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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number: 21-926/000
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and naproxen sodium 500 mg)
Indication: Migraine
Applicant: Pozen
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TABLE OF CONTENTS

1. Executive Summary3

1.1 Conclusions and Recommendations.....3

1.2 Brief Overview of Clinical Studies.....3

1.3 Statistical Issues and Findings5

2. Introduction6

2.1 Overview.....6

2.2 Data Sources7

3. Statistical Evaluation.....7

3.1 Evaluation of Efficacy7

 3.1.1 Study MT400-3017

 3.1.1.1 Objective of Study.....7

 3.1.1.2 Study Design7

 3.1.1.3 Efficacy Measures8

 3.1.1.4 Statistical Analysis Plan8

 3.1.1.5 Study Population8

 3.1.1.6 Applicant’s Efficacy Results12

 3.1.2 Study MT400-302.....14

 3.1.2.1 Objective of Study.....14

 3.1.2.2 Study Design14

 3.1.2.3 Efficacy Measures14

 3.1.2.4 Statistical Analysis Plan14

 3.1.2.5 Study Population14

 3.1.2.6 Applicant’s Efficacy Results18

 3.1.3 Reviewer’s Analysis.....19

 Analysis on Nausea20

3.2 Evaluation of Safety.....21

4. Findings in Special/Subgroup Populations22

4.1 Gender, Age, and Race22

4.2 Other Special/Subgroup Populations23

5. Summary and Conclusions.....23

5.1 Statistical Issues and Collective Evidence23

5.2 Conclusions and Recommendations.....25

Statistical Review and Evaluation

1. Executive Summary

1.1 Conclusions and Recommendations

The data and analyses based on both Studies 301 and 302 indicated that Trexima was statistically significantly superior to placebo for 2-hour pain relief, 2-hour photophobia-free and 2-hour phonophobia-free. Trexima was statistically significantly superior to placebo for 2-hour nausea-free in Study 302. Trexima was also statistically significantly superior to the components for sustained pain free.

1.2 Brief Overview of Clinical Studies

The submission had two identical randomized, double-blind, parallel-group, placebo and active controlled single attack studies in patients with moderate or severe migraine headache. Both studies compared a single Trexima tablet with placebo for relief of migraine pain and associated symptoms at 2 hours and compared Trexima to the individual active components (85 mg sumatriptan RT and 500 mg naproxen sodium) for sustained pain relief through 24 hours. Each study enrolled approximately 1600 patients to each of the four treatment groups in a 1:1:1:1 ratio at approximately 60 centers in the United States.

The primary endpoints for the superiority comparison between Trexima and placebo are at two hours post-dose for pain relief (no or mild pain), incidence of photophobia, incidence of phonophobia, and incidence of nausea.

The primary endpoints for the superiority comparisons between Trexima and its individual components, sumatriptan and naproxen sodium, are sustained pain-free at 24 hours, which is defined as no pain at 2 hours and no relapse of pain (to mild, moderate or severe) and no use of rescue medication during the 24-hour period after dosing.

The primary analyses for the superiority comparisons between Trexima and placebo are Cochran-Mantel-Haenszel (CMH) tests with two outcome categories and with pooled investigator sites as strata, which applies to endpoints of pain relief, incidence of photophobia, and incidence of phonophobia for both Studies. The primary analysis for the superiority comparison between Trexima and placebo for incidence of nausea is a Cochran-Mantel-Haenszel (CMH) test with two outcome categories and with pooled investigator sites as strata for Study 301, and is a logistic regression with the baseline symptom and pooled investigator sites as covariates for Study 302.

For both Studies, the primary analyses for the superiority comparisons between Trexima and its individual components, sumatriptan and naproxen sodium, are a Cochran-Mantel-Haenszel (CMH) test with two outcome categories and with pooled investigator sites as strata, which applies to endpoints of sustained pain-free at 24 hours. Pairwise comparisons of sumatriptan to placebo and of naproxen sodium to placebo are also done for pain relief at 2 hours, using a CMH test.

Results of primary analyses are presented in following tables.

Table 1.2.1 Study 301: Primary Efficacy Analyses at 2 Hours (ITT)

	Trexima N = 362	Placebo N = 382	p-Value
Pain Relief – n (%)	207 (57)	109 (29)	<0.001
Photophobia-free – n (%)	180 (50)	122 (32)	<0.001
Phonophobia-free – n (%)	204 (56)	128 (34)	<0.001
Nausea-free – n (%)	237 (65)	244 (64)	0.711

Table 1.2.2 Study 301: Primary Efficacy Analyses at 24 Hours (ITT)

	Trexima N = 362	Sumatriptan N = 362	Naproxen Sodium N = 364	Placebo N = 382
Sustained Pain-Free – n (%)	83 (23)	51 (14)	37 (10)	25 (7)
p-value vs. Trexima	-	<0.001	<0.001	<0.001

Table 1.2.3 Study 302: Primary Efficacy Analyses at 2 Hours (ITT)

	Trexima N = 364	Placebo N = 360	p-Value
Pain Relief – n (%)	237 (65)	102 (28)	<. 001
Photophobia-Free – n (%)	211 (58)	131 (36)	<. 001
Phonophobia-Free – n (%)	223 (61)	138 (38)	<. 001
Nausea-Free ¹ – n (%)	260 (71)	233 (65)	0.007

