Clinical trial results:
A Worldwide, Randomized, Double Blind, Placebo-Controlled, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Rizatriptan for the Acute Treatment of Migraine in Children and Adolescents

Summary

EudraCT number	2009-016374-32
Trial protocol	NL DE FI BE ES EE LV SE FR DK GB IT Outside EU/EEA
Global end of trial date	21 April 2011

Results information

Result version number	v1 (current)
This version publication date	01 March 2016
First version publication date	23 April 2015

Trial information

Trial identification

Sponsor protocol code	MK-0462-082

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01001234
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Registration Number: 2009_679, CTRI: CTRI/2010/091/000407

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 April 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 April 2011
Global end of trial reached?	Yes
Global end of trial date	21 April 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To evaluate the efficacy of rizatriptan compared to placebo in the treatment of acute migraine as measured by pain freedom at 2 hours in pediatric migraineurs between 12 and 17 years of age who have not, historically, achieved satisfactory response to treatment with non-steroidal anti-inflammatory drugs (NSAIDS) or acetaminophen (APAP).

2. To evaluate the safety and tolerability of rizatriptan in pediatric migraineurs between 12 and 17 years of age who have not, historically, achieved a satisfactory response to treatment with NSAIDS or APAP.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

The following additional measure defined for this individual study was in place for the protection of trial subjects: participants who did not obtain satisfactory relief of migraine pain at 2 hours after administration of Stage 2 study medication could have been treated with usual care at that time or any time thereafter if the headache did not resolve or recurred.

Background therapy:

Rescue therapy and treatments for non-qualifying migraines were limited to the participant’s usual care with the following exception: use of 5-hydroxytryptamine 1 (5-HT1) agonists and ergot derivatives were prohibited for 24 hours following the last dose of any study treatment.

Evidence for comparator: -

Actual start date of recruitment	30 November 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 8

Country: Number of subjects enrolled	Norway: 18
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	Latvia: 9
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	India: 190
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	United States: 1042
Worldwide total number of subjects	1382
EEA total number of subjects	141

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	372
Adolescents (12-17 years)	1010
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants randomized to double-blind study medication (Stage 1 - placebo or rizatriptan in a 20:1 ratio) at the Screening visit were given study drug and administration instructions. If a participant had not treated a qualifying migraine attack within up to 2-4 months, he/she may have been discontinued from the study.

Period 1

Period 1 title	All Randomized Participants (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/No Treatment

Arm description:

Stage 1 - Randomized to single placebo oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Responder (mild or no pain 15 minutes after dose), no further study medication was to be administered.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For participants randomized to placebo in Stage 1: a single placebo oral disintegrating tablet (ODT) was to be taken within 30 minutes of onset of qualifying migraine (defined as a migraine of moderate or intense severity).

Arm title	Rizatriptan/No Treatment

Arm description:

Stage 1 - Randomized to single rizatriptan 5 or 10 mg oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Responder (mild or no pain 15 minutes after dose), no further study medication was to be administered.

Arm type	Experimental
Investigational medicinal product name	Rizatriptan
Investigational medicinal product code	
Other name	Maxalt, MK-0462
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For participants randomized to rizatriptan in Stage 1: a single 5 or 10 mg rizatriptan ODT was to be taken within 30 minutes of onset of qualifying migraine.
Rizatriptan dose administered was based on participant weight at Screening: those <40 kg received 5 mg tablet, those ≥40 kg received 10 mg tablet.

Arm title	Placebo/Rizatriptan

Arm description:

Stage 1 - Randomized to single placebo oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Non-Responder (moderate or severe pain 15 minutes after dose), Stage 2 randomization was to occur and participants in this reporting group received single rizatriptan 5 or 10 mg oral tablet. Stage 2 dose was administered approximately 15 minutes post Stage 1 dose, to treat same qualifying migraine treated in Stage 1. Stage 2 randomization was in a ratio of 1:1 rizatriptan:placebo.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For participants randomized to placebo in Stage 1: a single placebo ODT was to be taken within 30 minutes of onset of qualifying migraine.

