CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(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/BLA Number	NDA 215-320
Supplement Number	N/A
Related IND Number	IND 124213
Drug Name	Combogesic® IV (acetaminophen 1000 mg and ibuprofen 300 mg/100 ml solution for infusion)
Indication(s)	for the relief of mild to moderate pain and for the management of moderate to severe pain as an adjunct to opioid analgesics
Applicant	AFT Pharmaceuticals
Date(s)	Submission: August 31, 2021
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Review Priority	Standard
Biometrics Division	Division of Biometric I
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Keywords	Combination drug; factorial design

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1 EXECUTIVE SUMMARY

This review assesses a Phase III Study AFT-MXIV-07 of Combogesic® IV for the treatment of acute postoperative pain after bunionectomy. The proposed indication of Combogesic® IV (the combination of acetaminophen 1000 mg and ibuprofen 300 mg/100 ml solution for infusion) is for the relief of mild to moderate pain and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary. The Applicant's primary results are not appropriate for the decision because they excluded assessments beyond the use of first rescue medication. The results from the reanalyses by carrying forward the pre-rescue pain intensity score up to 2 hours after each rescue treatment (ROCF 2 hours) and ROCF 4 hours support that Combogesic® IV provides superior analgesia to comparable doses of ibuprofen or acetaminophen monotherapy.

Study AFT-MXIV-07 is a Phase III, placebo-controlled, randomized, double-blind, parallel-design trial to investigate the analgesic efficacy of Combogesic® IV compared with the two individual components alone and placebo. Two hundred and seventy-six patients were randomized to the four treatment groups (Combogesic, Acetaminophen, Ibuprofen and Placebo) by ratio of 3:3:3:2 stratified by the two US sites. Two hundred and seventy-one patients completed the study. The primary endpoint was the Time-Adjusted Summed Pain Intensity Difference from baseline over 48 hours ($TASPID_{48}$). The Applicant analyzed the $TASPID_{48}$ on the Intent-To-Treat (ITT) population using an analysis of covariance (ANCOVA) model including treatment effect as the fixed factor and baseline pain intensity as the covariate per the concurred protocol.

The main concern is the Applicant's calculation of the primary endpoint. The Applicant calculated the $TASPID_{48}$ using all Visual Analogue Scale (VAS) pain intensity scores until the first pre-rescue VAS score (inclusive), which is not acceptable because what the Applicant calculated is the TASPID from baseline to the first pre-rescue instead of from baseline over 48 hours. To utilize all the assessments over 48 hours and correspond to the half-life of the rescue medications (oxycodone 5 or 10 mg every 4-6 hours and a secondary rescue analgesia 2-4 mg intravenous morphine sulphate every 4 hours), the Applicant conducted a sensitivity analysis using ROCF 4 hours. The statistical team also requested a reanalysis using ROCF 2 hours. The results from both ROCF 4 hours and ROCF 2 hours analyses support the conclusion that Combogesic® IV is superior to the other three arms ($P<0.001$). The results from sensitivity analyses, supplementary analyses and subgroup analyses by gender, age and race are also consistent with the primary finding.

From the statistical team's point of view, efficacy of the combination for this indication was established.

2 INTRODUCTION

The Applicant submitted an original New Drug Application for Combogesic® IV (acetaminophen 1000 mg and ibuprofen 300 mg in 100ml solution) Injection solution for the relief of mild to moderate pain and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary. The proposed name in the NDA submission is Combogesic® IV. The tradename Maxigesic® was used for the Applicant's product throughout the study report and therefore is used in this statistical review.

Currently Combogesic® (acetaminophen 325 mg and ibuprofen 97.5 mg) Tablets NDA 209471 resubmission is also being reviewed by the Division. Dr. John Lawrence's statistical review (dated September 30, 2020) for NDA 209471 SDN24 is located at https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8059c1d2

2.1 Overview

The primary support for the safety and efficacy of Combogesic® IV is based on the results of the pivotal phase III efficacy study, AFT-MXIV-07. The study protocol was submitted to IND124213 SDN0000 in the safety meeting package. Dr. Yan Zhou reviewed the protocol, and the statistical comments were conveyed to the Applicant via the advice letter dated May 26, 2016. The Applicant responded to the IR and resubmitted the protocol on September 15, 2016. Table 1 summarizes the trial to be assessed in this review.

Table 1 List of All Studies Included in Analysis

Trial ID	Phase and Design*	Treatment Period	Follow-up Period	Number of Subjects per Arm	Study Population
AFT-MXIV-07	Phase III MC, R, DB, PG, PC, AC	48 hours	5-9 days	• Maxigesic®: 75 • Acetaminophen: 76 • Ibuprofen: 75 • Placebo: 50	in subjects with acute postoperative pain after bunionectomy

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

2.2 Data Sources

The Applicant submitted this NDA to the FDA CDER Electronic Document Room (EDR). Electronic datasets are in SAS transport files complying with CDISC/SDTM and CDISC/ADaM standards. The clinical study reports and datasets are located at the following locations:

- NDA215320 SDN1: \\CDSESUB1\evsprod\NDA215320\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\aft-mxiv-07
- NDA215320 SDN8, statistical IR response dated January 14, 2022: \\CDSESUB1\evsprod\NDA215320\0007\m5
- NDA215320 SDN20, statistical IR response dated May 22, 2022: \\CDSESUB1\evsprod\NDA215320\0019\m5

3 STATISTICAL EVALUATION

The single pivotal Study AFT-MXIV-07 is entitled "Maxigesic® IV Bunionectomy Study: A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group and Placebo-Controlled Study of IV Maxigesic®, IV acetaminophen and IV ibuprofen for the Treatment of Acute Postoperative Pain After Bunionectomy".

3.1 Data and Analysis Quality

The statistical team can reproduce the Applicant's results using the submitted data.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study AFT-MXIV-07 is a Phase III, placebo-controlled, randomized, double-blind, parallel-design trial to investigate the analgesic efficacy of Maxigesic® IV compared with the two individual components alone and placebo. The study was conducted in two US sites in Texas and Maryland. Two hundred and seventy-six patients were randomized to the four treatment groups (Maxigesic, Acetaminophen, Ibuprofen and Placebo) by ratio of 3:3:3:2 stratified by study site. Administration of study drug began once the participant's eligibility had been confirmed by scoring at least 40 mm on the VAS scale (measured within 6 hours after the surgery) within 9 hours of discontinuation of the regional anesthesia on Day 1. Study drug was administered q6h for a maximum of 8 doses over the 48-hour double-blind treatment period.

To avoid possible biases the study was designed as a double-blind, randomized comparison. Blinding was achieved using intravenous infusion that was identical in appearance, packaging, and administration route. Each participant and the treatment received were identified by a unique randomization number. This unique randomization number was presented on the label of the study medication. Both participants and investigators were blinded to the treatment allocation. Table 2 summarizes the trial design.