¹analysis adjusted for baseline nausea

Table 1.2.4 Study 302: Primary Efficacy Analyses at 24 Hours (ITT)

	Trexima N = 364	Sumatriptan N = 361	Naproxen Sodium N = 356	Placebo N = 360
Sustained Pain-Free – n (%)	90 (25)	59 (16)	37 (10)	30 (8)
p-value vs. Trexima	-	0.009	<0.001	<0.001

1.3 Statistical Issues and Findings

An imbalance in incidence of nausea at baseline between Trexima and placebo were observed for both Studies 301 and 302, which might affect the evaluation of treatment differences of the 2-hour post-dose incidence of nausea. Statistical analysis on nausea-free at 2 hours is not significant for Study 301 using a CMH test stratified by pooled sites, and is significant for Study 302 using a logistic regression adjusted for baseline. Numerically, subjects treated with Trexima had a higher nausea-free rate at 2, 3 and 4 hours compared to placebo in both studies.

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2. Introduction

2.1 Overview

Migraine, as defined by the International Headache Society, is a chronic paroxysmal Disorder. A migraine attack is characterized by intense unilateral throbbing headache pain, which is accompanied by one or more secondary symptoms including nausea, sensitivity to light and sound, and occasionally vomiting. In about 10% of cases, migraine is associated with neurological symptoms known as aura, which are characterized by visual, sensory, speech, or motor dysfunction. Clinical disabilities are usually significant, with many patients requiring a period of bed rest. An individual attack lasts anywhere from 4 – 72 hours. Surveys found that patients want an acute treatment for migraine that provides: (a) rapid onset of pain relief, (b) freedom from pain, (c) no recurrence of headache and (d) absence of adverse effects. The International Headache Society Clinical Trial Committee has proposed that the pain-free response at 2 hours after dosing provides the best measure of rapidity of relief and acute freedom from pain while sustained pain-free is the preferred composite measure denoting freedom from pain and lack of relapse of headache.

Trexima tablets, a combination product, contain sumatriptan succinate and naproxen sodium and are intended for the acute treatment of migraine with or without aura in adults 18 years of age or older. Sumatriptan succinate (hereafter sumatriptan), developed by Glaxo and currently marketed in the U.S. by GlaxoSmithKline under the trade name Imitrex (NDA 20-132), is indicated for the acute treatment of migraine attacks. Naproxen sodium, a nonsteroidal anti-inflammatory agent (NSAID) developed by Syntex and currently marketed in the U.S. by Roche Pharmaceuticals under the trade name Anaprox (NDA 18-164), is indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis, tendonitis, bursitis, acute gout, and for the management of pain and primary dysmenorrhea.

An initial IND (#60,669) was submitted on July 26, 2000 covering the administration of sumatriptan and naproxen sodium marketed products in combination. The initial proof of-concept study (MT400-204), using over-encapsulated Imitrex (sumatriptan succinate) 50 mg tablets and naproxen sodium 500 mg tablets was conducted under this IND. A second IND (#68,436) was submitted on December 18, 2003 to conduct the clinical studies on the fixed dose combination selected.

The pivotal efficacy program in NDA 21-926 was comprised of two identical randomized, double-blind, parallel-group, placebo and active controlled single attack studies in patients with moderate or severe migraine headache. Both studies compared a single Trexima tablet with placebo for relief of migraine pain and associated symptoms at 2 hours and compared Trexima to the individual active components (85 mg sumatriptan RT and 500 mg naproxen sodium) for sustained pain relief through 24 hours. Each study enrolled approximately 1600 patients to each of the four treatment groups in a 1:1:1:1 ratio at approximately 60 centers in the United States.

2.2 Data Sources

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3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study MT400-301

3.1.1.1 Objective of Study

The objectives of the study were to demonstrate the superiority of Trexima (combination of sumatriptan as the succinate 85 mg and naproxen sodium 500 mg) versus placebo in the acute treatment of migraine, to demonstrate the superiority of Trexima versus the individual components (sumatriptan as the succinate 85 mg and naproxen sodium 500 mg), and to evaluate the safety of Trexima.

3.1.1.2 Study Design

This was a randomized, double-blind, parallel group, placebo-controlled, single dose multicenter study conducted in the US. Subjects were randomized in a ratio of 1:1:1:1 to receive Trexima, sumatriptan 85 mg, naproxen sodium 500 mg, or placebo orally.

The study consisted of a screening visit, at home treatment of a single migraine attack and a follow-up visit 1-5 days following treatment. Subjects had a baseline safety assessment performed at the screening visit including a review of medical history, review of migraine treatment history, physical examination, clinical laboratory tests, electrocardiogram (ECG), and a pregnancy test for females of childbearing potential. Blinded study drug was dispensed to eligible subjects at the end of the screening visit according to the randomization schedule provided by POZEN. When the subject's next migraine attack of moderate or severe intensity occurred, the subject reviewed the eligibility checklist and ascertained whether he/she continued to meet the eligibility criteria for use of study drug. Subjects eligible for treatment completed pain, clinical disability, and symptom (photophobia, phonophobia, nausea, vomiting) assessments on a diary card immediately prior to taking study drug. After taking the study drug, the subject completed assessments every 30 minutes for the first 2 hours, hourly from 2-4 hours, and then hourly while awake for the next 20 hours. Subjects were allowed to take rescue medication, if necessary, no sooner than 2 hours after taking the study drug. A Health Outcomes Productivity Assessment and The Patient Perception of Migraine Questionnaire (PPMQ) were completed 24 hours post-dosing. At the follow-up visit, safety assessments, diary review and concomitant medications review were conducted.