Investigational medicinal product name	Rizatriptan
Investigational medicinal product code	
Other name	Maxalt, MK-0462
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For participants randomized to rizatriptan in Stage 2 (must have taken placebo in Stage 1 and was Non-Responder [moderate or severe pain 15 minutes after dose] to be randomized at Stage 2): a single 5 or 10 mg rizatriptan ODT was to be taken approximately 15 minutes post Stage 1 dose, to treat same qualifying migraine treated in Stage 1.

Rizatriptan dose administered was based on participant weight at Screening: those <40 kg received 5 mg tablet, those ≥40 kg received 10 mg tablet.

Arm title	Placebo/Placebo

Arm description:

Stage 1 - Randomized to single placebo oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Non-Responder (moderate or severe pain 15 minutes after dose), Stage 2 randomization was to occur and participants in this reporting group received single placebo oral tablet. Stage 2 dose was administered approximately 15 minutes post Stage 1 dose, to treat same qualifying migraine treated in Stage 1. Stage 2 randomization was in a ratio of 1:1 rizatriptan:placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For participants randomized to placebo in Stage 1: a single placebo ODT was to be taken within 30 minutes of onset of qualifying migraine. For participants randomized to placebo in Stage 2: a single placebo ODT was to be taken approximately 15 minutes post Stage 1 dose, to treat same qualifying migraine treated in Stage 1.

Arm title	Rizatriptan/Placebo

Arm description:

Stage 1 - Randomized to single rizatriptan 5 or 10 mg oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Non-Responder

(moderate or severe pain 15 minutes after dose), allocated to receive single placebo oral tablet in Stage 2 to treat same qualifying migraine treated in Stage 1 (Stage 2 dose to be administered 15 minutes post Stage 1 dose).

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For participants allocated to placebo in Stage 2 (took rizatriptan in Stage 1 and was Non-Responder [moderate or severe pain 15 minutes after dose]): a single placebo ODT was to be taken approximately 15 minutes post Stage 1 dose, to treat same qualifying migraine treated in Stage 1.

Investigational medicinal product name	Rizatriptan
Investigational medicinal product code	
Other name	Maxalt, MK-0462
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For participants randomized to rizatriptan in Stage 1: a single 5 or 10 mg rizatriptan ODT was to be taken within 30 minutes of onset of qualifying migraine.

Rizatriptan dose administered was based on participant weight at Screening: those <40 kg received 5 mg tablet, those ≥40 kg received 10 mg tablet.

Number of subjects in period 1	Placebo/No Treatment	Rizatriptan/No Treatment	Placebo/Rizatriptan
Started	492	31	409
Treated	124	8	400
Completed	87	5	377
Not completed	405	26	32
Not treated: protocol violation	3	-	-
Consent withdrawn by subject	2	-	3
Physician decision	1	-	-
Not treated: adverse event	1	-	-
Not treated: pregnancy	3	-	-
Not treated: lost to follow-up	53	4	7
Lost to follow-up	-	-	1
Not treated: physician decision	37	4	-
Protocol deviation	34	3	19
Not treated: withdrawal by subject	23	2	2
Not treated: lack of qualifying event	248	13	-