Table 2 Summary of Trial Design

Screening Period		Study Day 0: Surgery	Study Days 1-3				Study Day 7 Follow-up Phone Call
Consent	Screening Assessments		Day 1: Post-surgery Qualification*	Day 1: Randomisation to Study Drug**	Day 1-3: Study Drug** administration	Day 3: Discharge	
Participants provided with information about the study	After consent, eligibility is checked	Standard distal first metatarsal bunionectomy procedure using a standardized regimen of regional anesthesia	Participants must be experiencing moderate to severe pain (≥ 40 mm on VAS) post-operatively to be randomized	Maxigesic® IV Acetaminophen Ibuprofen Placebo	Study drugs administered q6h for a total of 8 doses in 48 hours	Additional Post-operative pain medication prescribed	Follow up safety data

*within 9 hours discontinuation of the post-surgical anesthetic block
**100 mL solution for intravenous infusion

Source: Clinical Study Report Version 3 (Dated October 5, 2018), Table 3, page 31/183.

Subjects were allowed to receive supplemental analgesia with an opioid product (oxycodone 5 or 10 mg every 4-6 hours as needed) after surgery and before randomization to help control breakthrough pain if the regional anesthetic infusion failed to provide adequate anesthesia. Though sites were encouraged to use only the oxycodone as supplemental analgesia if adequate pain relief was not achieved with oral oxycodone, as a secondary rescue analgesia, 2-4 mg intravenous morphine sulphate was allowed to be administered every 4 hours, as needed. If the regional anesthetic infusion and supplemental primary and secondary analgesia do not effectively control the subject's postoperative pain, the subject was discontinued from the study and pain was managed per standard of care/investigator discretion.

Visual Analogue Scale (VAS) pain intensity scores were obtained by marking on a 100 mm VAS scale with anchors for "no pain" (0 mm) and "worst pain imaginable" (100 mm). The VAS was completed at rest. VAS pain intensity scores were assessed by participants at the scheduled time points as listed below:

- Baseline (immediately prior to the first dose of study medication)
- 5, 10, 15, 30, 45 minutes, 1, 1.5, 2, 3, 4, 5, 6 hours after the first dose of the study drug
- Immediately before and 2 hours after each subsequent dose (doses 2-8) of the study drug while awake
- At the end of 48 hours of double-blind treatment period
- Immediately before taking each dose of the rescue medication if additional analgesia is required.
- At the time of withdrawal (if applicable)

The primary efficacy endpoint was the time-adjusted Summed Pain Intensity Difference (SPID) from baseline over 48 hours ($TASPID_{48}$): $TASPID_{48}$(mm) = SPID (mm*hr) / time interval from baseline to the final VAS used in the SPID (hr). For the calculation of the SPID, intermittent missing VAS scores will be imputed by linear interpolation of adjacent values immediately preceding and following the missing value. Additionally, if a patient required rescue medication, the SPID will be calculated up until the first Pre-Rescue VAS pain assessment (inclusive).

Statistical comment: The calculation of the primary endpoint is not acceptable because what the Applicant calculated is $TASPID_{pre\text{-}rescue}$ instead of the concurred $SPID_{48}$. To utilize all the assessments over 48 hours and correspond to the half-life of the rescue medications (oxycodone 5 or 10 mg every 4-6 hours and a secondary rescue analgesia 2-4 mg intravenous morphine sulphate every 4 hours), the Applicant conducted a sensitivity analysis using ROCF 4 hours. The statistical team also requested a reanalysis using ROCF 2 hours.

3.2.2 Statistical Methodologies

Analysis Datasets: The Applicant's primary population for the efficacy analysis is the Intent-To-Treat (ITT) population, consisting of all subjects who receive at least 1 dose of study drug.

Primary Analysis: The Applicant performed primary efficacy analysis of TASPID until first rescue on the ITT population using an analysis of variance (ANOVA) model, which included treatment effect as the fixed factor. As per the Statistical Analysis Plan (SAP), an analysis of covariance (ANCOVA) model with baseline pain intensity as the covariate was initially tested. As the baseline VAS score was not significant effect in the initial model and there was no correlation between the $TASPID_{48}$ and baseline pain for any of the treatment groups, the covariate was dropped from the analysis.

The statistical reviewer performed a reanalysis of $TASPID_{48}$ by ROCF 2 hours using an ANCOVA model with treatment effect as the fixed factor and baseline pain intensity as the covariate per the SAP. Because the Applicant randomized the subjects stratified by study site, the statistical reviewer also performed a supplementary analysis using an ANOVA model including treatment, study site and baseline pain intensity for both ROCF 4 hours and ROCF 2 hours analyses.

Maxigesic® IV was compared with each of the three comparators using a sequential testing strategy to preserve the two-sided type I error rate at $\alpha=0.05$. The pairwise comparisons were conducted in the following sequence with the sequence of tests only continuing if the preceding test is statistically significant at $p<0.05$. The pairwise comparisons with Maxigesic® IV were conducted in the following sequence:

1. Placebo
2. Acetaminophen
3. Ibuprofen

Multiplicity Adjustment: There was no correction for multiple comparisons for the analyses of the secondary endpoints.

Subgroup Analyses: Analysis of the primary efficacy endpoint was also presented by gender, age, and race.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

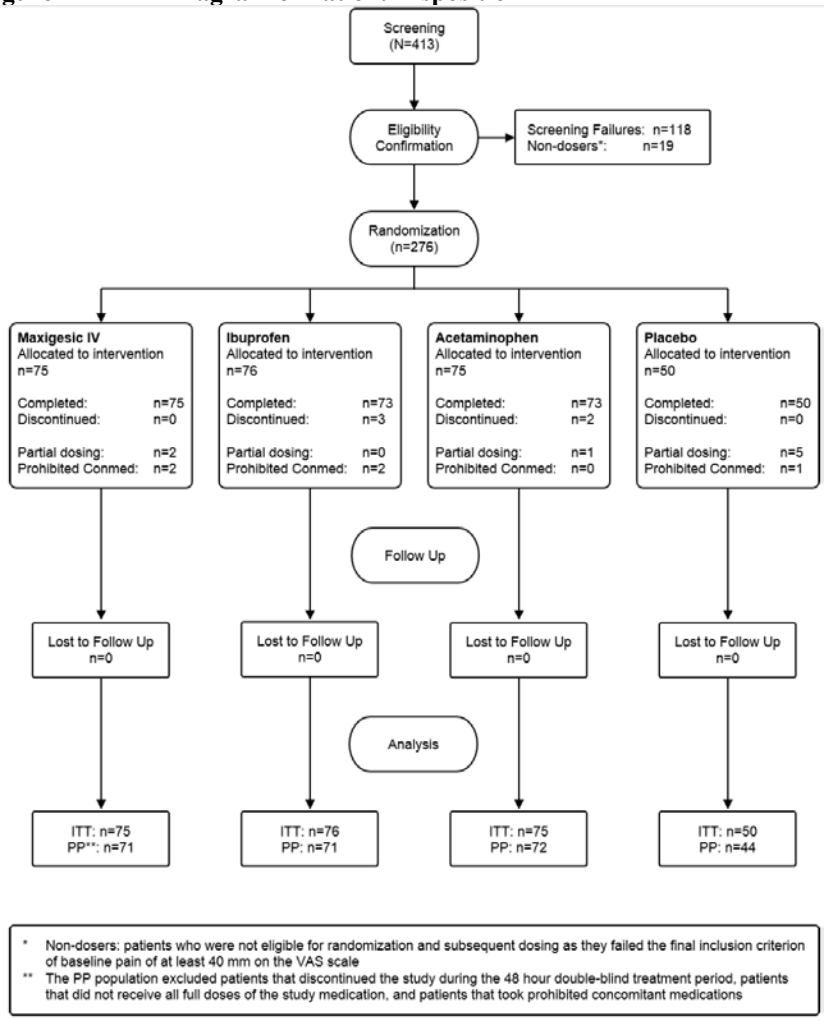
Two hundred and seventy-six patients from two US sites were randomized to the four treatment groups (Maxigesic, Acetaminophen, Ibuprofen and Placebo) by ratio of 3:3:3:2 stratified by study site. Two hundred and seventy-one patients completed the study. Table 3 and Figure 1 summarize the patient disposition.