The main inclusion criteria is that subjects were males or non-pregnant, non-lactating females 18-65

years of age, had a demonstrated history (at least 6 months) of migraine headaches according to the International Headache Society (IHS) criteria 1.1 or 1.2, had their first migraine prior to age 50, and had an average migraine headache frequency of 2-6 moderate or severe attacks per month in the previous three months.

3.1.1.3 Efficacy Measures

Efficacy evaluations included diary recordings of pain intensity and clinical disability (each rated on a scale of 0-3); symptoms of photophobia, phonophobia, nausea and vomiting, rated as present or absent; and use of rescue medication. In addition, subject Satisfaction Questionnaires were completed for previous migraine treatment and for study drug, and a Productivity Assessment for work and non-work activities during the treatment period was completed.

The primary endpoints for the superiority comparison between Trexima and placebo are at two hours post-dose for pain relief (no or mild pain), incidence of photophobia, incidence of phonophobia, and incidence of nausea.

The primary endpoints for the superiority comparisons between Trexima and its individual components, sumatriptan and naproxen sodium, are sustained pain-free at 24 hours, which is defined as no pain at 2 hours and no relapse of pain (to mild, moderate or severe) and no use of rescue medication during the 24-hour period after dosing.

3.1.1.4 Statistical Analysis Plan

All primary analyses would be performed using the Last Observation Carried Forward (LOCF) approach based on the Intent-to-treat (ITT) population.

The primary analyses for the superiority comparison between Trexima and placebo are Cochran-Mantel-Haenszel (CMH) tests with two outcome categories and with pooled investigator sites as strata, which applies to endpoints of pain relief, incidence of photophobia, incidence of phonophobia, and incidence of nausea.

The primary analyses for the superiority comparisons between Trexima and its individual components, sumatriptan and naproxen sodium, are a CMH test with two outcome categories and with pooled investigator sites as strata, which applies to endpoints of sustained pain-free at 24 hours. Pairwise comparisons of sumatriptan to placebo and of naproxen sodium to placebo are also done for pain relief at 2 hours, using a CMH test.

3.1.1.5 Study Population

A total of 1875 subjects were screened and 1736 were randomized. Of these, 1495 treated a migraine with study drug, and 1475 returned diary cards. Fourteen hundred seventy (1470) subjects completed

at least one post-treatment diary card assessment and treated their migraine as instructed, while it was moderate or severe; these 1470 subjects comprised the efficacy ITT population. Twenty-one subjects had a major protocol violation; thus, there were 1449 subjects in the per protocol population. The following table (adapted from Study report, p53 in MT400-301) presents the patient disposition information.

Table 3.1.1.5.1 Patient Disposition

	Trexima	Sumatriptan	Naproxen Sodium	Placebo	Total
Screened					1875
Randomized	433	434	434	435	1736
Treated (Safety Population)	367	370	371	387	1495
Efficacy Intent-to-Treat Population ¹	362	362	364	382	1470
Per Protocol Population ²	357	355	362	375	1449

¹Includes all subjects who ingested study drug, recorded moderate or severe pain at baseline and recorded at least one post-dose pain assessment

²Excludes all subjects with a major protocol violation

The demographic characteristics of the study population at screening are summarized in Table 3.1.1.5.2 (adapted from Study report, p57).

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Table 3.1.1.5.2 Demographic and Baseline Information (Safety)

	Trexima N = 367	Sumatriptan N = 370	Naproxen Sodium N = 371	Placebo N = 387	p-Value
Gender – n (%)					0.795
Male	47 (13)	47 (13)	42 (11)	42 (11)	
Female	320 (87)	323 (87)	329 (89)	345 (89)	
Ethnicity – n (%)					0.570
Hispanic or Latino	53 (14)	52 (14)	59 (16)	60 (16)	
Not Hispanic or Latino	314 (86)	318 (86)	312 (84)	326 (84)	
Unknown	0	0	0	1 (<1)	
Race – n (%)					0.858
White	327 (89)	330 (89)	335 (90)	343 (89)	
Black	26 (7)	27 (7)	27 (7)	32 (8)	
Asian	4 (1)	5 (1)	2 (<1)	0	
Native American	4 (1)	1 (<1)	0	5 (1)	
Pacific Islander	0	2 (<1)	0	0	
Other	5 (1)	5 (1)	7 (2)	6 (2)	
Unknown	1 (<1)	0	0	1 (<1)	
Smoker – n (%)					0.661
Yes	49 (13)	53 (14)	43 (12)	53 (14)	
No	318 (87)	317 (86)	328 (88)	334 (86)	
Age (years)					0.450
N	367	370	371	387	
Mean (±SD)	39.4 (11.2)	40.3 (11.4)	40.4 (11.6)	40.6 (10.7)	
Median	40	41	41	42	
Min – Max	18 – 65	18 – 65	18 – 65	18 – 65	
Age Category (years)					0.280
18-35	139 (38)	141 (38)	136 (37)	125 (32)	
36-55	197 (54)	192 (52)	193 (52)	230 (59)	
>55	31 (8)	37 (10)	42 (11)	32 (8)	
Height (in)					0.166
N	366	370	371	387	
Mean (±SD)	65.4 (3.5)	65.4 (3.2)	65.0 (3.2)	65.0 (3.2)	
Median	65	65	65	65	
Min – Max	56.0 – 76.0	58.0 – 75.5	55.5 – 77.0	56.0 – 78.0	
Weight (lb)					0.596
N	366	370	371	387	
Mean (±SD)	162 (36.4)	162 (40.6)	160 (38.0)	164 (40.4)	
Median	156	152	155	154	
Min – Max	94.0 – 308	95.0 – 322	96.0 – 452	89.0 – 333	

