.2)	106 (97.2)	214 (97.7)
Patients completed the study	104 (94.5)	105 (96.3)	209 (95.4)
Reason for treatment discontinuation			
Lack of efficacy	2 (1.8)	1 (0.9)	3 (1.4)
Adverse event	0	1 (0.9)	1 (0.5)
Reason for early termination of pain assessment			
Lack of efficacy	2 (1.8)	1 (0.9)	3 (1.4)
Adverse event	0	2 (1.8)	2 (0.9)
Reason for discontinuation from study			
Lack of efficacy	1 (0.9)	0	1 (0.5)
Withdrawal by patient	3 (2.7)	2 (1.8)	5 (2.3)
Lost to follow up	2 (1.8)	2 (1.8)	4 (1.8)

Source: Clinical Study Report Section 10.1, Table 14.1.1

The demographic and other background characteristics for all patients in the primary efficacy analysis set are presented in the appendix. The majority of patients (98%) were female. The mean age was 38.9 years in the N1539 30 mg group and 41.0 years in the placebo group. About 63% of patients were white. The overall mean height and weight were 1.6 m and 70.8 kg respectively, with a mean body mass index (BMI) of 26.7 kg/m^2. The demographic and other background characteristics were comparable between the two treatment groups.

Results and Conclusions

There were 110 patients from the N1539 30 mg treatment group and 109 patients from the placebo group included in the primary efficacy analysis. I confirmed the applicant's primary efficacy analysis. Results are shown in Table 3. The difference in $SPID_{24}$ between the treatment groups was statistically significant ($p = 0.0210$), indicating that there was a positive N1539 30 mg treatment effect on total pain reduction from baseline during the first 24 hours after the initial dose of the study drug. 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 $SPID_{48}$ ($p = 0.0039$). In the analyses of $SPID_{24}$ and $SPID_{48}$, both baseline PI score and investigational site were statistically significant covariates. However, interactions between treatment and each of the covariates were not statistically significant. These analyses suggest that the treatment effect of N1539 30 mg was same among the different investigational sites, and was not dependent on the baseline pain score.

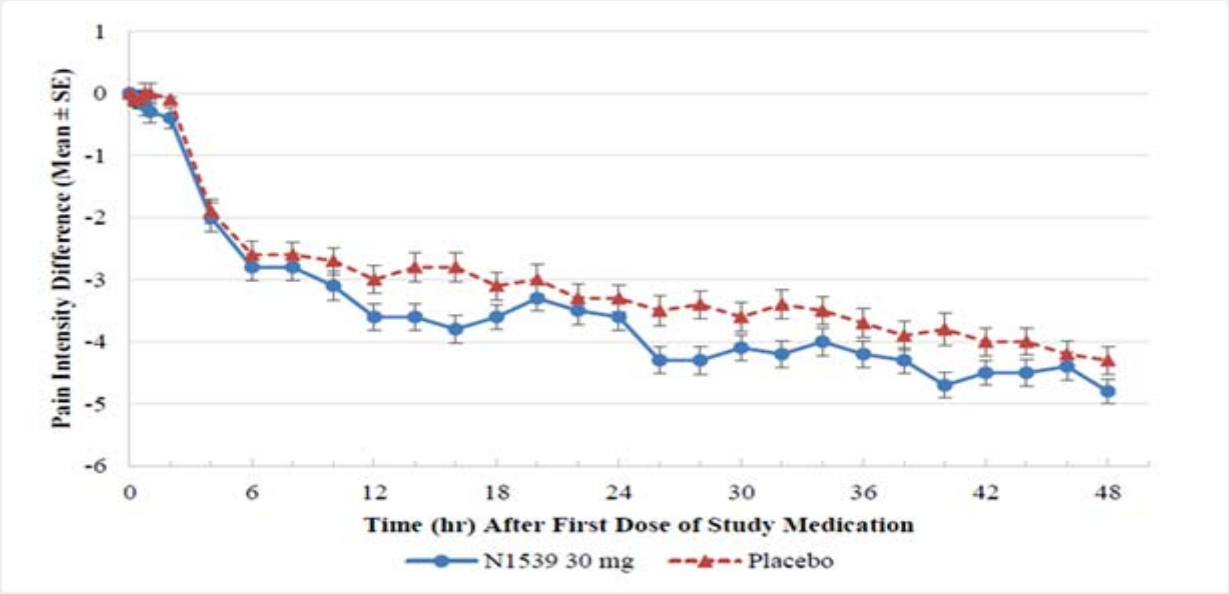
Table 3: Summary of SPID (primary efficacy endpoint)
W2LOCF Analysis

Parameter	N1539 30 mg (N=110) LS mean (SE)	Placebo (N=109) LS mean (SE)	Difference in LS mean (SE)	P-value
Applicant's primary efficacy endpoint: $SPID_{24}$	-4166.7 (214.8)	-3479.8 (215.6)	-686.9 (295.4)	0.0210
Our preferred primary efficacy endpoint: $SPID_{48}$	-10408 (445.7)	-8618.1 (447.5)	-1789.5 (608.2)	0.0039

Source: Reviewer's analyses. LS: least square, SE: standard error.

The average of the PID over time for each treatment group is displayed in Figure 1 and the analysis results of SPID at various time intervals are shown in Table 4. Both PID curves and analyses of SPID show that there were no significant differences in PID during the last six hours of the dosing interval which suggests end-of-dose failure.

Figure 1: Summary of PID Values (Mean ± SE) Hour 0-48 – W2LOCF Analysis



Source: Clinical Study Report Section 11.4.1.2, Figure 2.

Table 4: Summary of SPID at Various Time Intervals
W2LOCF Analysis

Parameter	N1539 30 mg (N=110) LS mean (SE)	Placebo (N=109) LS mean (SE)	Difference in LS mean (SE)	P-value
$SPID_{6}$	-572.2 (52.7)	-502.2 (52.9)	-70.0 (72.5)	0.3352
$SPID_{12}$	-1705.4 (105.3)	-1452.0 (105.7)	-253.5 (144.7)	0.0813
$SPID_{12-24}$	-2461.2 (124.5)	-2027.3 (125.0)	-433.4 (171.4)	0.0120
$SPID_{18-24}$	-1182.1 (64.8)	-1048.9 (65.1)	-133.2 (89.1)	0.1365
$SPID_{36-48}$	-3227.5 (131.9)	-2743.8 (132.4)	-483.6 (181.3)	0.0082

$SPID_{42-48}$	-1601.2 (67.6)	-1404.2 (67.8)	-197.0 (92.9)	0.0351

Source: Reviewer's analyses. LS: least square, SE: standard error.

Sensitivity analyses of all SPIDs using the LOCF, BOCF and OBSERVED methods showed that the N1539 30 mg treated patients had numerically more total pain reduction than the placebo treated patients at all planned time intervals. However, $SPID_{24}$ and $SPID_{48}$ were only statistically significant different between two treatment groups using the OBSERVED analysis method.

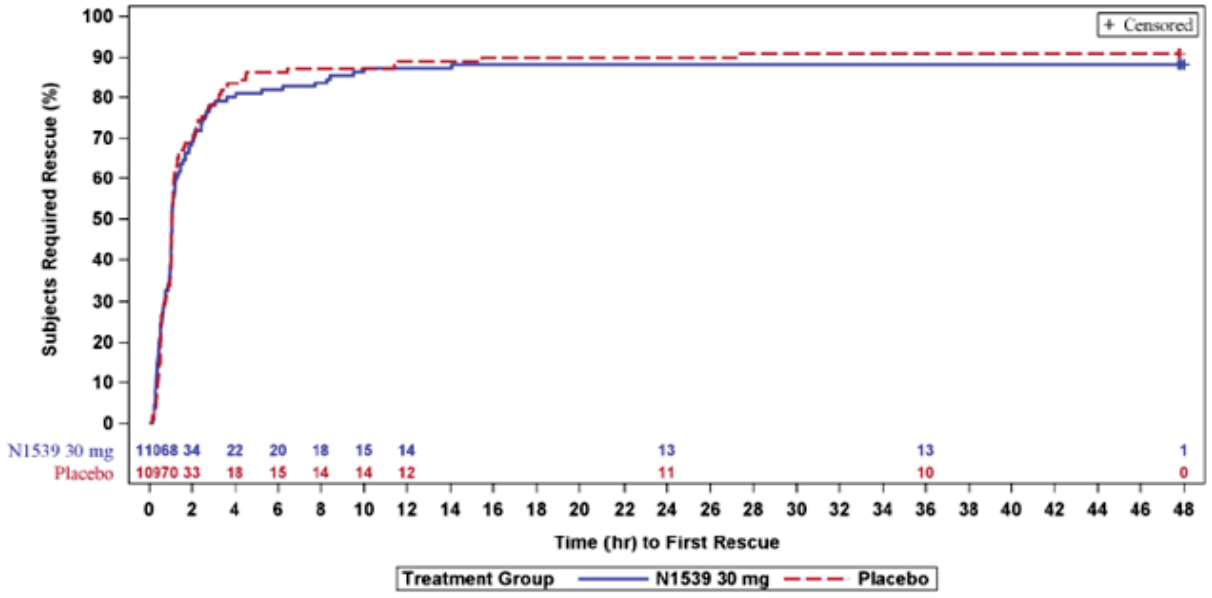
Patients with inadequate pain control following randomization could request rescue analgesia (oral oxycodone 5 mg up to every two hours). There were 88% of patients in the N1539 30 mg treatment group and 91% of patients in the placebo group who used rescue analgesia during 48 hours following the randomization. The median time to the first dose of rescue medication was 1 hour in both groups and the KM estimates of time to the first rescue use was not statistically significant between two treatment groups (p = 0.7572) (Table 5 and Figure 2).