Table 3 Patient Disposition

	Maxigesic	Ibuprofen	Acetaminophen	Placebo	Total
Randomized	75	76	75	50	276
Intention-To-Treat population	**75**	**76**	**75**	**50**	**276**
Completed	75	73	73	50	271

Source: Statistical team's analysis using Applicant's adam-adsl.

Figure 1 Diagram of Patient Disposition



Source: Clinical Study Report Version 3 (Dated October 5, 2018), Table 11, page 65/183.

Tables 4 and 5 summarize the demographic and baseline characteristics for the efficacy analysis population. Mean and standard deviation (SD) as well as median and range are reported for continuous variables; frequency and proportion are reported for categorical variables. Among the 276 participants treated, mean age was 42 years old; mean weight was 77 kg; 19% were male; 62% were Caucasian, and 77% were Not Hispanic or Latino. More female participants were enrolled than male participants, which reflects the pain model used in this study (bunionectomy). The demographic and baseline characteristics were broadly comparable across the four treatment groups.

Table 4 Demographic Information (ITT)

	Maxigesic® N=75	Ibuprofen N=76	Acetaminophen N=75	Placebo N=50	Total N=276
Age (Years)					
N	75	76	75	50	276
Mean (SD)	42.3 (11.6)	43.3 (12.3)	41.9 (12.5)	41.7 (12.7)	42.4 (12.2)
Median	41.0	44.5	41.0	38.5	43.0
Min ; Max	21 ; 65	18 ; 63	19 ; 65	20 ; 65	18 ; 65
Sex					
Male	13 (17.3%)	11 (14.5%)	17 (22.7%)	10 (20.0%)	51 (18.5%)
Female	62 (82.7%)	65 (85.5%)	58 (77.3%)	40 (80.0%)	225 (81.5%)
Race					
White	48 (64.0%)	39 (51.3%)	55 (73.3%)	29 (58.0%)	171 (62.0%)
Black or African American	23 (30.7%)	32 (42.1%)	17 (22.7%)	20 (40.0%)	92 (33.3%)
Asian	3 (4.0%)	3 (3.9%)	2 (2.7%)	1 (2.0%)	9 (3.3%)
Multiple	1 (1.3%)	2 (2.6%)	1 (1.3%)	0 (0.0%)	4 (1.4%)
Ethnicity					
Hispanic or Latino	18 (24.0%)	15 (19.7%)	18 (24.0%)	7 (14.0%)	58 (21.0%)
Not Hispanic or Latino	56 (74.7%)	60 (78.9%)	56 (74.7%)	41 (82.0%)	213 (77.2%)
Not Stated	0 (0.0%)	1 (1.3%)	1 (1.3%)	2 (4.0%)	4 (1.4%)
Unknown	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Height (cm)					
N	75	76	75	50	276
Mean (SD)	166.3 (8.4)	166.3 (10.0)	166.8 (8.9)	166.7 (7.9)	166.5 (8.9)
Median	165.1	164.5	165.1	166.8	165.1
Min ; Max	152.4 ; 193.0	151.0 ; 199.0	149.9 ; 191.0	152.4 ; 182.9	149.9 ; 199.0
Weight (kg)					
N	75	76	75	50	276
Mean (SD)	79.2 (15.5)	75.6 (17.0)	74.2 (15.6)	79.5 (15.5)	76.9 (16.0)
Median	76.2	73.3	74.0	75.2	75.0
Min ; Max	54.0 ; 124.3	52.0 ; 131.0	46.0 ; 112.9	52.2 ; 111.0	46.0 ; 131.0
BMI (kg/m²)					
N	75	76	75	50	276
Mean (SD)	28.5 (4.6)	27.2 (5.1)	26.6 (5.3)	28.5 (4.8)	27.7 (5.0)
Median	28.5	26.7	26.0	27.7	27.1
Min ; Max	18.7 ; 38.8	18.0 ; 39.8	17.1 ; 40.0	20.8 ; 39.3	17.1 ; 40.0

Source: Clinical Study Report Version 3 (Dated October 5, 2018), Table 11, page 68/183.

Table 5 Baseline Characteristics (ITT)

	Maxigesic® N=75	Ibuprofen N=76	Acetaminophen N=75	Placebo N=50	Total N=276
Surgery Duration (min)					
N	75	76	75	50	276
Mean (SD)	36.6 (14.5)	35.1 (12.3)	36.1 (12.8)	35.8 (12.6)	35.9 (13.0)
Median	35.0	33.5	34.0	36.5	34.0
Min ; Max	18 ; 88	16 ; 73	16 ; 70	15 ; 60	15 ; 88
Informed Consent to Randomization (days)					
N	75	76	75	50	276
Mean (SD)	15.2 (6.9)	14.5 (6.9)	15.5 (7.1)	14.5 (5.8)	14.9 (6.8)
Median	14.0	13.0	13.0	14.0	14.0
Min ; Max	5 ; 28	5 ; 28	6 ; 29	5 ; 26	5 ; 29
Randomization to Treatment Start (min)					
N	75	76	75	50	276
Mean (SD)	7.0 (5.0)	7.3 (6.1)	7.0 (5.0)	6.7 (4.9)	7.0 (5.3)
Median	6.0	5.0	6.0	5.5	5.5
Min ; Max	1 ; 28	0 ; 37	1 ; 36	0 ; 26	0 ; 37
VAS (mm)					
N	75	76	75	50	276
Mean (SD)	69.3 (15.8)	68.9 (14.4)	66.2 (14.2)	68.1 (15.8)	68.1 (15.0)
Median	68.0	67.5	65.0	67.5	67.0
Min ; Max	41 ; 100	40 ; 100	41 ; 100	42 ; 100	40 ; 100
Systolic Blood Pressure (mmHg)					
N	75	76	75	50	276
Mean (SD)	115.2 (15.0)	116.7 (14.5)	117.4 (17.1)	116.2 (13.8)	116.4 (15.2)
Median	113.0	114.0	114.0	115.5	114.0
Min ; Max	86 ; 158	92 ; 159	88 ; 183	90 ; 144	86 ; 183
Diastolic Blood Pressure (mmHg)					
N	75	76	75	50	276
Mean (SD)	72.7 (8.8)	73.1 (8.9)	72.5 (9.6)	72.3 (9.5)	72.7 (9.1)
Median	73.0	72.0	72.0	71.5	72.0
Min ; Max	47 ; 91	56 ; 97	55 ; 106	57 ; 93	47 ; 106
Heart Rate (beats/min)					
N	75	76	75	50	276
Mean (SD)	78.1 (11.3)	77.2 (9.8)	77.9 (11.3)	78.5 (10.4)	77.9 (10.7)
Median	78.0	78.5	79.0	79.0	79.0
Min ; Max	56 ; 113	50 ; 102	53 ; 106	56 ; 105	50 ; 113
Respiratory Rate (breaths/min)					
N	75	76	75	50	276
Mean (SD)	17.1 (3.1)	16.5 (2.7)	16.6 (2.7)	17.4 (3.3)	16.9 (2.9)
Median	16.0	16.0	16.0	16.0	16.0
Min ; Max	12 ; 32	8 ; 24	9 ; 28	12 ; 28	8 ; 32
Temperature (C)					
N	75	76	75	50	276
Mean (SD)	36.9 (0.35)	37.0 (0.46)	36.9 (0.31)	36.9 (0.47)	36.9 (0.40)
Median	36.9	36.9	36.8	36.8	36.9
Min ; Max	36.1 ; 37.9	36.2 ; 38.2	36.1 ; 38.0	36.1 ; 38.4	36.1 ; 38.4