A summary of migraine history at screening is presented in Table 3.1.1.5.3 (adapted from Study report, p58).

Table 3.1.1.5.3 Migraine History at Screening (Safety)

	Trexima N = 367	Sumatriptan N = 370	Naproxen Sodium N = 371	Placebo N = 387
Migraine Characteristics at Screening – n (%)				
Without Aura	279 (76)	277 (75)	293 (79)	282 (73)
With Aura	45 (12)	54 (15)	34 (9)	47 (12)
With and Without Aura	43 (12)	39 (11)	44 (12)	58 (15)
Time from First Migraine Attack (years)				
N	367	370	371	387
Mean (SD)	17.6 (12.0)	18.5 (12.6)	18.3 (12.8)	17.9 (12.1)
Median	15	17	15	16
Min - Max	0 – 54	0 – 51	0 – 64	0 – 58

Baseline characteristics of the migraine treated with study drug are summarized in Table 3.1.1.5.4 (adapted from Study report, p59). A difference was noted for unilateral pain, with 66% of subjects treated with Trexima indicating unilateral pain vs. 70% to 75% of the other treatment groups with unilateral pain. A smaller percent of subjects in the Trexima treatment group as compared to the other treatment groups, had aura at baseline (19% vs. 23% to 26%). There appeared to be a baseline imbalance in the incidence of nausea with a greater incidence of subjects treated with Trexima with nausea compared to the other treatment groups (56% vs. 48% to 49%).

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Table 3.1.1.5.4 Baseline Characteristics of the Treated Migraine (ITT)

Characteristic n (%)	Trexima N = 362	Sumatriptan N = 362	Naproxen Sodium N = 364	Placebo N = 382	p-Value
Pain ¹					
Moderate Pain	212 (59)	219 (60)	212 (58)	230 (60)	-
Severe Pain	150 (41)	143 (40)	152 (42)	152 (40)	0.914
Photophobia	300 (83)	302 (83)	301 (83)	310 (81)	0.857
Phonophobia	293 (81)	286 (79)	296 (81)	316 (83)	0.619
Nausea	201 (56)	174 (48)	175 (48)	188 (49)	0.149
Aura	70 (19)	91 (25)	95 (26)	89 (23)	0.087
Pain Only on 1 Side of the Head ²	238 (66)	272 (75)	253 (70)	277 (73)	0.044
Pulsating, Throbbing or Pounding	326 (90)	329 (91)	330 (91)	354 (93)	0.529
Worsens with Activity	316 (87)	326 (90)	314 (86)	344 (90)	0.220

¹ For pain severity, none and mild were not included in the analysis.

² One subject in the Trexima group did not answer the unilateral pain question.

3.1.1.6 Applicant's Efficacy Results

The primary efficacy analyses for the superiority comparison between Trexima and placebo are CMH tests stratified by the pooled sites. The results are presented in the following table (adapted from Study report, p60).

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Table 3.1.1.6.1 Primary Efficacy Analyses at 2 Hours (ITT)

	Trexima N = 362	Placebo N = 382	p-Value
Pain Relief – n (%)	207 (57)	109 (29)	<0.001
Photophobia-free – n (%)	180 (50)	122 (32)	<0.001
Phonophobia-free – n (%)	204 (56)	128 (34)	<0.001
Nausea-free – n (%)	237 (65)	244 (64)	0.711

Pain relief was achieved at 2 hours post-dose by 57% of subjects taking Trexima and 29% of subjects taking placebo. The treatment difference was statistically significant ($p < 0.001$).

The percentages of subjects who were photophobia-free and phonophobia-free at 2 hours after dosing were significantly greater in the Trexima treatment group (50% and 56%, respectively) than in the placebo treatment group (32% and 34%, respectively) ($p < 0.001$). At 2 hours post-dosing, there was no significant difference in the percentages of subjects receiving Trexima or placebo who were nausea-free (65% and 64%, respectively).

The primary efficacy results for the superiority comparison between Trexima and its components are CMH tests stratified by the pooled sites. The results are presented in the following table (adapted from Study report, p62). In the Trexima treatment group, 23% of subjects had a sustained pain-free response at 24 hours, compared to 14% of subjects in the sumatriptan treatment group, and 10% in the naproxen sodium treatment group. Differences between the Trexima treatment group and each of the components were statistically significant ($p < 0.001$).