Table 5: Summary of Time to First Rescue and Number of Patients Requiring Rescue

	KM Estimates Time to First Rescue – Hrs (95% CI)			Number of Patients (%) Using Rescue		
Treatment Group	**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: Reviewer's analyses.
Note: for number of patients using rescue
(1) The p-value was derived from the CMH test that was adjusted for investigational site;
(2) For Hour 24-48, patients discontinued in the first day were not included.

Figure 2: Time to First Use of Rescue Analgesia



Source: Clinical Study Report Section 11.4.1.2, Figure 3.

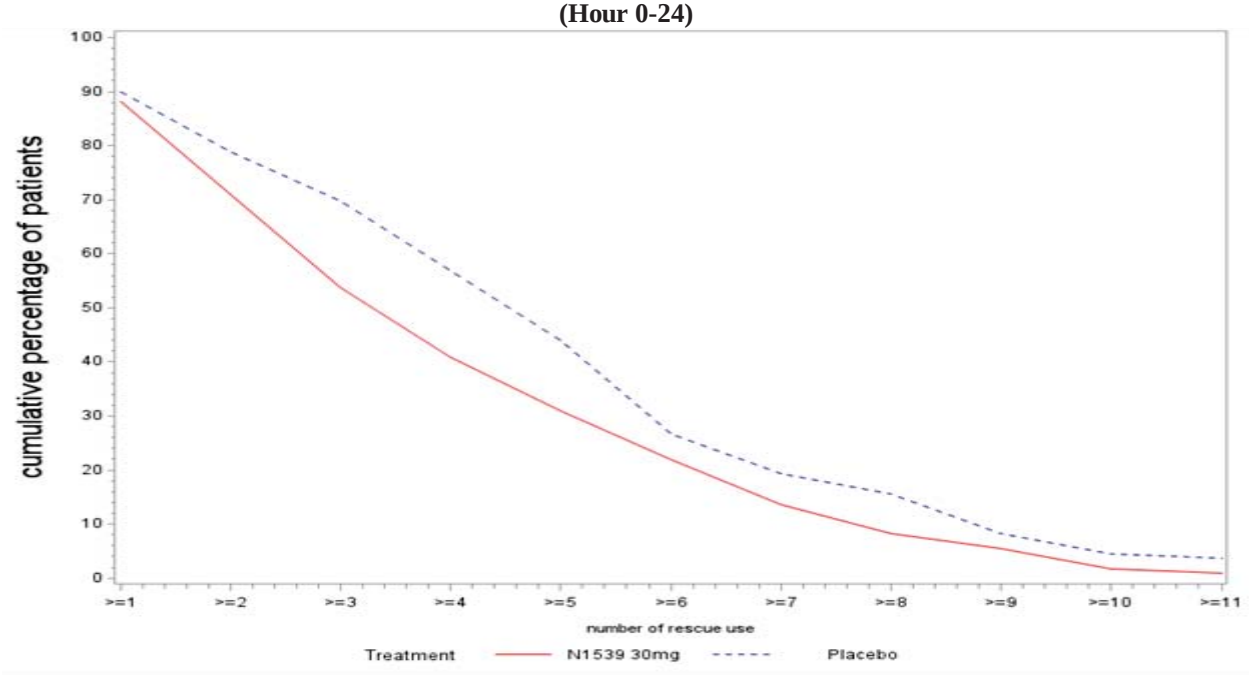
The number of rescue analgesia doses required per patient is shown in Table 6. For the N1539 30 mg treatment group, the average doses of rescue medications were 3.4, 1.6 and 4.9 for Hour 0-24, 24-48 and 0-48 respectively, while for the placebo group, the average doses of rescue medications were 4.2, 2.6 and 6.8 for Hour 0-24, 24-48 and 0-48 respectively. To further explore the usage of rescue medications, I explored the number of times patients requested and received rescue medications. In Figure 3-5, I present the percentages of patients who took various amounts of rescue medications for pain control for each treatment group. The x-axis shows the number of doses and the y-axis shows the percentage of patients. As you can see, more patients in the placebo group used rescue medications than patients in the N1539 30 mg treatment group. This may be a reason why comparisons of the average number of rescue use were statistically significant between two treatment groups for Hour 0-24, 24-48 and 0-48.

Table 6: Number of Rescue Analgesia Required per Patient

	N1539 30 mg (N = 110)					**Placebo (N = 109)**					
	Mean (SD)	**Median**	**Min**	**Max**	**LS mean (SE)**	**Mean (SD)**	**Median**	**Min**	**Max**	**LS mean (SE)**	**P-value**
Hour 0-24	3.4 (2.6)	3	0	11	3.7 (0.2)	4.2 (2.9)	4	0	11	4.4 (0.2)	0.0275
Hour 24-48	1.6 (2.1)	1	0	10	1.8 (0.2)	2.6 (2.5)	2	0	10	2.7 (0.2)	0.0009
Hour 0-48	4.9 (4.4)	4	0	20	5.4 (0.4)	6.8 (5.0)	6	0	21	7.1 (0.4)	0.0027

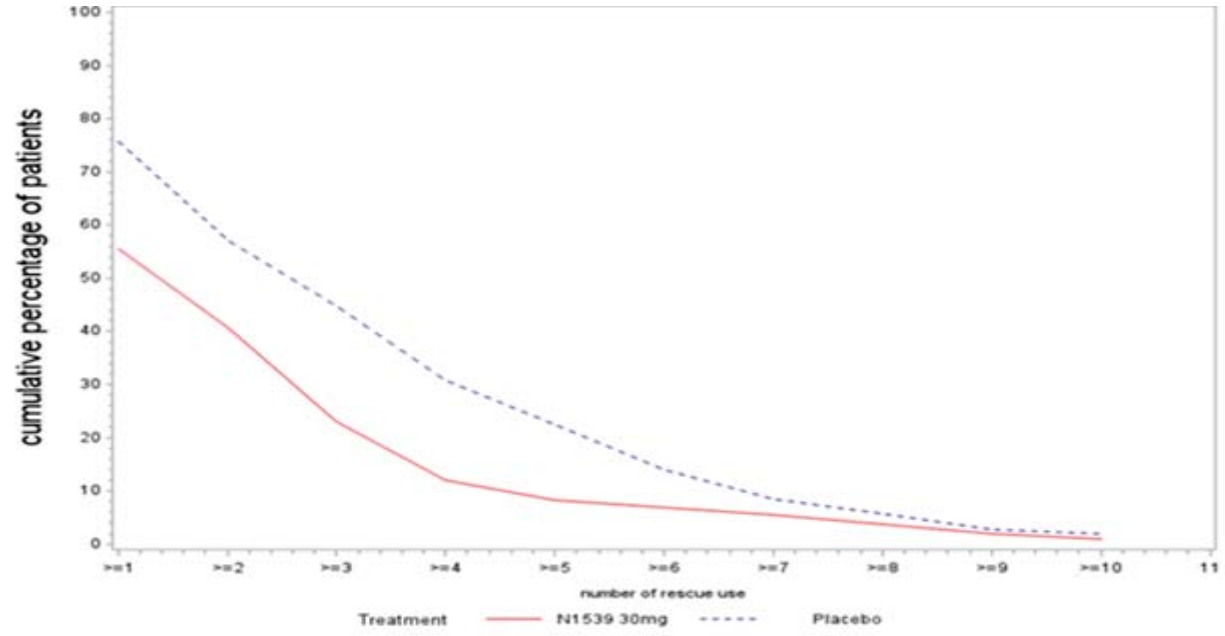
Source: Reviewer's analyses.