Source: Clinical Study Report Version 3 (Dated October 5, 2018), Tables 12-15, pages 69-70/183.

Table 6 summarizes the treatment compliance. Overall, there were no obvious differences in the study drug usage and compliance among the four treatment groups.

Table 6 Study Drug Usage and Compliance (ITT)

	Maxigesic® N=75	Ibuprofen N=76	Acetaminophen N=75	Placebo N=50	Total N=276
First 24 Hours					
Total Dose (mL)					
N (Missing)	75 (0)	76 (0)	75 (0)	49 (1)	275 (1)
Mean (SD)	399.6 (2.4)	394.7 (32.2)	397.3 (23.1)	393.9 (42.9)	396.6 (27.5)
Median	400.0	400.0	400.0	400.0	400.0
Min ; Max	380 ; 400	200 ; 400	200 ; 400	100 ; 400	100 ; 400
Dose Compliance (%)					
N (Missing)	75 (0)	76 (0)	75 (0)	49 (1)	275 (1)
Mean (SD)	99.9 (0.6)	98.7 (8.1)	99.3 (5.8)	98.5 (10.7)	99.2 (6.9)
Median	100.0	100.0	100.0	100.0	100.0
Min ; Max	95 ; 100	50 ; 100	50 ; 100	25 ; 100	25 ; 100
Next 24 Hours					
Total Dose (mL)					
N (Missing)	75 (0)	74 (0)	74 (0)	50 (0)	273 (0)
Mean (SD)	400.0 (0.0)	397.3 (23.2)	395.5 (35.0)	394.2 (29.6)	397.0 (25.2)
Median	400.0	400.0	400.0	400.0	400.0
Min ; Max	400 ; 400	200 ; 400	100 ; 400	200 ; 400	100 ; 400
Dose Compliance (%)					
N (Missing)	75 (0)	74 (0)	74 (0)	50 (0)	273 (0)
Mean (SD)	100.0 (0.0)	99.3 (5.8)	98.9 (8.8)	98.6 (7.4)	99.2 (6.3)
Median	100.0	100.0	100.0	100.0	100.0
Min ; Max	100 ; 100	50 ; 100	25 ; 100	50 ; 100	25 ; 100

Source: Clinical Study Report Version 3 (Dated October 5, 2018), Table 16, pages 71/183.

3.2.4 Results and Conclusions

This section includes the results from the Applicant's primary analysis, the FDA's reanalysis, Applicant's sensitivity analyses and the FDA's supplementary analyses.

The main concern is the Applicant's calculation of the primary endpoint. The Applicant calculated the $TASPID_{48}$ using all VAS pain intensity scores until the first pre-rescue VAS score (inclusive), which is not acceptable because what the Applicant calculated is the TASPID from baseline to the first pre-rescue instead of from baseline over 48 hours. To utilize all the assessments over 48 hours and correspond to the half-life of the rescue medications (oxycodone 5 or 10 mg every 4-6 hours and a secondary rescue analgesia 2-4 mg intravenous morphine sulphate every 4 hours), the Applicant conducted a sensitivity analysis using ROCF 4 hours. The statistical team also requested a reanalysis using ROCF 2 hours. The results from both ROCF 4 hours and ROCF 2 hours analyses support the conclusion that Combogesic® IV is superior to the other three arms ($P<0.001$), which are also confirmed by the results from a sensitivity analysis using the scheduled and pre-rescue assessments.

The Applicant analyzed the $TASPID_{48}$ on the ITT population using an ANCOVA model including treatment effect as the fixed factor and baseline pain intensity as the covariate per the concurred protocol. Because the Applicant randomized the subjects stratified by study site, the statistical reviewer also performed a supplementary analysis using an ANCOVA model including treatment, study site and baseline pain intensity for both ROCF 4 hours and ROCF 2 hours. The results from the supplementary analyses are also consistent with the primary finding.

Following are the three sensitivity analyses conducted by the Applicant:

- Sensitivity Analysis 1 (until First Pre-Rescue): Calculate the $TASPID_{48}$ using all VAS pain assessments recorded up until the first Pre-Rescue VAS score (inclusive), and by carrying forward the first Pre-Rescue VAS score until the end of participation in the study.

- Sensitivity Analysis 2 (Scheduled and Pre-Rescue): Calculate the $TASPID_{48}$ using the full complement of VAS pain assessments (includes both Scheduled AND Pre-Rescue VAS scores recorded by each patient).

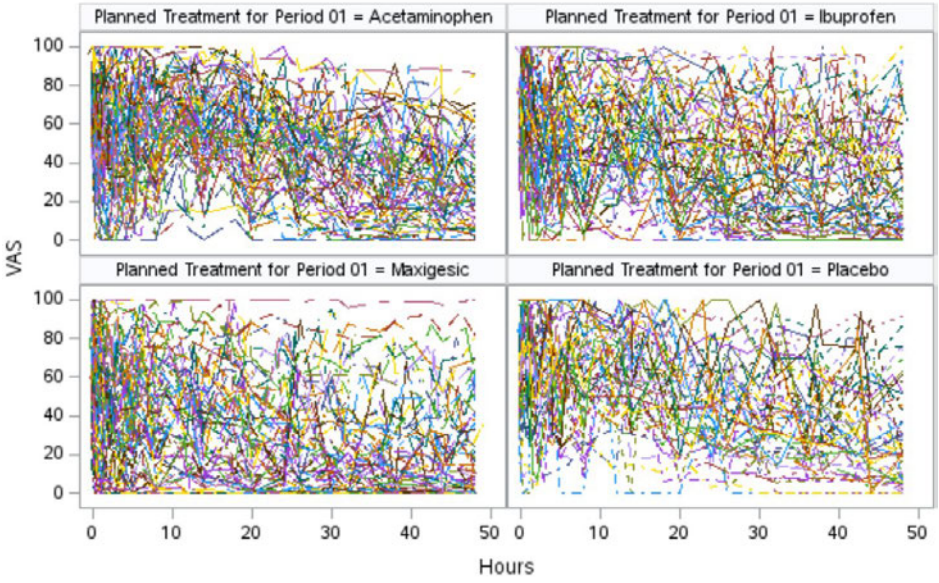
- Sensitivity Analysis 3 (ROCF 4 hours): Calculate the $TASPID_{48}$ by carrying forward the Pre-Rescue VAS score up to 4 hours after each rescue treatment. 4 hours is consistent with the duration of action of both rescue medications (oxycodone and morphine). In the event that a patient requires two or more doses of rescue medication within a 4-hour interval, a subsequent Pre-Rescue VAS score will override the previous one (i.e. Pre-Rescue VAS scores will not supplant subsequent Pre-Rescue VAS scores).