Table 3.1.1.6.2 Primary Efficacy Analyses at 24 Hours (ITT)

	Trexima N = 362	Sumatriptan N = 362	Naproxen Sodium N = 364	Placebo N = 382
Sustained Pain-Free – n (%)	83 (23)	51 (14)	37 (10)	25 (7)
p-value vs. Trexima	-	<0.001	<0.001	<0.001

3.1.2 Study MT400-302

3.1.2.1 Objective of Study

The objectives of the study were identical to Study 301 (see Section 3.1.1.1).

3.1.2.2 Study Design

The design was identical to Study 301 (see Section 3.1.1.2).

3.1.2.3 Efficacy Measures

The efficacy measures and endpoints were identical to Study 301 (see Section 3.1.1.3).

3.1.2.4 Statistical Analysis Plan

The statistical analysis plan was identical to Study 301 (see Section 3.1.1.4) except for analyzing nausea-free at 2-hour.

In the Statistical Analysis Plan dated March 21, 2005, the protocol stated that “If any of the baseline symptoms (i.e. pain, nausea, photophobia and phonophobia) suggest a treatment imbalance, as evidenced by a p-value of <0.15 for overall treatment differences, then the primary analysis (Trexima versus placebo at 2 hours) for that symptom will be adjusted for baseline. Logistic Regression, with the baseline symptom and pooled investigator sites as covariates, will be done instead of the Cochran-Mantel-Haenszel test.”

The applicant provided documents to indicate that the database was locked on March 29, 2005 and the study unblinded to treatment assignments on March 30, 2005. Therefore, the change was done prospectively.

3.1.2.5 Study Population

A total of 1768 subjects were screened and 1677 were randomized. Of these, 1461 treated a migraine with study drug, and 1444 returned diary cards. Fourteen hundred and forty-one (1441) subjects completed at least one post-treatment diary card assessment and treated their migraine as instructed, while it was moderate or severe; these 1441 subjects comprised the efficacy ITT population. Forty-eight subjects had a major protocol violation; thus, there were 1393 subjects in the per protocol population. The following table (adapted from Study report, p52 in MT400-302) presents the patient disposition information.

Table 3.1.2.5.1 Patient Disposition

	Trexima	Sumatriptan	Naproxen Sodium	Placebo	Total
Screened					1768
Randomized	422	415	419	421	1677
Treated (Safety Population)	370	365	361	365	1461
Efficacy Intent-to-Treat Population ¹	364	361	356	360	1441
Per Protocol Population ²	355	344	343	351	1393

¹Includes all subjects who took study drug, recorded moderate or severe pain at baseline and recorded at least one post-dose pain assessment

²Excludes all subjects with a major protocol violation and all subjects at site 355 (see Section 10.2)

Source: Section 14.1.2

The demographic characteristics of the study population at screening are summarized in Table 3.1.2.5.2 (adapted from Study report, p56).

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Table 3.1.2.5.2 Demographic and Baseline Information (Safety)

	Trexima	Sumatriptan	Naproxen Sodium	Placebo	p-Value
	N = 370	N = 365	N = 361	N = 365	
Gender – n (%)					0.768
Male	48 (13)	52 (14)	50 (14)	57 (16)	
Female	322 (87)	313 (86)	311 (86)	308 (84)	
Ethnicity – n (%)					0.654
Hispanic or Latino	19 (5)	15 (4)	17 (5)	14 (4)	
Not Hispanic or Latino	351 (95)	350 (96)	344 (95)	351 (96)	
Race – n (%)					0.338
White	332 (90)	313 (86)	322 (89)	322 (88)	
Black	34 (9)	46 (13)	29 (8)	32 (9)	
Asian	0	1 (< 1)	2 (< 1)	3 (< 1)	
Native American	0	3 (< 1)	2 (< 1)	3 (< 1)	
Pacific Islander	0	0	1 (< 1)	0	
Other	4 (1)	2 (< 1)	5 (1)	5 (1)	
Smoker – n (%)					0.962
Yes	58 (16)	60 (16)	56 (16)	57 (16)	
No	312 (84)	305 (84)	305 (84)	308 (84)	
Age (years)					
N	370	365	361	365	0.681
Mean (\pm SD)	40.3 (11.4)	40.1 (10.9)	39.4 (11.3)	40.0 (11.1)	
Median	40	40	40	41	
Min – Max	18 – 65	18 – 65	18 – 65	18 – 65	
Age - (n %)					0.058
18-35 years	135 (36)	129 (35)	137 (38)	121 (33)	
36-55 years	188 (51)	210 (58)	194 (54)	216 (59)	
>55 years	47 (13)	26 (7)	30 (8)	29 (8)	
Height (in)					0.810
N	370	364	361	364	
Mean (\pm SD)	65.6 (3.4)	65.7 (3.2)	65.7 (3.4)	65.8 (3.4)	
Median	65.0	65.5	65.0	65.2	
Min – Max	56.0 – 77.0	56.0 – 77.0	56.0 – 77.0	56.0 – 78.0	
Weight (lb)					0.235
N	370	364	361	364	
Mean (\pm SD)	164.5 (41.0)	169.4 (42.7)	165.6 (38.1)	164.5 (39.6)	
Median	158	163	158	155	
Min – Max	93 – 320	102 – 361	102- 308	95 - 280	

A summary of migraine history at screening is presented in Table 3.1.2.5.3 (adapted from Study report, p57).