Figure 3: Percentage of Patients with Different Frequency of Rescue Use (Hour 0-24)



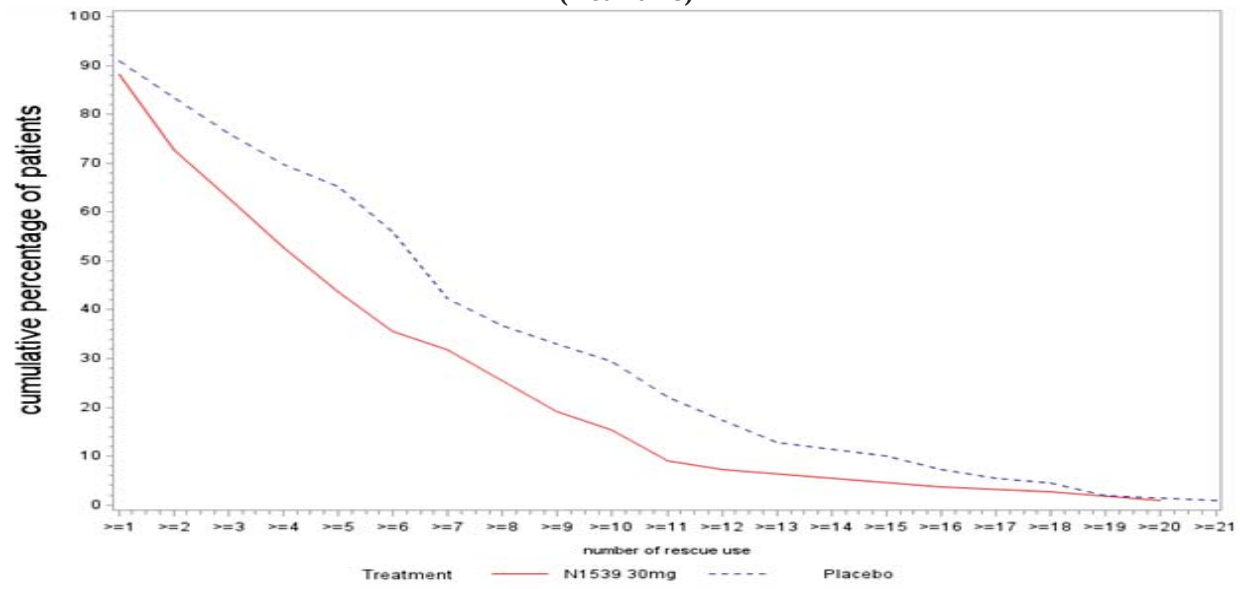
Source: Reviewer's analyses

Figure 4: Percentage of Patients with Different Frequency of Rescue Use (Hour 24-48)



Source: Reviewer's analyses

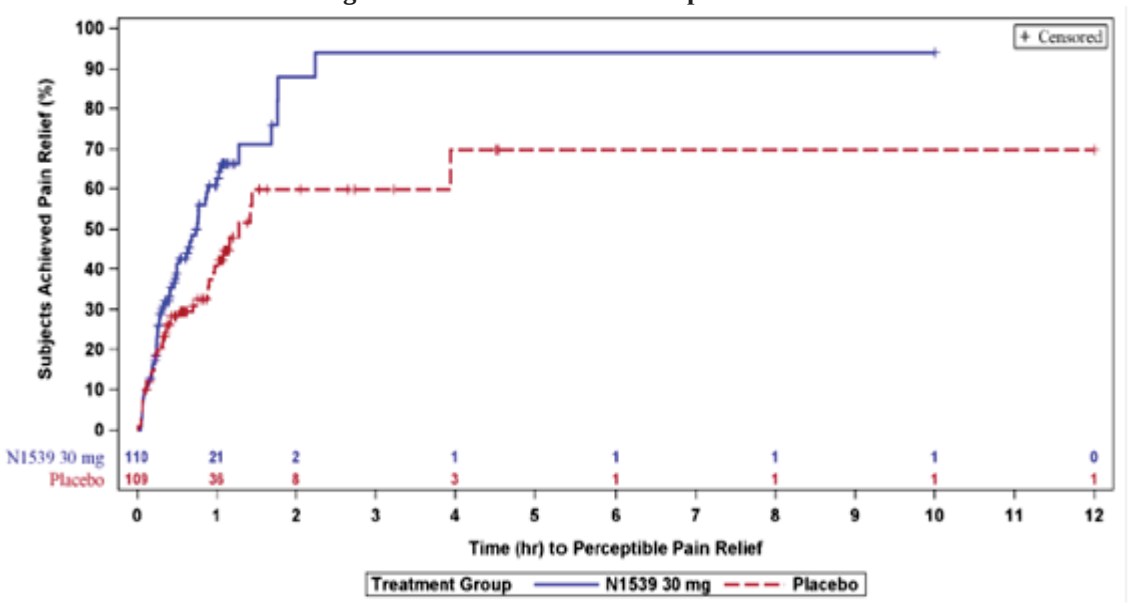
Figure 5: Percentage of Patients with Different Frequency of Rescue Use (Hour 0-48)



Source: Reviewer's analyses

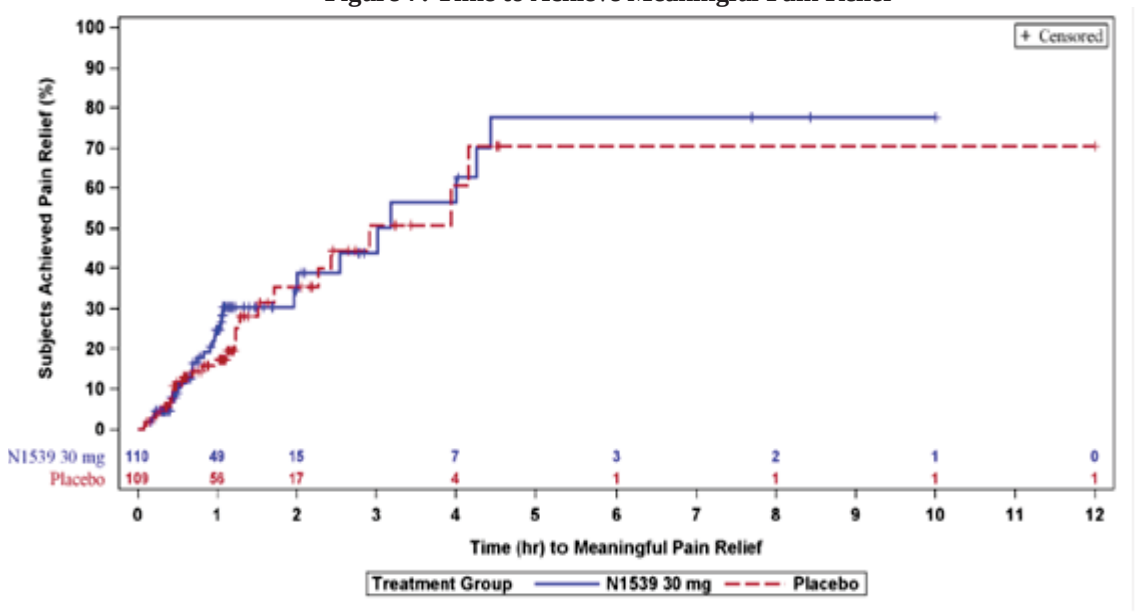
The time to perceptible and meaningful pain relief were evaluated using the double-stop watch method. The KM plots of time to achieve perceptible and meaningful pain relief are provided in Figure 6 and 7, and a summary of time to pain relief is shown in Table 7. Overall, less than 27% of patients experienced meaningful pain relief within the first 12 hours. In the N1539 30 mg treatment group, the median time to meaningful pain relief was 3 hours after taking the treatment drug. As the median time to the first time of rescue use was 1 hour in the N1539 30 mg treatment group, meaningful pain relief was achieved after the rescue analgesic use.

Figure 6: Time to Achieve Perceptible Pain Relief



Source: Clinical Study Report Section 11.4.1.2, Figure 4.

Figure 7: Time to Achieve Meaningful Pain Relief



Source: Clinical Study Report Section 11.4.1.2, Figure 5.

Table 7: Summary of Time to Pain Relief Analysis

Parameter/Statistics	N1539 30 mg (N = 110)		Placebo (N=109)
Time to Perceptible PR (hrs)			
Patients 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, NE)
75% (95% CI)	1.69 (1.03, 2.24)		NE (3.94, NE)
Log-Rank Test		0.0050	
Time to Meaningful PR (hrs)			
Patients 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, NE)
75% (95% CI)	4.43 (3.18, NE)		NE (3.94, NE)
Log-Rank Test		0.5096	

Source: Clinical Study Report Section 11.4.1.2, Table 9. NE: not estimable.

3.2.2 Study REC-15-016

Study Design and Endpoints

Study REC-15-016 was a phase 3, MC, R, DB, PC study in patients with moderate to severe pain following unilateral bunionectomy. The study was conducted at four centers in the United States from January 2016 until June 2016. Study REC-15-016 had a similar design to Study REC-15-015.

The primary objective of the study was to demonstrate the analgesic efficacy of N1539 30 mg compared with placebo in patients with moderate to severe pain following unilateral

bunionectomy. The primary efficacy endpoint was $SPID_{48}$. Secondary efficacy endpoints were similar to Study REC-15-015, except that the secondary efficacy endpoints also included $SPID_{12-48}$.

Statistical Methodologies

The statistical methods utilized to analyze the efficacy endpoints in Study REC-15-016 are similar to the methods used in Study REC-15-015.

Patient Disposition, Demographic and Baseline Characteristics

The disposition of all randomized patients is shown in Table 8. A total of 201 patients were randomized and 191 (95%) patients completed the 48-hour pain assessment. There were five (5%) patients in each treatment group who didn't complete the 48-hour pain assessment and the main reason was lack of efficacy in both groups.