Statistical comment: Sensitivity Analysis 1 is not acceptable because the first pre-rescue VAS score was carried forward until the end of participation in the study, which covered the effect of later treatment dosing, and the results from Sensitivity Analysis 1 do not sound reasonable

because the treatment effects of the two single dose groups are negative. The results from Sensitivity Analyses 2 and 3 are consistent with the primary finding.

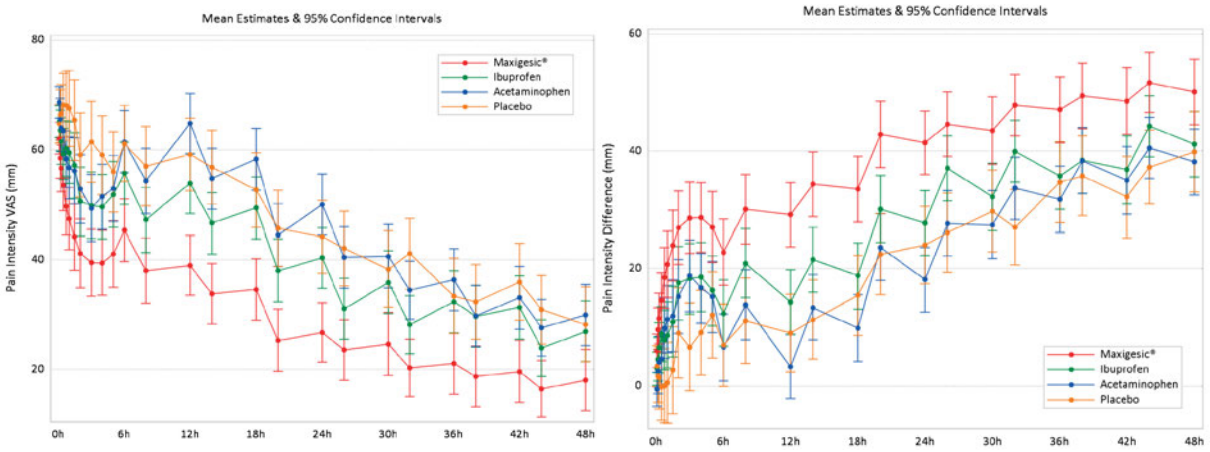
Figure 2 illustrates the observed pain intensity scores by treatment group. The horizontal axis is the time in hours from the baseline and the vertical axis is the VAS pain intensity score (mm). The Maxigesic group has the densest data in the lower left whereas the placebo group has the least dense data in the lower left, which indicates the pain score might be lower for the same time after treatment and the time might be shorter for the same VAS pain intensity scores in the Maxigesic group than those in other groups. Figure 3 demonstrates mean VAS pain intensity and mean difference by treatment group over 48 hours treatment period.

Figure 2 Observed VAS Pain Intensity Scores (mm)



Source: statistical reviewer's analysis using variable aval from dataset advas.xpt.

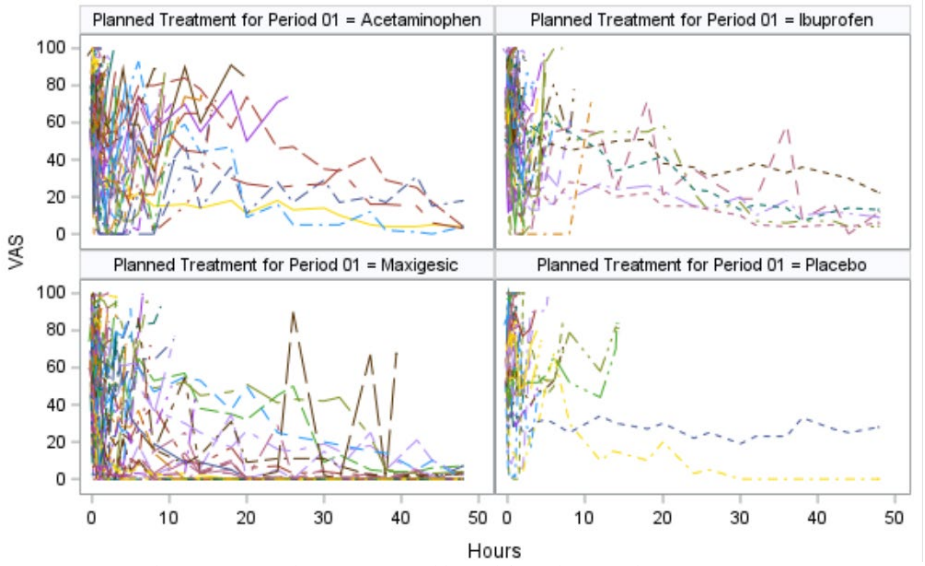
Figure 3 Mean VAS and Mean VAS Difference over 48 Hours (mm)



Source: Clinical Study Version 3 (Dated October 5, 2018), Figure 4 on page 73 and Figure 11 on page 89/183.

Applicant's Primary Analysis: Figure 4 illustrates the VAS pain intensity scores (mm) used in the Applicant's primary analysis. Table 7 and Figure 5 summarize the results of Applicant's primary analysis.

Figure 4 Applicant's Primary Analysis Data: until First Dose of Rescue



Source: statistical reviewer's analysis using variable aval from dataset advas.xpt.