Number of subjects in period 1	Placebo/Placebo	Rizatriptan/Placebo
Started	410	40
Treated	405	40
Completed	385	40
Not completed	25	0
Not treated: protocol violation	-	-
Consent withdrawn by subject	-	-
Physician decision	-	-
Not treated: adverse event	-	-
Not treated: pregnancy	-	-
Not treated: lost to follow-up	5	-
Lost to follow-up	2	-
Not treated: physician decision	-	-
Protocol deviation	18	-
Not treated: withdrawal by subject	-	-
Not treated: lack of qualifying event	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo/No Treatment
Reporting group description:	
Stage 1 - Randomized to single placebo oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Responder (mild or no pain 15 minutes after dose), no further study medication was to be administered.	
Reporting group title	Rizatriptan/No Treatment
Reporting group description:	
Stage 1 - Randomized to single rizatriptan 5 or 10 mg oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Responder (mild or no pain 15 minutes after dose), no further study medication was to be administered.	
Reporting group title	Placebo/Rizatriptan
Reporting group description:	
Stage 1 - Randomized to single placebo oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Non-Responder (moderate or severe pain 15 minutes after dose), Stage 2 randomization was to occur and participants in this reporting group received single rizatriptan 5 or 10 mg oral tablet. Stage 2 dose was administered approximately 15 minutes post Stage 1 dose, to treat same qualifying migraine treated in Stage 1. Stage 2 randomization was in a ratio of 1:1 rizatriptan:placebo.	
Reporting group title	Placebo/Placebo
Reporting group description:	
Stage 1 - Randomized to single placebo oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Non-Responder (moderate or severe pain 15 minutes after dose), Stage 2 randomization was to occur and participants in this reporting group received single placebo oral tablet. Stage 2 dose was administered approximately 15 minutes post Stage 1 dose, to treat same qualifying migraine treated in Stage 1. Stage 2 randomization was in a ratio of 1:1 rizatriptan:placebo.	
Reporting group title	Rizatriptan/Placebo
Reporting group description:	
Stage 1 - Randomized to single rizatriptan 5 or 10 mg oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Non-Responder (moderate or severe pain 15 minutes after dose), allocated to receive single placebo oral tablet in Stage 2 to treat same qualifying migraine treated in Stage 1 (Stage 2 dose to be administered 15 minutes post Stage 1 dose).	

Reporting group values	Placebo/No Treatment	Rizatriptan/No Treatment	Placebo/Rizatriptan
Number of subjects	492	31	409
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	130	6	111
Adolescents (12-17 years)	362	25	298
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0

Gender categorical Units: Subjects			
Female	259	20	233
Male	233	11	176

Reporting group values	Placebo/Placebo	Rizatriptan/Placebo	Total
Number of subjects	410	40	1382
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	111	14	372
Adolescents (12-17 years)	299	26	1010
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	241	20	773
Male	169	20	609

End points

End points reporting groups

Reporting group title	Placebo/No Treatment

Reporting group description:

Stage 1 - Randomized to single placebo oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Responder (mild or no pain 15 minutes after dose), no further study medication was to be administered.

Reporting group title	Rizatriptan/No Treatment

Reporting group description:

Stage 1 - Randomized to single rizatriptan 5 or 10 mg oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Responder (mild or no pain 15 minutes after dose), no further study medication was to be administered.

Reporting group title	Placebo/Rizatriptan

Reporting group description:

Stage 1 - Randomized to single placebo oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Non-Responder (moderate or severe pain 15 minutes after dose), Stage 2 randomization was to occur and participants in this reporting group received single rizatriptan 5 or 10 mg oral tablet. Stage 2 dose was administered approximately 15 minutes post Stage 1 dose, to treat same qualifying migraine treated in Stage 1. Stage 2 randomization was in a ratio of 1:1 rizatriptan:placebo.

Reporting group title	Placebo/Placebo

Reporting group description:

Stage 1 - Randomized to single placebo oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Non-Responder (moderate or severe pain 15 minutes after dose), Stage 2 randomization was to occur and participants in this reporting group received single placebo oral tablet. Stage 2 dose was administered approximately 15 minutes post Stage 1 dose, to treat same qualifying migraine treated in Stage 1. Stage 2 randomization was in a ratio of 1:1 rizatriptan:placebo.

Reporting group title	Rizatriptan/Placebo

Reporting group description:

Stage 1 - Randomized to single rizatriptan 5 or 10 mg oral tablet to be taken within 30 minutes of onset of qualifying migraine / Stage 2 - If Stage 1 dose was taken and participant was Non-Responder (moderate or severe pain 15 minutes after dose), allocated to receive single placebo oral tablet in Stage 2 to treat same qualifying migraine treated in Stage 1 (Stage 2 dose to be administered 15 minutes post Stage 1 dose).

Subject analysis set title	Placebo in Stage 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Includes participants who did not respond to placebo in Stage 1, were randomized to and took placebo in Stage 2 and had both Stage 2 baseline migraine severity (moderate or severe) and at least one post Stage 2 dose efficacy measurement prior to or including the 2 hour post dose time point. Those randomized to rizatriptan in Stage 1 were excluded.