Table 8: Patient disposition in Study REC-15-016 – Number (%) of Patients

	N1539 30 mg n (%)	Placebo n (%)	Overall n (%)
Patients randomized	100	101	201
Patients treated with >= 1 dose of study drug	100 (100)	101 (100)	201 (100)
Patients completed treatment	95(95)	97 (96)	192 (95.5)
Patients completed 48-hour pain assessment	95 (95)	96 (95)	191 (95)
Patients completed the study	97 (97)	97 (96)	194 (96.5)
Reason for treatment discontinuation			
Lack of efficacy	4 (4)	4 (4)	8 (4)
Adverse event	1 (1)	0	1 (0.5)
Reason for early termination of pain assessment			
Lack of efficacy	4 (4)	4 (4)	8 (4)
Adverse event	1 (1)	1 (1)	2 (1)
Reason for discontinuation from study			
Lack of efficacy	1 (1)	0	1 (0.5)
Withdrawal by patient	2 (2)	2 (2)	4 (2)
Lost to follow up	0	2 (2)	2 (1)

Source: Clinical Study Report Section 10.1, Table 14.1.1

The demographic and other background characteristics for all patients in the primary efficacy analysis set are presented in the appendix. The majority of patients (85%) were female. The mean age was 46.7 years in the N1539 30 mg group and 48.4 years in the placebo group. About 64% of patients were white. The overall mean height and weight were 1.6 m and 73.7 kg respectively, with a mean body mass index (BMI) of 27.6 kg/m^2.The demographic and other background characteristics were comparable between the two treatment groups.

Results and Conclusions

There were 100 patients from the N1539 30 mg treatment group and 101 patients from the placebo group included in the primary efficacy analysis. I confirmed the applicant's primary efficacy analysis. Results are shown in Table 9. The difference in $SPID_{48}$ between the treatment groups was statistically significant (p = 0.0032), indicating that there was a positive treatment effect on total pain reduction from baseline during 48 hours after the initial dose of the study drug. In the analyses of $SPID_{48}$, both baseline PI score and investigational site were statistically significant covariates. However, interactions between treatment and each of the covariates were not statistically significant. These analyses suggest that the treatment effect of N1539 30 mg was same among the different investigational sites, and was not dependent on the baseline pain score.

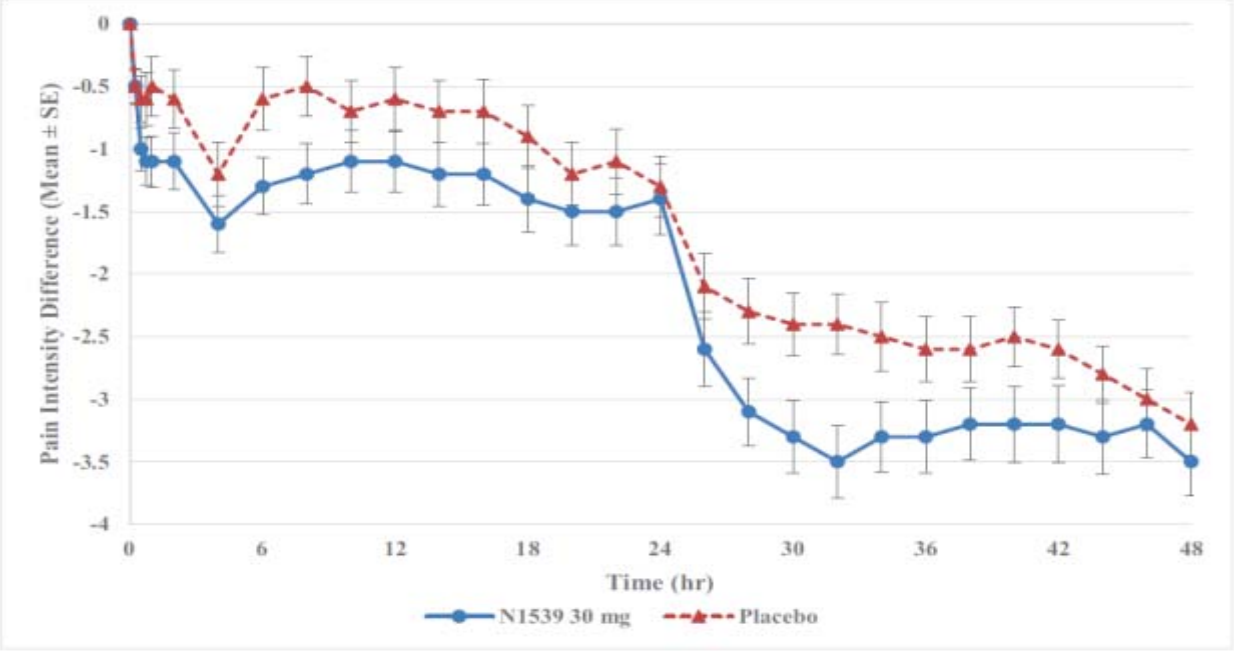
Table 9: Summary of $SPID_{48}$ (primary efficacy endpoint) W2LOCF Analysis

Parameter	N1539 30 mg (N=100) LS mean (SE)	Placebo (N=101) LS mean (SE)	Difference in LS mean (SE)	P-value
$SPID_{48}$	-6951.4 (521.6)	-4815.4 (519.4)	-2136.0 (716.2)	0.0032

Source: Reviewer's analyses. LS: least square, SE: standard error.

The average of the PID over time for each treatment group is displayed in Figure 8 and the analysis results of SPID at various time intervals are shown in Table 10. The analyses of SPID show that there were no significant differences in PID during the last six hours of the dosing interval which suggests end-of-dose failure.

Figure 8: Summary of PID Values (Mean ± SE) Hour 0-48 – W2LOCF Analysis



Source: Clinical Study Report Section 11.4.1.2, Figure 2.

Table 10: Summary of SPID at Various Time Intervals
W2LOCF Analysis

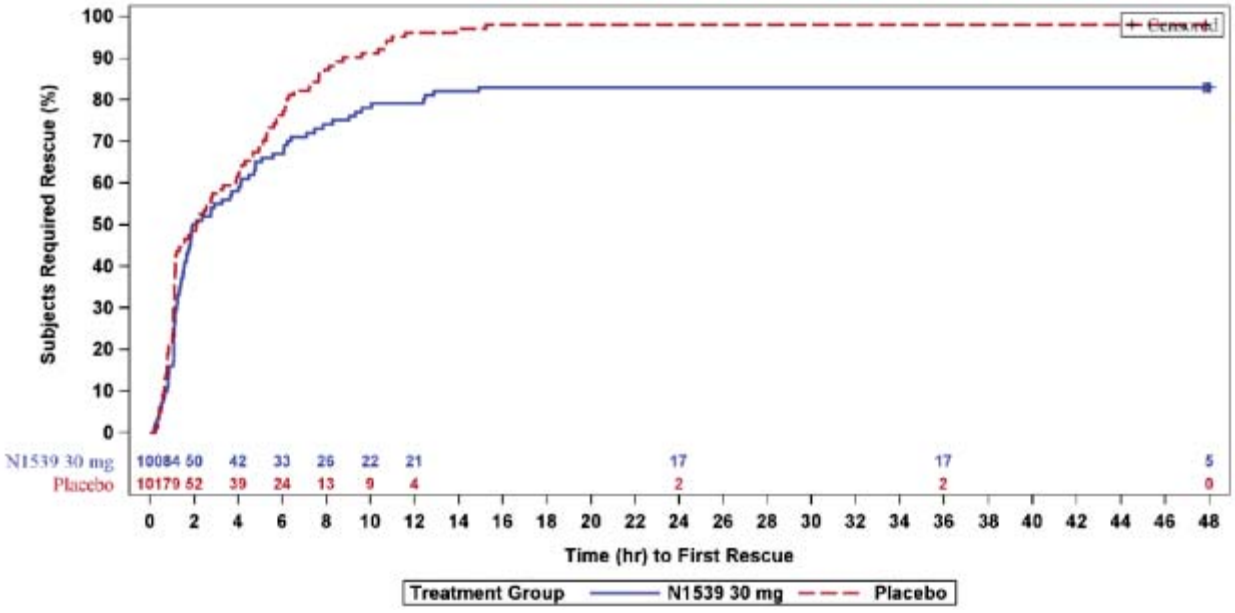
Parameter	N1539 30 mg (N=100) LS mean (SE)	Placebo (N=101) LS mean (SE)	Difference in LS mean (SE)	P-value
$SPID_{12-24}$	-1114.9 (148.0)	-683.9 (147.4)	-431.0 (203.2)	0.0352
$SPID_{18-24}$	-583.1 (78.8)	-423.4 (78.5)	-159.7 (108.3)	0.1417
$SPID_{36-48}$	-2417.6 (159.8)	-1942.5 (159.2)	-475.1 (219.4)	0.0316
$SPID_{42-48}$	-1221.7 (82.4)	-1050.7 (82.1)	-170.9 (113.2)	0.1325

Source: Reviewer's analyses. LS: least square, SE: standard error.

Sensitivity analyses of SPIDs at various time intervals using the LOCF, BOCF and OBSERVED methods had similar results to the analyses using the W2LOCF method, except that $SPID_6$ was not statistically significant different between two treatment groups using the LOCF and BOCF analysis method.

As in Study REC-15-015, patients with inadequate pain control following randomization could request rescue analgesia (oral oxycodone 5 mg up to every two hours). There were 83% of patients in the N1539 30 mg treatment group and 98% of patients in the placebo group who used rescue analgesia during 48 hours following the randomization. The median time to the first dose of rescue medication was 2 hour in both groups and the KM estimates of time to the first rescue use was statistically significant between two treatment groups (p = 0.0076) (Table 11 and Figure 9).

Figure 9: Time to First Use of Rescue Analgesia



Source: Clinical Study Report Section 11.4.1.2, Figure 3.