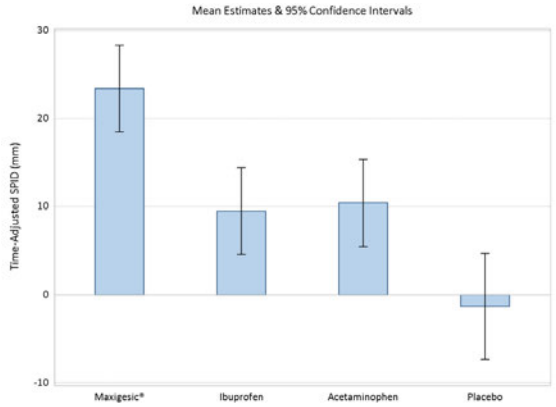
Table 7 Applicant's Primary Analysis Results

	Maxigesic® N=75	Ibuprofen N=76	Acetaminophen N=75	Placebo N=50
N	75	76	75	50
Mean (SE)	23.41 (2.89)	9.51 (2.53)	10.42 (2.49)	-1.30 (2.08)
Median	23.10	5.40	3.45	-4.00
Min ; Max	-34.08 ; 74.17	-30.68 ; 79.98	-26.78 ; 65.43	-22.42 ; 47.50
Mean Estimate (SE)	23.41 (2.50)	9.51 (2.49)	10.42 (2.50)	-1.30 (3.07)
95% Confidence Interval	18.48 ; 28.34	4.61 ; 14.40	5.49 ; 15.35	-7.33 ; 4.74
Difference Estimate (SE)	-	13.90 (3.53)	12.99 (3.54)	24.71 (3.96)
95% Confidence Interval	-	6.95 ; 20.85	6.02 ; 19.96	16.92 ; 32.50
p-value	-	<0.001	<0.001	<0.001

Model TASPID = Treatment (no significant correlation between TASPID and baseline pain in any treatment group).

Source: Clinical Study Report Version 3 (Dated October 5, 2018), Table 17, page 72/183, using ANOVA model of $TASPID_{48}$ with treatment as the fixed effect (no significant correlation between TASPID and baseline pain in any treatment group and the effect was not significant in the initial ANCOVA model).

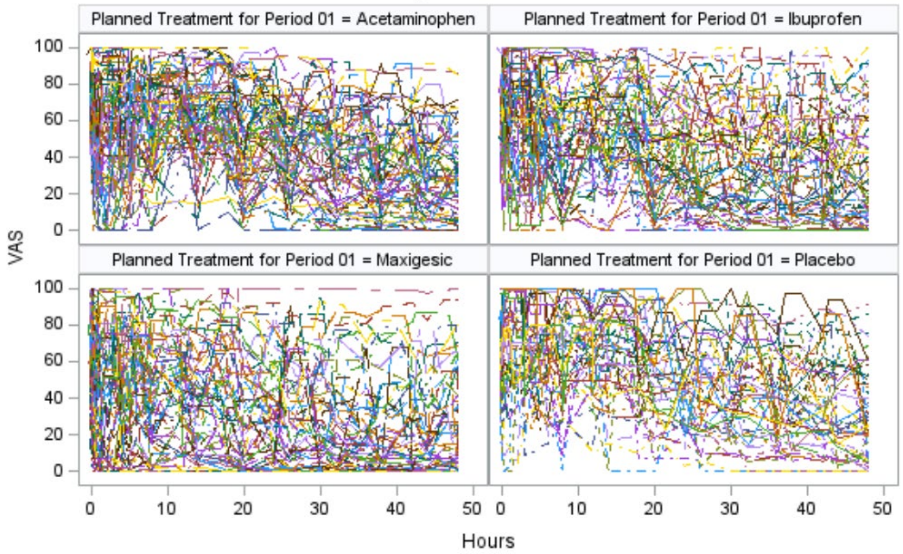
Figure 5 Applicant's Primary Analysis Results



Source: Clinical Study Version 3 (Dated October 5, 2018), Figure 4, page 73/183.

FDA's Reanalysis: Figure 6 illustrates the VAS pain intensity scores (mm) used in FDA's primary analysis. Table 8 and Figure 7 summarize the FDA's reanalysis results.

Figure 6 FDA's Reanalysis Data: ROCF 2 hours



Source: statistical reviewer's analysis using variable aval from dataset advas.xpt.

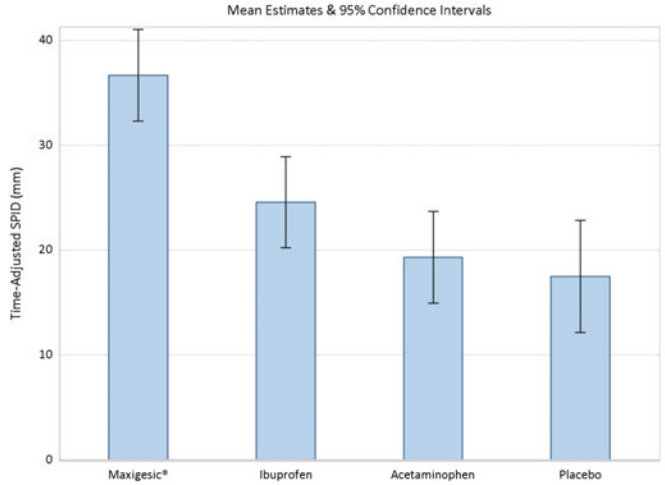
Table 8 FDA's Reanalysis Results

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

Model TASPID = Treatment + Baseline Pain

Source: Clinical Study Report Version 4 (Dated January 4, 2022), Table 21, page 78/185, using ANCOVA model of $TASPID_{48}$ with treatment as the fixed effect and baseline pain intensity as the covariate.

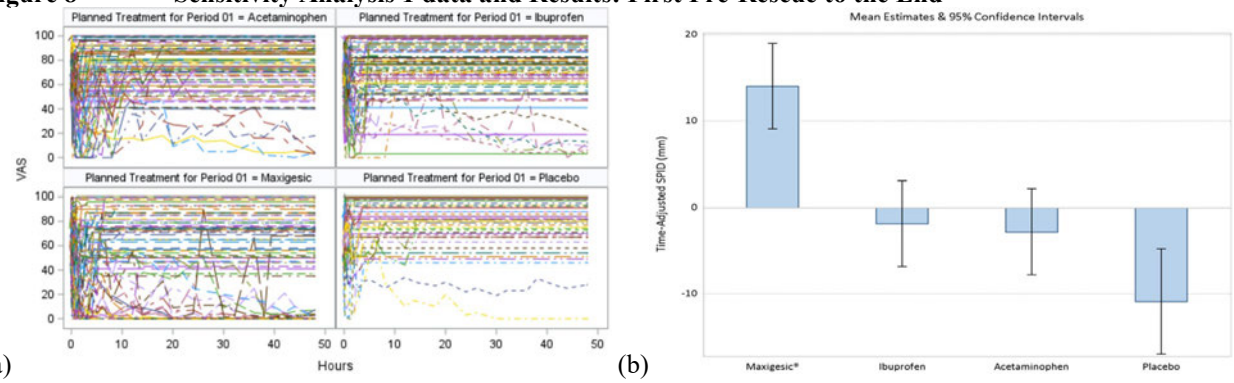
Figure 7 FDA's Reanalysis Results



Source: Clinical Study Report Version 4 (Dated January 4, 2022), Figure 8, page 79/185, using ANCOVA model of $TASPID_{48}$ with treatment as the fixed effect and baseline pain intensity as the covariate.

Sensitivity Analyses of Primary Endpoint: Figures 8-10 illustrate the VAS pain intensity scores (mm) and results for the three Sensitivity Analyses.