Table 3.1.2.5.3 Migraine History at Screening

	Trexima	Sumatriptan	Naproxen Sodium	Placebo
	N = 370	N = 365	N = 361	N = 365
Migraine Characteristics at Screening – n (%)				
Without Aura	285 (77)	267 (73)	259 (72)	258 (71)
With Aura	42 (11)	52 (14)	45 (12)	57 (16)
With and Without Aura	43 (12)	46 (13)	57 (16)	50 (14)
Time from First Migraine Attack (years)				
N	370	365	361	365
Mean (SD)	18.8 (12.3)	18.1 (12.1)	17.4 (12.0)	18.7 (12.5)
Median	17	16	15	18
Min - Max	0 – 54	0 – 55	0 – 52	0 – 56

Baseline characteristics of the migraine treated with study drug are summarized in Table 3.1.2.5.4 (adapted from Study report, p58). No differences between groups was noted for baseline characteristics with the exception of incidence of nausea, with a greater incidence of nausea in subjects treated with Trexima, sumatriptan and naproxen compared to placebo (48%, 46%, 49% vs. 41%, respectively). The degree of nausea imbalance precluded use of logistic regression over CMH for nausea.

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Table 3.1.2.5.4 Baseline Characteristics of the Treated Migraine

	Trexima N = 364 n (%)	Sumatriptan N = 361 n (%)	Naproxen Sodium N = 356 n (%)	Placebo N = 360 n (%)	p-Value
Pain¹					0.948
Moderate Pain	227 (62)	232 (64)	228 (64)	227 (63)	
Severe Pain	137 (38)	129 (36)	128 (36)	133 (37)	
Photophobia	288 (79)	296 (82)	287 (81)	286 (79)	0.780
Phonophobia	281 (77)	286 (79)	265 (74)	278 (77)	0.509
Nausea	176 (48)	167 (46)	174 (49)	149 (41)	0.149
Aura ²	76 (21)	86 (24)	75 (21)	86 (24)	0.616
Pain Only on 1 Side of the Head ²	267 (73)	255 (71)	254 (71)	253 (70)	0.791
Pulsating, Throbbing or Pounding ²	322 (88)	322 (89)	321 (90)	323 (90)	0.963
Worsens with Activity ²	312 (86)	315 (87)	313 (88)	317 (88)	0.744

¹ For pain severity, none and mild were not included in the analysis.

² One subject in the Trexima group did not answer the migraine characteristics questions.

3.1.2.6 Applicant's Efficacy Results

The primary efficacy analyses for the superiority comparison between Trexima and placebo are CMH tests stratified by the pooled sites. The results are presented in the following table (adapted from Study report, p59).

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Table 3.1.2.6.1 Primary Efficacy Analyses at 2 Hours (ITT)

	Trexima	Placebo	p-Value
	N = 364	N = 360	
Pain Relief – n (%)	237 (65)	102 (28)	<. 001
Photophobia-Free – n (%)	211 (58)	131 (36)	<. 001
Phonophobia-Free – n (%)	223 (61)	138 (38)	<. 001
Nausea-Free¹ – n (%)	260 (71)	233 (65)	0.007

¹analysis adjusted for baseline nausea

Pain relief was achieved at 2 hours post-dose by 65% of subjects taking Trexima and 28% of subjects taking placebo. The treatment difference was statistically significant ($p < 0.001$).

The primary efficacy results for the superiority comparison between Trexima and its components are CMH tests stratified by the pooled sites. The results are presented in the following table (adapted from Study report, p60). In the Trexima treatment group, 25% of subjects had a sustained pain-free response at 24 hours, compared to 16% of subjects in the sumatriptan treatment group, and 10% in the naproxen sodium treatment group. Differences between the Trexima treatment group and each of the components were statistically significant ($p < 0.01$).

Table 3.1.2.6.2 Primary Efficacy Analyses at 24 Hours (ITT)

	Trexima N = 364	Sumatriptan N = 361	Naproxen Sodium N = 356	Placebo N = 360
Sustained Pain-Free – n (%)	90 (25)	59 (16)	37 (10)	30 (8)
p-value vs. Trexima	-	0.009	<0.001	<0.001

3.1.3 Reviewer's Analysis

The reviewer validated the applicant's analyses according to the protocols.

There are many small sites in both studies. The primary analysis is a CMH test stratified by pooled sites. To check whether there is any impact caused by sites, a CMH test without stratification by sites is performed which gives p-value .0001 for both studies.

The primary endpoint is based on a binary transformation on pain relief. To check whether there is

any impact using such transformation, a CMH test with pain relief's original 4-point scales gives p-value .0001 for both studies.

For checking baseline balance of pain relief, a CMH test using original 4-point scales gives p-value .6479 for Study 301, and .8472 for Study 302, respectively.

Analysis on Nausea

For Study 301: The numbers and percentages for nausea free at 2 hours are 237/362 (65.5%) for trexima group, and 244/382 (63.9%) for placebo group, respectively. P-value for nausea free at 2 hours, using a CMH test stratified by pooled site, is .7114. Since there are many small sites in this study, p-value using a CMH test without stratification by sites is .6494.

The numbers and percentages for nausea free at baseline are 1161/362 (44.5%) for trexima group, and 194/382 (50.8%) for placebo group, respectively. P-value for nausea free at baseline using a CMH test is .0852. Adjusting for baseline, p-value using a logistic regression for nausea free at 2 hours is .2301.