Table 11: Summary of Time to First Rescue and Number of Patients Requiring Rescue

Treatment Group	KM Estimates Time to First Rescue – Hrs (95% CI) 25%tile	50%tile	75%tile	Number of Patients (%) Using Rescue Hour 0-24	Hour 24-48	Hour 0-48

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%)	48(50.5%)	83 (83%)
Placebo (N=101)	1.06 (0.78, 1.11)	2.09 (1.15, 3.31)	5.73 (4.61, 7.23)	99 (98%)	71 (73.2%)	99 (98%)
Comparisons	Log-rank p-value = 0.0076			p=0.0002	p=0.0009	p=0.0002

Source: Reviewer's analyses.
Note: for number of patients using rescue
(1) The p-value was derived from the CMH test that was adjusted for investigational site;
(2) For Hour 24-48, patients discontinued in the first day were not included.

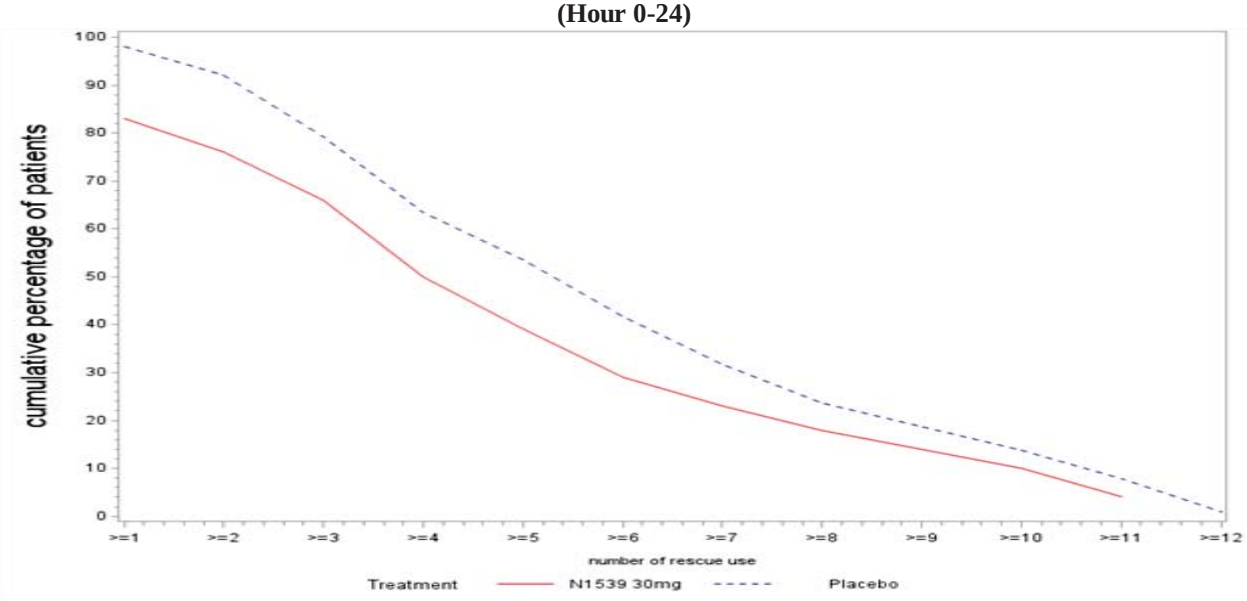
The number of rescue analgesia doses required per patient is shown in Table 12. For the N1539 30 mg treatment group, the average doses of rescue medications were 4.1, 1.7 and 5.8 for Hour 0-24, 24-48 and 0-48 respectively, while for the placebo group, the average doses of rescue medications were 5.2, 2.7 and 7.8 for Hour 0-24, 24-48 and 0-48 respectively. As in Study REC-15-015, to further explore the usage of rescue medications, I explored the number of times patients requested and received rescue medications. In Figure 10-12, I present the percentages of patients who took various amounts of rescue medications for pain control for each treatment group. As you can see, more patients in the placebo group used rescue medications than patients in the N1539 30 mg treatment group which may be a reason why comparisons of the average number of rescue use were statistically significant between two treatment groups for Hour 0-24, 24-48 and 0-48.

Table 12: Number of Rescue Analgesia Required per Patient

	N1539 30 mg (N = 100)					**Placebo (N = 101)**					
	Mean (SD)	**Median**	**Min**	**Max**	**LS mean (SE)**	**Mean (SD)**	**Median**	**Min**	**Max**	**LS mean (SE)**	**P-value**
Hour 0-24	4.1 (3.2)	4	0	11	4.0 (0.3)	5.2 (3.1)	5	0	12	5.1 (0.3)	0.0025
Hour 24-48	1.7 (2.7)	1	0	11	1.6 (0.2)	2.7 (2.9)	2	0	11	2.5 (0.2)	0.0108
Hour 0-48	5.8 (5.5)	4	0	21	5.5 (0.5)	7.8 (5.6)	6	0	22	7.5 (0.5)	0.0014

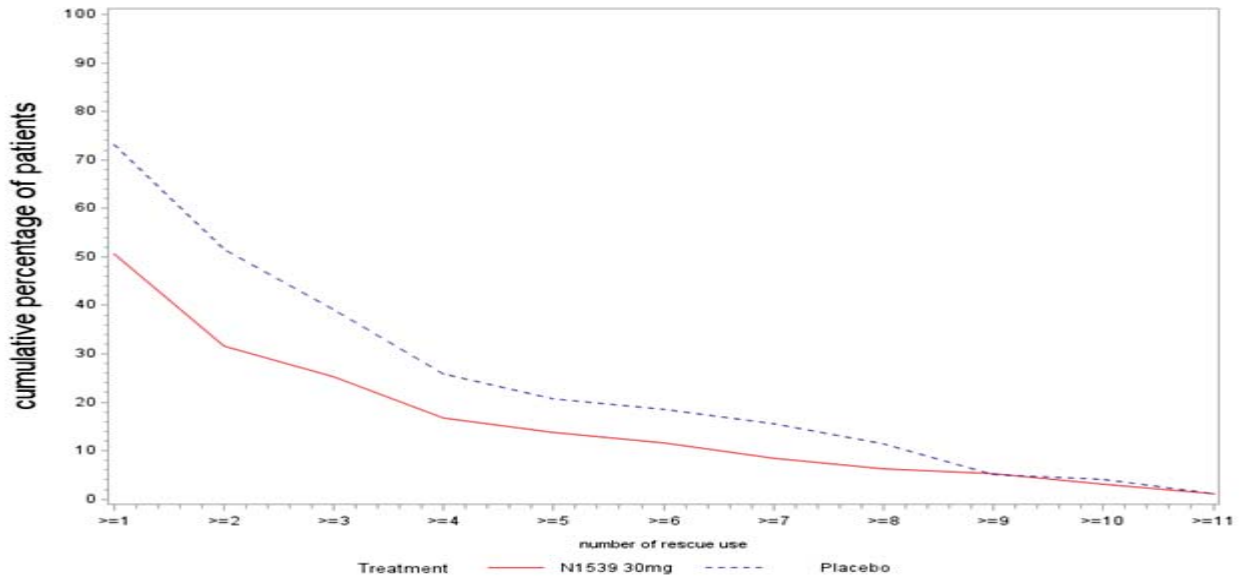
Source: Reviewer's analyses.

Figure 10: Percentage of Patients with Different Frequency of Rescue Use (Hour 0-24)



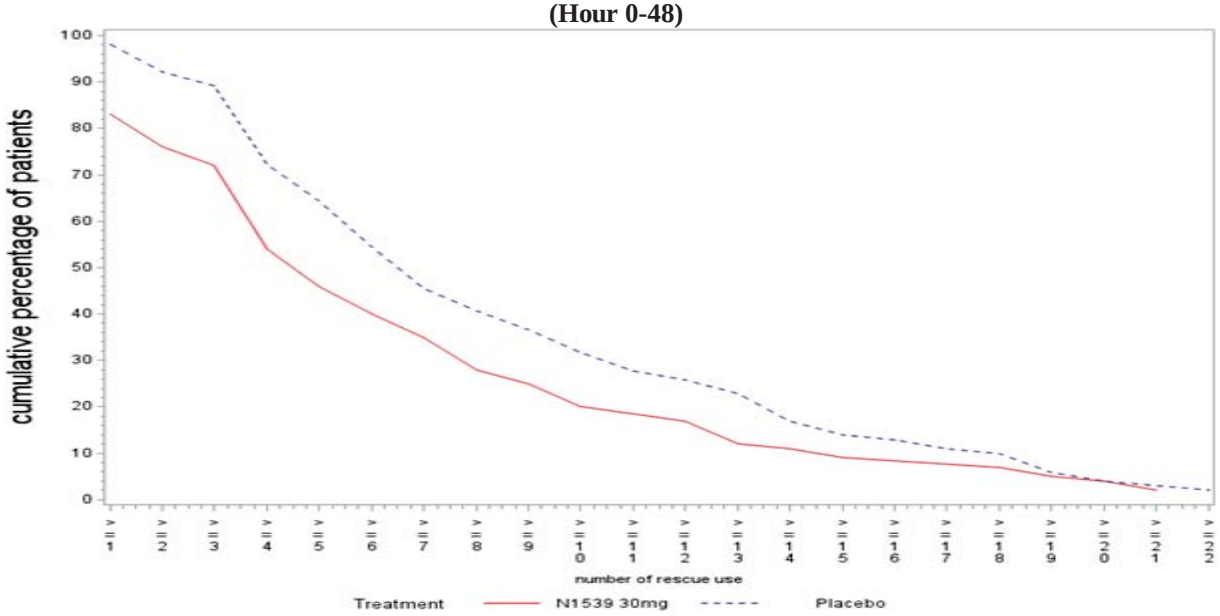
Source: Reviewer's analyses

Figure 11: Percentage of Patients with Different Frequency of Rescue Use (Hour 24-48)