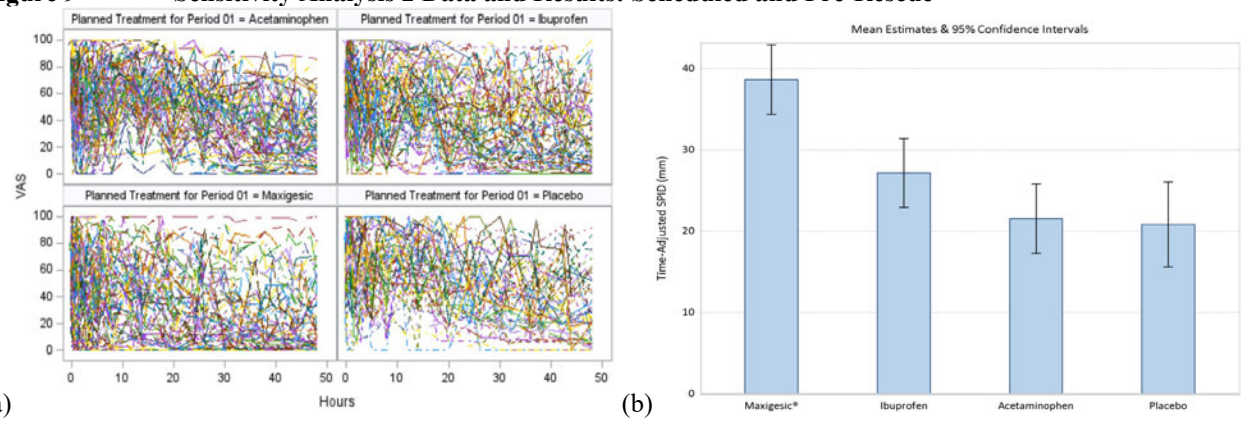
Figure 8 Sensitivity Analysis 1 data and Results: First Pre-Rescue to the End



(a) (b)

Source:(a) statistical reviewer's analysis using variable aval from dataset advas.xpt; (b) Clinical Study Report Version 3 (Dated October 5, 2018), Figure 5, page 74/183, using ANOVA model of $TASPID_{48}$ with treatment as the fixed effect.

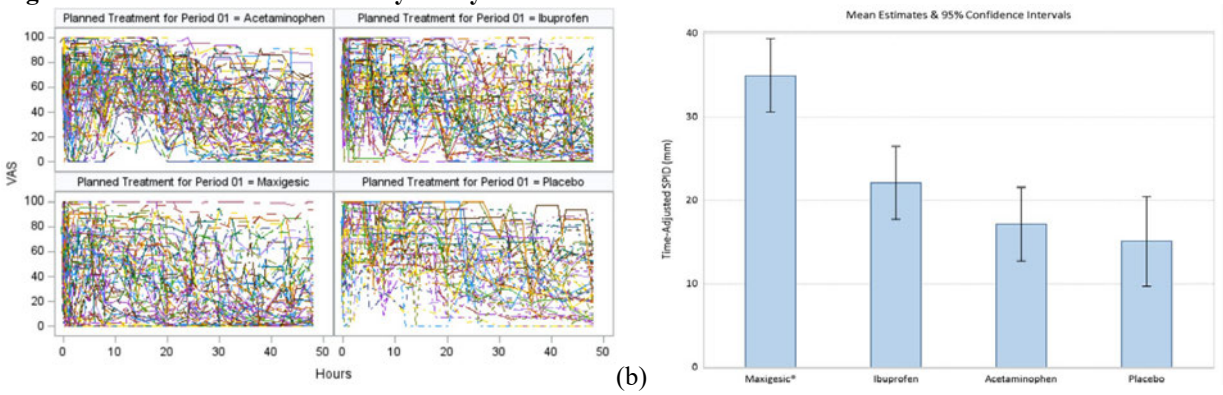
Figure 9 Sensitivity Analysis 2 Data and Results: Scheduled and Pre-Rescue



(a) (b)

Source: (a) statistical reviewer's analysis using variable aval from dataset advas.xpt; (b) Clinical Study Report Version 3 (Dated October 5, 2018), Figure 6, page 76/183, using ANCOVA model of $TASPID_{48}$ with treatment as the fixed effect and baseline pain intensity as the covariate.

Figure 10 Sensitivity Analysis 3 Data and Results: ROCF 4 hours



(b)

Source: (a) statistical reviewer's analysis using variable aval from dataset advas.xpt; (b) Clinical Study Report Version 3 (Dated October 5, 2018), Figure 7, page 77/183, using ANCOVA model of $TASPID_{48}$ with treatment as the fixed effect and baseline pain intensity as the covariate.

4 FINDINGS IN SUBGROUP POPULATIONS

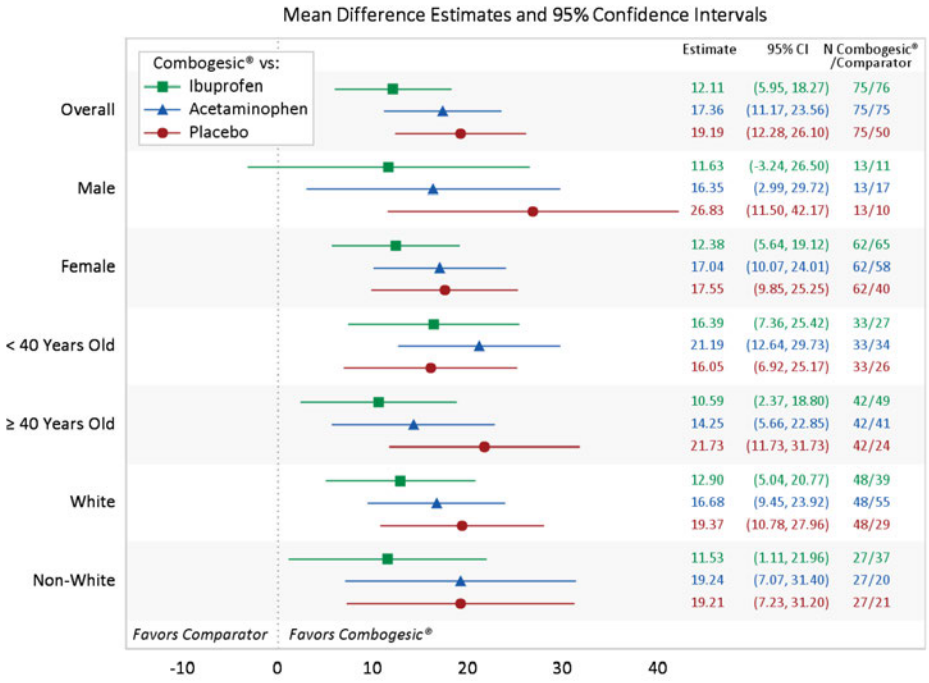
The subgroup analyses presented in this section are all exploratory. The main objective of the exploratory subgroup analysis is to assess consistency across subgroups with respect to the primary analysis results. Because of the exploratory purpose of the subgroup analyses, the p-values are not presented here. The estimated treatment effect in the primary endpoint $TASPID_{48}$ with ROCF 2 hours is consistent across gender, age, and race subgroups. There were no important differences in the results within these subgroups compared to the overall analysis. The statistical team confirmed the applicant's subgroup analysis in the updated clinical study report version 5. Table 9 summarizes the mean estimates and their 95% CI, and Figure 11 illustrates the mean difference estimates and their 95% CI.