The nausea incidence over time in subjects receiving Trexima is presented in Table 3.1.3.1. By 2 hours, the incidence of nausea in subjects treated with Trexima is lower than that in subjects treated with placebo (35% and 36%, respectively).

Table 3.1.3.1 Study 301: Incidence of Nausea over Time (ITT Population)

Treatment Group Symptom	HOURS POST-DOSE				
	0.0	1.0	2.0	3.0	4.0
Trexima (N=362)					
Absent	161 (44%)	172 (48%)	237 (65%)	261 (72%)	266 (73%)
Present	201 (56%)	190 (52%)	125 (35%)	101 (28%)	96 (27%)
Sumatriptan (N=362)					
Absent	188 (52%)	185 (51%)	233 (64%)	250 (69%)	250 (69%)
Present	174 (48%)	177 (49%)	129 (36%)	112 (31%)	112 (31%)
Naproxen (N=364)					
Absent	189 (52%)	215 (59%)	249 (68%)	244 (67%)	247 (68%)
Present	175 (48%)	149 (41%)	115 (32%)	120 (33%)	117 (32%)
Placebo (N=382)					
Absent	194 (51%)	213 (56%)	244 (64%)	218 (57%)	213 (56%)
Present	188 (49%)	169 (44%)	138 (36%)	164 (43%)	169 (44%)
P-Values ¹					
Trexima vs. Placebo			0.711		<.001
Trexima vs. Sumatriptan			0.557		0.140

¹ P-Values are from the Cochran-Mantel-Haenszel test, with pooled investigator site as the strata.

Although analysis on nausea free at 2 hours was not significant, an imbalance at baseline between Trexima and placebo might confound the evaluation. However, subjects treated with Trexima had a higher nausea-free rate at 2, 3 and 4 hours compared to placebo.

For Study 302: The numbers and percentages for nausea free at 2 hours are 260/364 (71.4%) for trexima group, and 233/360 (64.7%) for placebo group, respectively. P-value for nausea free at 2 hours, using a CMH test stratified by pooled site, is .0557. Since there are many small sites in this study, p-value using a CMH test without stratification by sites is .0531.

The nausea incidence over time in subjects receiving Trexima is presented in Table 3.1.3.2. The numbers and percentages for nausea free at baseline are 188/364 (51.7%) for trexima group, and 211/360 (58.6%) for placebo group, respectively. P-value for nausea free at baseline using a CMH test is .0598. Adjusting for baseline, p-value using a logistic regression for nausea free at 2 hours is .0072.

Table 3.1.3.2 Study 302: Incidence of Nausea over Time (ITT Population)

Treatment Group Symptom	HOURS POST - DOSE				
	0.0	1.0	2.0	3.0	4.0
Trexima (N=364)					
Absent	188 (52%)	189 (52%)	260 (71%)	285 (78%)	295 (81%)
Present	176 (48%)	175 (48%)	104 (29%)	79 (22%)	69 (19%)
Sumatriptan (N=361)					
Absent	194 (54%)	185 (51%)	238 (66%)	260 (72%)	257 (71%)
Present	167 (46%)	176 (49%)	123 (34%)	101 (28%)	104 (29%)
Naproxen (N=356)					
Absent	182 (51%)	216 (61%)	248 (70%)	249 (70%)	240 (67%)
Present	174 (49%)	140 (39%)	108 (30%)	107 (30%)	116 (33%)
Placebo (N=360)					
Absent	211 (59%)	221 (61%)	233 (65%)	217 (60%)	199 (55%)
Present	149 (41%)	139 (39%)	127 (35%)	143 (40%)	161 (45%)
P-Values¹					
Trexima vs. Placebo			0.056		<0.001
Trexima vs. Sumatriptan			0.141		0.002
P-Values²					
Trexima vs. Placebo			0.007		<0.001
Trexima vs. Sumatriptan			0.070		<0.001

¹ P-Values are from the Cochran-Mantel-Haenszel test, with pooled investigator site as the strata.

² P-Values are from Logistic Regression, with pooled investigator site and baseline nausea as covariables.

Analysis on nausea free at 2 hours was statistically significant after adjusting for baseline. Subjects treated with Trexima also had a higher nausea-free rate at 2, 3 and 4 hours compared to placebo.

3.2 Evaluation of Safety

See Clinical Review.

4. Findings in Special/Subgroup Populations

4.1 Gender, Age, and Race

Table 4.1.1 indicates that for Study 301 percentages of pain relief at 2 hours in three treatment groups are greater than that in place group, respectively.

Table 4.1.1 Study 301: Pain Relief at 2 Hours by Gender

Gender	Trexima	Sumatriptan	Naproxen	Placebo
Male	21/46 (46%)	26/47 (55%)	19/41 (46%)	9/42 (21%)
Female	186/316 (59%)	156/315 (50%)	139/323 (43%)	100/340 (29%)

Table 4.1.2 indicates that for Study 301 percentages of pain relief at 2 hours in three treatment groups are greater than that in place group, respectively.