Source: Reviewer's analyses

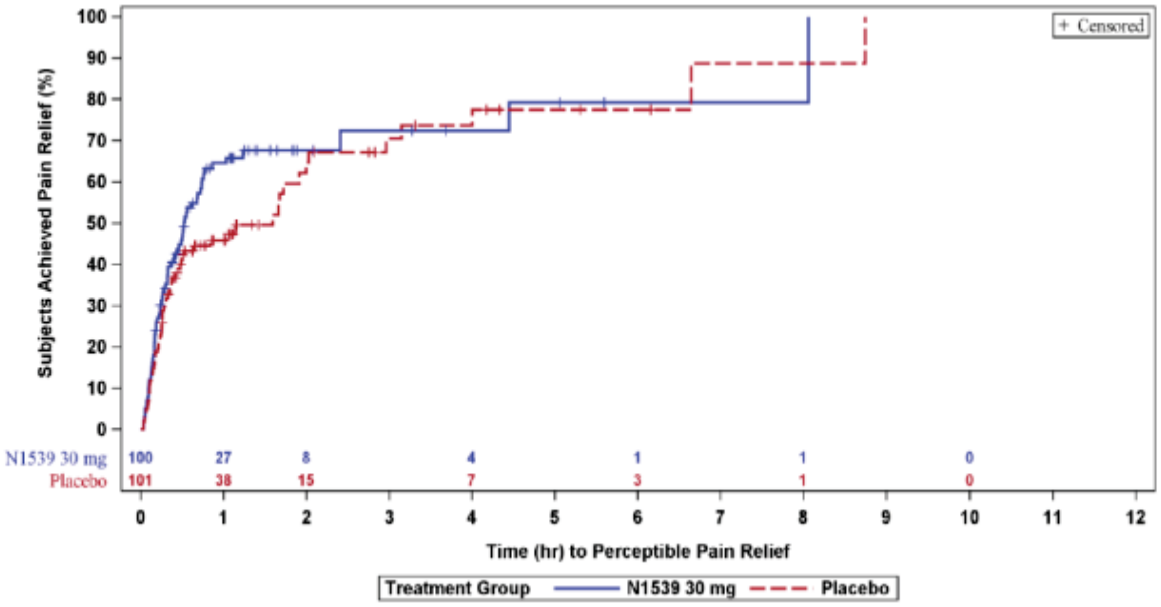
Figure 12: Percentage of Patients with Different Frequency of Rescue Use (Hour 0-48)



Source: Reviewer's analyses

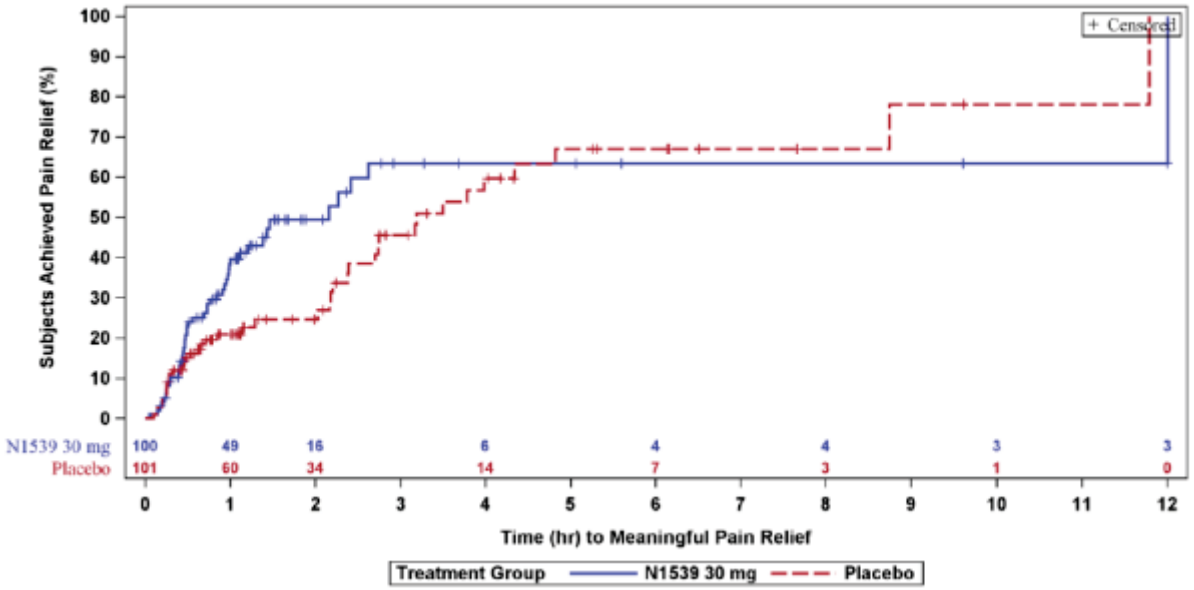
Similar to Study REC-15-015, the time to perceptible and meaningful pain relief were also evaluated using the double-stop watch method. The KM plots of time to achieve perceptible and meaningful pain relief are provided in Figure 13 and 14, and a summary of time to pain relief is shown in Table 13. Overall, less than 50% of patients experienced meaningful pain relief within the first 12 hours. In the N1539 30 mg treatment group, the median time to meaningful pain relief was 2.2 hours after taking the treatment drug. As the median time to the first time of rescue use was 2 hour in the N1539 30 mg treatment group, meaningful pain relief was achieved after the rescue analgesic use.

Figure 13: Time to Achieve Perceptible Pain Relief



Source: Clinical Study Report Section 11.4.1.2, Figure 4.

Figure 14: Time to Achieve Meaningful Pain Relief



Source: Clinical Study Report Section 11.4.1.2, Figure 5.

Table 13: Summary of Time to Pain Relief Analysis

Parameter/Statistics	N1539 30 mg (N = 100)		Placebo (N=101)
Time to Perceptible PR (hrs)			
Patients Achieved Endpoint, n (%)	66 (66.0)		59 (58.4)
25% (95% CI)	0.18 (0.14, 0.27)		0.25 (0.16, 0.35)
50% (95% CI)	0.52 (0.35, 0.74)		1.59 (0.48, 2.00)
75% (95% CI)	4.45 (1.03, 8.06)		4.00 (2.00, 8.75)
Log-Rank Test		0.1228	
Time to Meaningful PR (hrs)			
Patients Achieved Endpoint, n (%)	46 (46.0)		40 (39.6)
25% (95% CI)	0.56 (0.44, 0.95)		2.03 (0.62, 2.38)
50% (95% CI)	2.16 (1.00, 12.01)		3.19 (2.39, 4.82)
75% (95% CI)	12.01 (2.62, 12.01)		8.75 (4.35, 11.79)
Log-Rank Test		0.1048	

Source: Clinical Study Report Section 11.4.1.2, Table 9.

3.3 Evaluation of Safety

The safety database has 1045 patients who received two or more doses of study drug including 748 patients who received two or more doses at the proposed to-be-market dose of 30 mg of the study drug. There was one death in the placebo group and none in the study drug group. There were no serious adverse events (SAEs) associated with the study drug. In the post-operative population, the most commonly reported treatment emergent adverse events (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. However, none of the trials that evaluated this drug were powered to specifically determine safety risk. The overall safety profile of the study drug is consistent with what has been observed in patients treated with oral meloxicam and IV NSAIDs as a class. The reader is

referred to Dr. Timothy Jiang's review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In Study REC-15-015, since the majority of patients (98%) were female and there were only two patients older than 65 years of age, the applicant only conducted subgroup analyses by race for $SPID_{24}$, $SPID_6$, $SPID_{12}$ and $SPID_{48}$. The applicant also conducted subgroup analyses for $SPID_{24}$ by investigation site. As I explained in Section 3.2.1, the interaction between treatment and site was not statistically significant when an ANCOVA model was used to analyze $SPID_{24}$ and $SPID_{48}$, which suggest that the treatment effect of N1539 30 mg was same among the different investigational sites. I only conducted subgroup analyses by race for $SPID_{24}$ and $SPID_{48}$.

In Study REC-15-016, the applicant conducted subgroup analyses for $SPID_{48}$ by age, sex, race and investigation site. However, the majority of patients were female (85%) and less than 65 years of age (92%). Furthermore, the interaction between treatment and site was not statistically significant when an ANCOVA model was used to analyze $SPID_{48}$. Therefore, I only conducted subgroup analyses by race for the primary endpoint $SPID_{48}$.

The subgroup analyses by race compared white patients with non-white patients which included black or African American, Asian, native Hawaiian or other Pacific Islander and patients of other races. For each race group, descriptive statistics were provided and averages of PID over time for each treatment group were depicted. Pain scores recorded before each use of rescue were handled by the W2LOCF method described in Section 3.2.1.