Subject analysis set title	Rizatriptan in Stage 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Includes participants who did not respond to placebo in Stage 1, were randomized to and took rizatriptan in Stage 2 and had both Stage 2 baseline migraine severity (moderate or severe) and at least one post Stage 2 dose efficacy measurement prior to or including the 2 hour post dose time point. Those randomized to rizatriptan in Stage 1 were excluded.

Primary: Pain freedom at 2 hours post dose in participants between 12 and 17 years of age

End point title	Pain freedom at 2 hours post dose in participants between 12 and 17 years of age

End point description:

Pain intensity was assessed using a 5-Face Pain Scale ranging from 1=no pain to 5=very bad pain. Pain freedom was defined as a reduction in severity from a rating of 3, 4 or 5 (moderate or severe pain) at

the Stage 2 baseline (15 minutes post Stage 1 dose) to a rating of 1 (no pain) at 2 hours post Stage 2 dose. Missing data were imputed by carrying forward the preceding Stage 2 pain intensity values. Missing Stage 2 baseline values were imputed by carrying forward the Stage 1 baseline value, if available.

End point type	Primary

End point timeframe:

2 hours post Stage 2 dose

End point values	Rizatriptan in Stage 2	Placebo in Stage 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	284[1]	286[2]		
Units: Participants				
2-hour pain freedom	87	63		
No 2-hour pain freedom	197	223		

Notes:

[1] - Participants between 12 and 17 years of age who received rizatriptan during Stage 2 of the study.

[2] - Participants between 12 and 17 years of age who received placebo during Stage 2 of the study.

Statistical analyses

Statistical analysis title	Pain freedom at 2 hours post dose

Statistical analysis description:

Pain freedom at 2 hours post dose in participants between 12 and 17 years of age. The comparison of rizatriptan versus placebo with respect to the primary outcome was conducted using a logistic regression model with factors for treatment, Stage 2 baseline pain severity (moderate or severe) and region (United States [US] or ex-US). Model-derived odds ratio and a two-sided p-value were provided. An odds ratio >1 is in favor of the rizatriptan group.

Comparison groups	Rizatriptan in Stage 2 v Placebo in Stage 2
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.025 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	2.26

Notes:

[3] - Testing of primary endpoint and secondary endpoints was conducted sequentially in a pre-specified order, thus strongly controlling Type I error.

[4] - The statistical significance level for the primary endpoint was α=0.0477, and had been adjusted to account for the interim sample size adjustment.

Secondary: Pain relief at 2 hours post dose in participants between 12 and 17 years of age

End point title	Pain relief at 2 hours post dose in participants between 12 and 17 years of age

End point description:

Pain intensity was assessed using a 5-Face Pain Scale ranging from 1=no pain to 5=very bad pain. Pain

relief was defined as a reduction in severity from a rating of 3, 4 or 5 (moderate or severe pain) at the Stage 2 baseline (15 minutes post Stage 1 dose) to a rating of 2 or 1 (mild or no pain) at 2 hours post Stage 2 dose. Missing data were imputed by carrying forward the preceding Stage 2 pain intensity values. Missing Stage 2 baseline values were imputed by carrying forward the Stage 1 baseline value, if available.

End point type	Secondary

End point timeframe:

2 hours post Stage 2 dose

End point values	Rizatriptan in Stage 2	Placebo in Stage 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	284[5]	286[6]		
Units: Participants				
2-hour pain relief	167	147		
No 2-hr pain relief	117	139		

Notes:

[5] - Participants between 12 and 17 years of age who received rizatriptan during Stage 2 of the study.

[6] - Participants between 12 and 17 years of age who received placebo during Stage 2 of the study.

Statistical analyses

Statistical analysis title	Pain Relief at 2 Hours Post Dose

Statistical analysis description:

Pain relief at 2 hours post dose in participants between 12 and 17 years of age. The comparison of rizatriptan vs placebo with respect to pain relief at 2 hrs post Stage 2 dose for participants between 12 and 17 years of age was conducted using a logistic regression model with factors for treatment, Stage 2 baseline pain severity (moderate or severe) and region (US or ex-US). Model-derived odds ratio and a two-sided p-value were provided. An odds ratio >1 is in favor of the rizatriptan group.