Table 4.1.2 Study 301: Pain Relief at 2 Hours by Age

Age	Trexima	Sumatriptan	Naproxen	Placebo
18-35	73/136 (54%)	62/137 (45%)	59/135 (44%)	34/122 (28%)
36-55	113/195 (58%)	102/189 (54%)	80/187 (43%)	66/228 (29%)
> 55	21/31 (68%)	18/36 (50%)	19/42 (45%)	9/32 (28%)

Table 4.1.3 indicates that for Study 302 percentages of pain relief at 2 hours in three treatment groups are greater than that in place group, respectively.

Table 4.1.3 Study 302: Pain Relief at 2 Hours by Gender

Gender	Trexima	Sumatriptan	Naproxen	Placebo
Male	24/47 (51%)	31/51 (61%)	23/49 (47%)	13/56 (23%)
Female	213/317 (67%)	169/310 (55%)	134/307 (44%)	89/304 (29%)

Table 4.1.4 indicates that for Study 302 percentages of pain relief at 2 hours in three treatment groups are greater than that in place group, respectively.

Table 4.1.4 Study 302: Pain Relief at 2 Hours by Age

Age	Trexima	Sumatriptan	Naproxen	Placebo
18-35	76/130 (58%)	63/126 (50%)	64/134 (48%)	38/120 (32%)
36-55	127/187 (68%)	119/210 (57%)	83/192 (43%)	58/214 (27%)
> 55	34/47 (72%)	18/25 (72%)	10/30 (33%)	6/26 (23%)

Since majority patients are white, pain relief at 2 hours by race is not performed.

4.2 Other Special/Subgroup Populations

There is no analysis performed for other subgroup.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

For Study 301: this study assessed the efficacy and safety of Trexima versus placebo and components, sumatriptan 85 mg and naproxen sodium 500 mg, in the acute treatment of moderate or severe migraine. The data and analyses indicated that Trexima was statistically significantly superior to placebo for the primary endpoints of 2-hour pain relief, 2-hour photophobia-free and 2-hour phonophobia-free. Trexima was also statistically significantly superior to the components for the primary endpoint of sustained pain free.

Although analysis on nausea free at 2 hours was not significant, an imbalance in incidence of nausea at baseline between Trexima and placebo might confound the evaluation. However, subjects treated with Trexima had a higher nausea-free rate at 2, 3 and 4 hours compared to placebo.

Results of primary analyses are presented in Table 5.1.1 and Table 5.1.2.

Table 5.1.1 Study 301: Primary Efficacy Analyses at 2 Hours (ITT)

	Trexima N = 362	Placebo N = 382	p-Value
Pain Relief – n (%)	207 (57)	109 (29)	<0.001
Photophobia-free – n (%)	180 (50)	122 (32)	<0.001
Phonophobia-free – n (%)	204 (56)	128 (34)	<0.001
Nausea-free – n (%)	237 (65)	244 (64)	0.711

Table 5.1.2 Study 301: Primary Efficacy Analyses at 24 Hours (ITT)

	Trexima N = 362	Sumatriptan N = 362	Naproxen Sodium N = 364	Placebo N = 382
Sustained Pain-Free – n (%)	83 (23)	51 (14)	37 (10)	25 (7)
p-value vs. Trexima	-	<0.001	<0.001	<0.001

For Study 302: this study assessed the efficacy and safety of Trexima versus placebo and components, sumatriptan 85 mg and naproxen sodium 500 mg, in the acute treatment of moderate or severe migraine. The data and analyses indicated that Trexima was statistically significantly superior to placebo for the primary endpoints of 2-hour pain relief, 2-hour photophobia-free, 2-hour phonophobia-free, and 2-hour nausea-free. Trexima was also statistically significantly superior to the components for the primary endpoint of sustained pain free.

Results of primary analyses are presented in Table 5.1.3 and Table 5.1.4.

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Table 5.1.3 Study 302: Primary Efficacy Analyses at 2 Hours (ITT)

	Trexima	Placebo	p-Value
	N = 364	N = 360	
Pain Relief – n (%)	237 (65)	102 (28)	<. 001
Photophobia-Free – n (%)	211 (58)	131 (36)	<. 001
Phonophobia-Free – n (%)	223 (61)	138 (38)	<. 001
Nausea-Free¹ – n (%)	260 (71)	233 (65)	0.007

¹analysis adjusted for baseline nausea

Table 5.1.4 Study 302: Primary Efficacy Analyses at 24 Hours (ITT)

	Trexima N = 364	Sumatriptan N = 361	Naproxen Sodium N = 356	Placebo N = 360
Sustained Pain-Free – n (%)	90 (25)	59 (16)	37 (10)	30 (8)
p-value vs. Trexima	-	0.009	<0.001	<0.001

5.2 Conclusions and Recommendations

The data and analyses based on both Studies 301 and 302 indicated that Trexima was statistically significantly superior to placebo for 2-hour pain relief, 2-hour photophobia-free and 2-hour phonophobia-free. Trexima was statistically significantly superior to placebo for 2-hour nausea-free in Study 302. Trexima was also statistically significantly superior to the components for sustained pain free.

An imbalance in incidence of nausea at baseline between Trexima and placebo were observed for both Studies 301 and 302, which might affect the evaluation. Statistical analysis on nausea-free at 2 hours is not significant for Study 301 using a CMH test stratified by pooled sites, and is significant for Study 302 using a logistic regression adjusted for baseline. Numerically, subjects treated with Trexima had a higher nausea-free rate at 2, 3 and 4 hours compared to placebo in both studies.

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