4.1 Age, sex and race

For Study REC-15-015, the results of the subgroup analysis by race are presented in Table 14 and the averages of PID values over time are displayed for white patients in Figure 15 and non-white patients in Figure 16. Non-white patients appeared to have greater pain reduction than the white patients. However, regardless of race, there is a consistent positive treatment effect for $SPID_{24}$ and $SPID_{48}$.

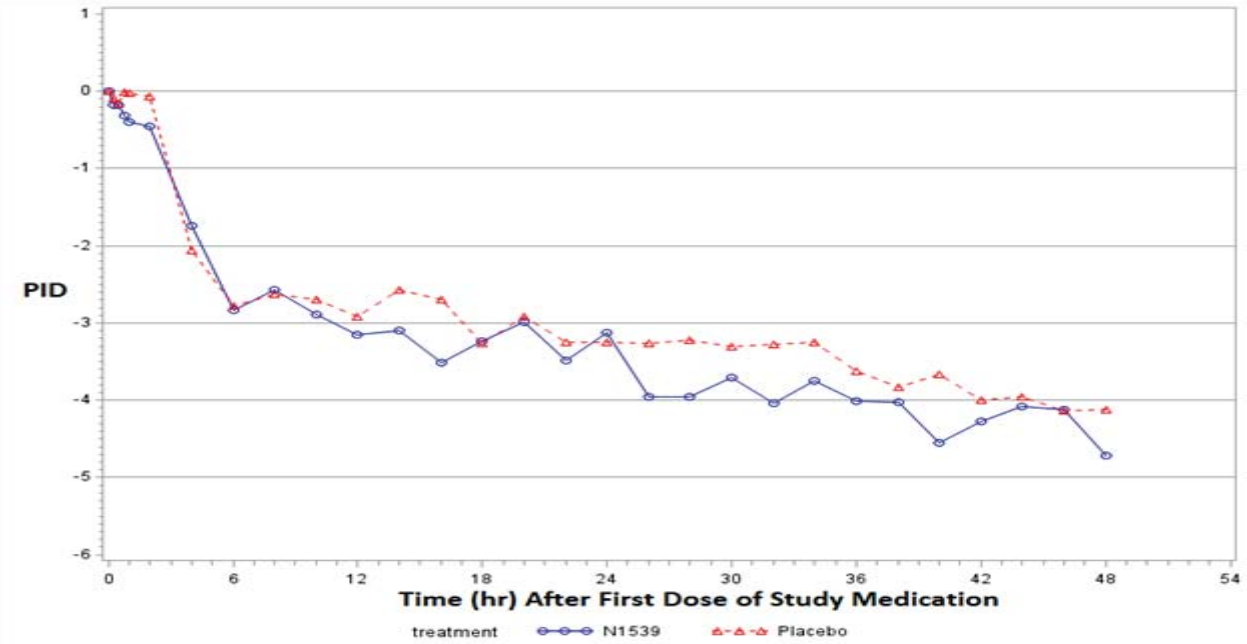
Table 14: Reviewer's subgroup analyses by race for Study REC-15-015 (w2LOCF analysis)

Parameter	White patients		Non-White patients	
	N1539 30 mg (n=69)	**Placebo** (n=69)	**N1539 30 mg** (n=41)	**Placebo** (n=40)
Baseline Pain				
Mean (SD)	7.3 (1.6)	7.6 (1.7)	7.1 (1.5)	7.1 (1.7)
Sponsor's primary efficacy endpoint: $SPID_{24}$				
Mean	-3934.6	-3709.5	-4679.8	-3934.5
(SD)	(2505.3)	(2388)	(2359.5)	(2505.3)
Difference	-225.1		-745.3	
Our preferred primary efficacy				

endpoint: $SPID_{48}$				
Mean	-9825.9	-8939.6	-11445.8	-9069
(SD)	(5250.6)	(5093.3)	(4622.1)	(6197.5)
Difference	-886.3		-2376.8	

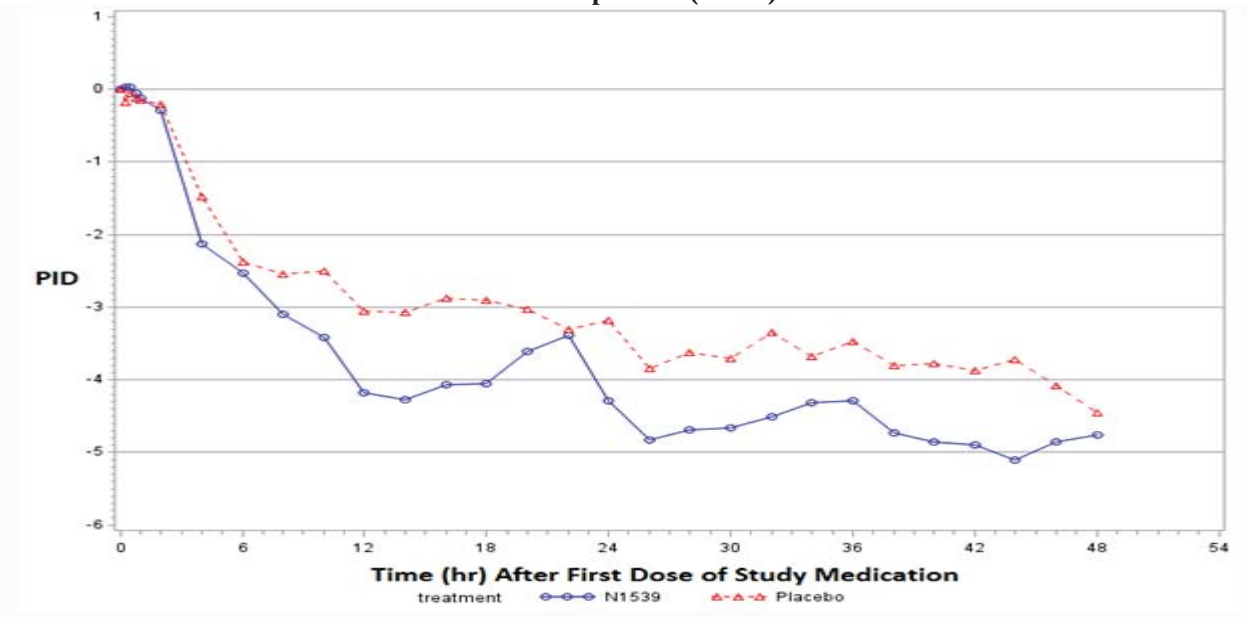
Source: Reviewer's analyses

Figure 15: Mean of PID values across time for Study REC-15-015 – W2LOCF analysis white patients (n = 138)



Source: Reviewer's analyses

Figure 16: Mean of PID values across time for Study REC-15-015 – W2LOCF analysis non-white patients (n = 81)



Source: Reviewer's analyses

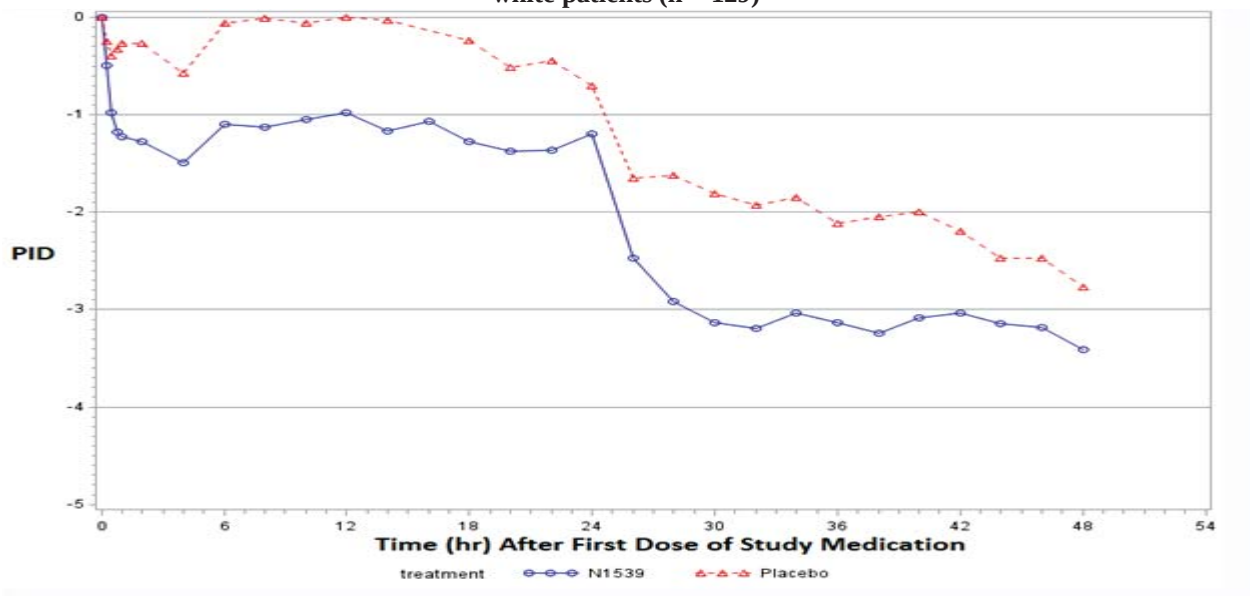
For Study REC-15-016, the results of the subgroup analysis by race are presented in Table 15 and the averages of PID values over time are displayed for white patients in Figure 17 and non-white patients in Figure 18. Baseline pain scores were generally higher in the non-white patients compared to the white patients. As seen, the treatment effect is not consistent across race groups. Placebo treated non-white patients had numerically greater pain reduction than N1539 30 mg treated non-white patients. As we discuss in Section 1 and Section 3.2, N1539 30 mg is not suitable for use as an acute pain analgesic. Therefore, we don't need to further explore the differences in $SPID_{48}$ between race groups.