Table 9 Subgroup Analyses by Gender, Age and Race (ITT)

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

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

Figure 11 Forest Plots for Subgroup Analyses



Source: Clinical Study Report Version 5 (Dated May 20, 2022), Figure 29, page 144/188, using ANCOVA model of $TASPID_{48}$ with treatment as the fixed effect and baseline pain as the covariate on the ITT population.

5 SUMMARY AND CONCLUSIONS

This section summarizes the main statistical issues we identified and our recommendations.

5.1 Statistical Issues

The main concern is the Applicant's calculation of the primary endpoint. The Applicant calculated the $TASPID_{48}$ using VAS scores until the first pre-rescue VAS score (inclusive), which is not acceptable because what the Applicant calculated is the TASPID from baseline to the first pre-rescue instead of from baseline over 48 hours. To utilize all the assessments over 48 hours and correspond to the half-life of the rescue medications (oxycodone 5 or 10 mg every 4-6 hours and a secondary rescue analgesia 2-4 mg intravenous morphine sulphate every 4 hours), the Applicant conducted a sensitivity analysis using ROCF 4 hours. The statistical team also requested a reanalysis using ROCF 2 hours. The results from both ROCF 4 hours and ROCF 2 hours analyses support the conclusion that Combogesic® IV is superior to the other three arms ($P<0.001$).

5.2 Conclusions and Recommendations

From the statistical team's point of view, efficacy of the combination for this indication was established.

5.3 Labeling Recommendations

The statistical team has the following recommendations regarding the proposed labeling in Section 14.1 (Phase 3 Clinical Efficacy Study):

- Primary Efficacy Endpoint Analysis: The applicant's primary efficacy endpoint calculation is not appropriate because they excluded results beyond first rescue. Change

  (b) (4)

  to

  'The primary efficacy endpoint was the time-adjusted Sum of Pain Intensity Differences over 48 hours ($SPID_{48}$) with each pre-rescue Visual Analogue Scale (VAS) carried forward up to 2 hours. An analysis of covariance was used for the primary efficacy analysis with treatment as the fixed effect and baseline pain intensity score as the covariate on the intent to treat population.'

- Statistical Results:
  - According to FDA's primary analysis, update the statistical results (b) (4)

    (b) (4)

(b) (4) to 'The analysis of time-adjusted SPID48 demonstrated that COMBOGESIC® IV (least square mean (LSM) = 36.7, SE = 2.2) provided more effective pain relief than placebo (LSM = 17.5, SE = 2.7), acetaminophen (LSM = 19.3, SE = 2.2) or ibuprofen (LSM = 24.6, SE = 2.2)'.

- Delete (b) (4) because the group statistics are reported in the text and Figure 1.
- Replace Figure 1 with the following figure.

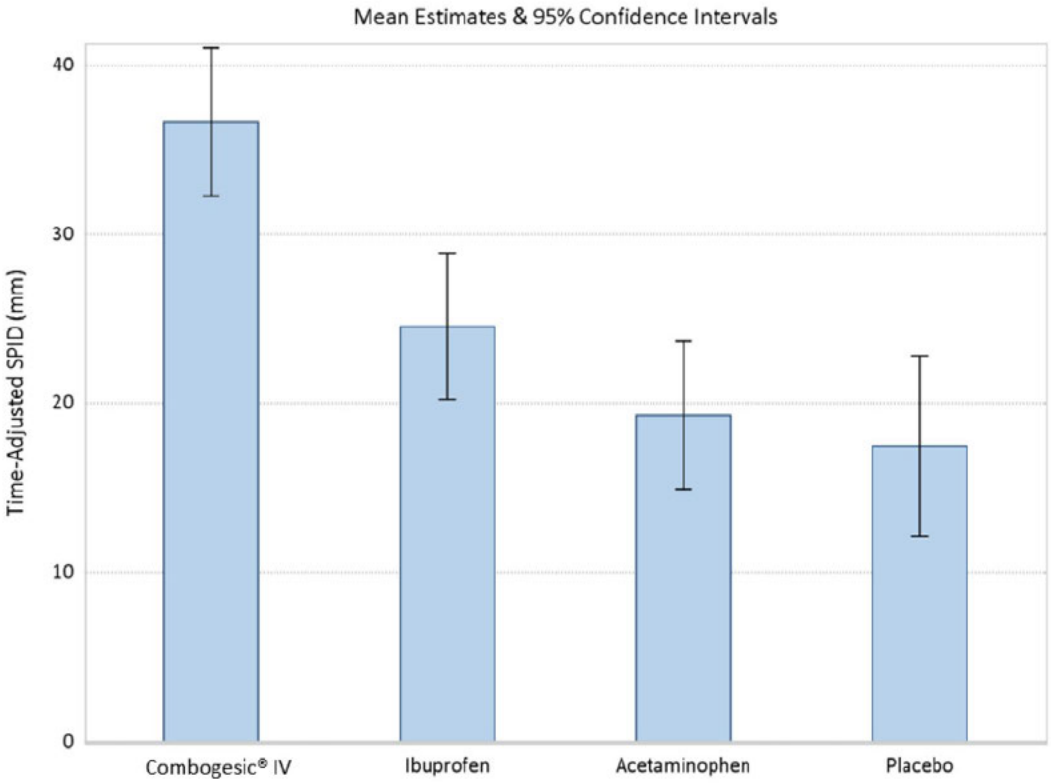


Figure 1: Time-adjusted $SPID_{48}$ with Pre-Rescue VAS Score Carried Forward up to 2 Hours

(b) (4)

6 REFERENCE

- NDA215320 SDN1: \\CDSESUB1\evsprod\NDA215320\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\aft-mxiv-07

- NDA215320 SDN8, statistical IR response dated January 14, 2022: \\CDSESUB1\evsprod\NDA215320\0007\m5

- NDA215320 SDN20, statistical IR response dated May 22, 2022: \\CDSESUB1\evsprod\NDA215320\0019\m5

- IND124213 SDN1 (Study Protocol AFT-MXIV-07), not found in DARRTS.

- IND124213 SDN1 Statistical review (dated May 16, 2016) on protocol AFT-MXIV-07: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af803e7847&_afrRedirect=218856197786594

- IND124213 Advice letter (dated May 26, 2016): https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af803ea35e&_afrRedirect=220648401213160

- IND124213 SDN8 Applicant responded to the IR and resubmitted protocol on September 15, 2016, not found in DARRTS.

- IND124213 SDN15 (Pre NDA meeting) submitted on June 5, 2018 \\CDSESUB1\evsprod\IND124213\0012

- IND124213 SDN15 (Pre NDA meeting) meeting minutes dated August 29, 2018 https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804b237f&_afrRedirect=236781229141986

- NDA 209471 SDN24 statistical review dated September 30, 2020 https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8059c1d2

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/

JING HAN
06/27/2022 05:36:26 PM

KATHERINE B MEAKER
06/27/2022 06:09:30 PM

SUE JANE WANG
06/27/2022 06:19:16 PM
I concur with this NDA review.