Table 15: Reviewer's subgroup analyses by race for Study REC-15-016 (w2LOCF analysis)

Parameter	White patients		Non-White patients	
	N1539 30 mg (n=61)	**Placebo** (n=68)	**N1539 30 mg** (n=39)	**Placebo** (n=33)
Baseline Pain				
Mean (SD)	6.4 (1.8)	6.6 (1.7)	7.0 (2.0)	7.8 (1.8)
$SPID_{48}$				
Mean	-6143.1	-3317.2	-6983.2	-8215.7
(SD)	(6576.4)	(5256.6)	(6169.7)	(5026.1)
Difference	-2825.9		1232.5	

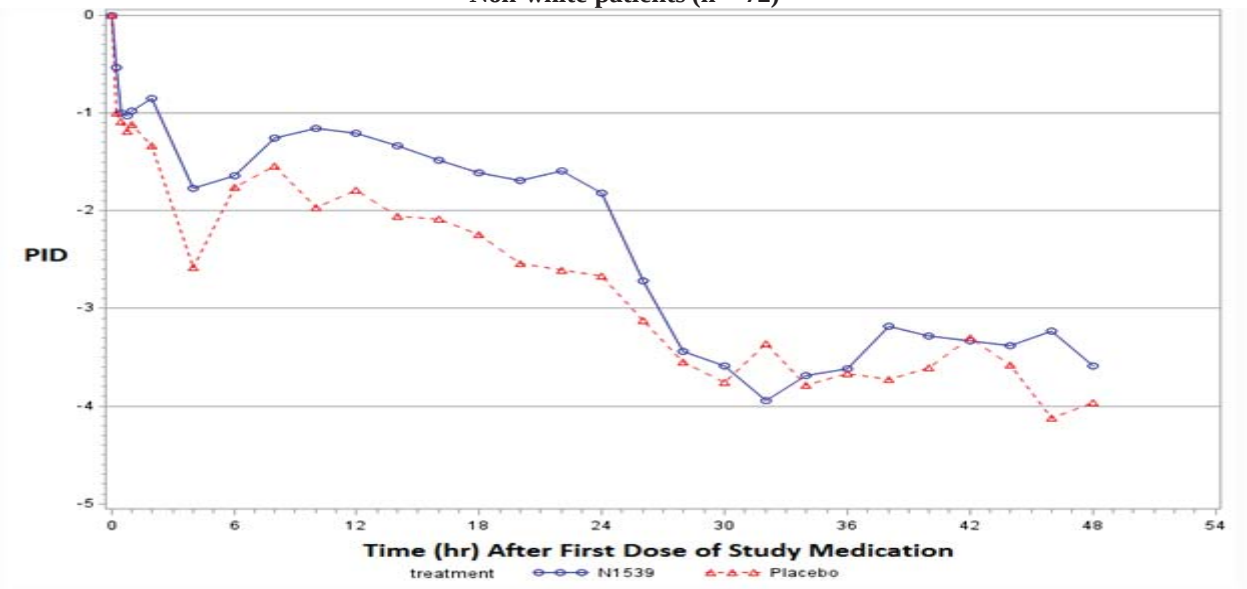
Source: Reviewer's analyses

Figure 17: Mean of PID values across time for Study REC-15-016 – W2LOCF analysis white patients (n = 129)



Source: Reviewer's analyses

Figure 18: Mean of PID values across time for Study REC-15-016 – W2LOCF analysis Non-white patients (n = 72)



Source: Reviewer's analyses

4.2 Other Special/Subgroup Populations

No other subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were two main statistical issues identified in the review of the two studies submitted to support the efficacy of N1539 30 mg for management of moderate to severe pain in adults. First, in Study REC-15-015, the primary efficacy endpoint $SPID_{24}$ did not evaluate multiple-dose efficacy. Second, the LOCF method was used to impute missing pain scores. I was able to adequately address these concerns. First, I evaluated $SPID_{48}$ in two studies. Second, since there were very few patients who didn't complete the 48-hour pain assessment, the single imputation method is acceptable to impute missing pain scores.

5.2 Collective Evidence

The efficacy of N1539 30 mg was evaluated by the summed pain intensity difference from baseline to 48 hours after dosing. In Study REC-15-015 and Study REC-15-016, the N1539 30 mg group had a statistically significant greater pain reduction compared to the placebo group. However, the analyses of PID show that there were no significant differences in PID during the last six hours of the dosing interval which suggests end-of-dose failure. In addition, the time to the first use rescue analgesic was short, the use of rescue analgesics was frequent, and in most cases, meaningful pain relief was achieved after the first use of rescue analgesic. The later may indicate a delayed onset of drug action.

In the 74-day filing communication letter dated October 1, 2017, the agency made the following comments:

1. You are proposing a 30 mg once daily intravenous (IV) dose for an acute analgesic indication. As was previously conveyed to you, this dosing regimen is unusual for a parenteral analgesic. Although you state that the primary endpoints, SPID24 and SPID48, are successful in both studies REC-15-015 and REC-15-016, respectively, the results for the key secondary analysis for rescue analgesic use do not suggest that your product is suitable for use as an acute pain analgesic.

   For Study REC-15-015, the curves for Time to First use of Rescue Analgesia (Fig 3, Clinical Study Report-REC-15-015) essentially overlap between groups, and the median time to first dose of rescue (oxycodone 5 mg) was one hour for both groups (Table 7, Clinical Study Report- REC-15-015). The number of rescue analgesics for the first 24 hours was 3.66 versus 4.38 for treatment and placebo, respectively (Table 8, Clinical Study Report- REC-15-015).

   Similarly, in Study REC-15-016, the median time to first dose of rescue (oxycodone 5 mg) was approximately two hours for both groups (Table 7, Clinical Study Report-REC-15-016). The number of rescue analgesics for the first 24 hours was 3.97 versus 5.06 for treatment and placebo, respectively (Table 8, Study Report- REC-15-016).

   The short time to rescue analgesic use and the frequent requirement for rescue analgesics in the two studied models (abdominoplasty and bunionectomy) suggest that the proposed study drug, given 30 mg IV daily, is not suitable as a standalone analgesic for the management of acute pain. 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 4 times over 24 hours raises serious concerns about the clinical relevance of this finding.

   Provide justification to support the use of your product as an analgesic for acute pain given the findings of a short time to first rescue use and frequent rescue medication use.

2. As conveyed at the Pre-NDA meeting, "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. You 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."

   Provide a SPID12-24 for both studies REC-15-015 and REC-15-016.

The applicant responded on November 2, 2017. They compared their product to other currently approved analgesics for acute pain in which patients were allowed higher doses of opioids in combination with acetaminophen every 4 to 6 hours for control pain symptoms. They argued that the increased potency of the immediate-release combination products may have led to fewer doses of rescue analgesia for the approved analgesics, and the differences in number of rescue doses used between two treatment groups were similar to that of other currently approved analgesics for acute pain. For time to the first rescue use, the applicant stated there were highly statistically significant differences between N1539 and placebo in two Phase 2 studies, and time to the first rescue use is not the most important measurement of efficacy for an analgesic in an acute pain setting. The applicant also argued that the difference in pain reduction between treatment groups did appear to decrease at the end of the dosing interval; however, the direction of the effect was maintained. Further arguments were that these studies were not powered to detect a difference from placebo at these time intervals and the reduction of treatment effect at the end of the dosing interval is not unexpected and similar to end of dosing interval effects that

have been observed with other approved analgesic products they chosen to compare with. The clinical review team determined that the applicant's responses were not adequate to address these concerns. As there were no significant differences in PID during the last six hours of the dosing interval (indicative of end-of-dose failure), there were higher numbers of doses of rescue analgesia used by patients and a relatively short time to the first use of rescue medication in studies REC-15-015 and REC-15-016, the applicant's product is not suitable for use as an acute pain analgesic.

5.3 Conclusions and Recommendations

Based on my analyses of the summed pain intensity differences in the two studies reviewed, there was evidence of end-of-dose failure. In addition, the time to the first use rescue analgesic was short, the use of rescue analgesics was frequent, and in most cases, meaningful pain relief was achieved after the first use of rescue analgesic. There is not adequate evidence to demonstrate that N1539, given 30 mg IV daily, is suitable as a standalone analgesic for the management of acute pain. We recommend a complete response (CR) to this NDA from a statistical perspective.

5.4 Labeling Recommendations

As we recommend a CR to this NDA, the labeling is not reviewed at current stage.

Appendix

Demographics of Study REC-15-015

Source: Clinical Study Report Section 11.2.1

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	-

Demographics of Study REC-15-016

Source: Clinical Study Report Section 11.2.1

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	-

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

/s/

YAN ZHOU
04/17/2018

DAVID M PETULLO
04/17/2018
I concur.