Comparison groups	Rizatriptan in Stage 2 v Placebo in Stage 2
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.9

Notes:

[7] - Secondary endpoints were to be formally tested only if the test of the primary endpoint was statistically significant at the α=0.0477 level. The secondary endpoints were then tested sequentially in a pre-specified order, each at the α=0.05 level.

Secondary: Pain freedom at 2 hours post dose in participants between 6 and 17 years of age

End point title	Pain freedom at 2 hours post dose in participants between 6 and 17 years of age

End point description:

Pain intensity was assessed using a 5-Face Pain Scale ranging from 1=no pain to 5=very bad pain. Pain

freedom was defined as a reduction in severity from a rating of 3, 4 or 5 (moderate or severe pain) at the Stage 2 baseline (15 minutes post Stage 1 dose) to a rating of 1 (no pain) at 2 hours post Stage 2 dose. Missing data were imputed by carrying forward the preceding Stage 2 pain intensity values. Missing Stage 2 baseline values were imputed by carrying forward the Stage 1 baseline value, if available.

End point type	Secondary

End point timeframe:

2 hours post Stage 2 dose

End point values	Rizatriptan in Stage 2	Placebo in Stage 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	382[8]	388[9]		
Units: Participants				
2-hour pain freedom	126	94		
No 2-hour pain freedom	256	294		

Notes:

[8] - Participants between 6 and 17 years of age who received rizatriptan during Stage 2 of the study.

[9] - Participants between 6 and 17 years of age who received placebo during Stage 2 of the study.

Statistical analyses

Statistical analysis title	Pain freedom at 2 hours post dose

Statistical analysis description:

The comparison of rizatriptan versus placebo with respect to pain freedom at 2 hours post Stage 2 dose for participants between 6 and 17 years of age was conducted using a logistic regression model with factors for treatment, Stage 2 baseline pain severity (moderate or severe), age (6 to 11 years old or 12 to 17 years old), and region (US or ex-US). Model-derived odds ratio and a two-sided p-value were provided. An odds ratio >1 is in favor of the rizatriptan group.

Comparison groups	Rizatriptan in Stage 2 v Placebo in Stage 2
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [10]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	2.1

Notes:

[10] - This second secondary hypothesis was not formally tested since the first secondary was not statistically significant.

Secondary: Pain relief at 2 hours post dose in participants between 6 and 17 years of age

End point title	Pain relief at 2 hours post dose in participants between 6 and 17 years of age

End point description:

Pain intensity was assessed using a 5-Face Pain Scale ranging from 1=no pain to 5=very bad pain. Pain relief was defined as a reduction in severity from a rating of 3, 4 or 5 (moderate or severe pain) at the

Stage 2 baseline (15 minutes post Stage 1 dose) to a rating of 2 or 1 (mild or no pain) at 2 hours post Stage 2 dose. Missing data were imputed by carrying forward the preceding Stage 2 pain intensity values. Missing Stage 2 baseline values were imputed by carrying forward the Stage 1 baseline value, if available.

End point type	Secondary

End point timeframe:

2 hours post Stage 2 dose

End point values	Rizatriptan in Stage 2	Placebo in Stage 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	382[11]	388[12]		
Units: participants				
2-hour pain relief	220	204		
No 2-hour pain relief	162	184		

Notes:

[11] - Participants between 6 and 17 years of age who received rizatriptan during Stage 2 of the study.

[12] - Participants between 6 and 17 years of age who received placebo during Stage 2 of the study.

Statistical analyses

Statistical analysis title	Pain relief at 2 hours post dose

Statistical analysis description:

The comparison of rizatriptan versus placebo with respect to pain relief at 2 hours post Stage 2 dose for participants between 6 and 17 years of age was conducted using a logistic regression model with factors for treatment, Stage 2 baseline pain severity (moderate or severe), age (6 to 11 years old or 12 to 17 years old), and region (US or ex-US). Model-derived odds ratio and a two-sided p-value were provided. An odds ratio >1 is in favor of the rizatriptan group.

Comparison groups	Rizatriptan in Stage 2 v Placebo in Stage 2
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.178 [13]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.63

Notes:

[13] - This third secondary hypothesis was not formally tested since the first secondary was not statistically significant.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Up to 14 days post dose

Adverse event reporting additional description:

Includes all randomized participants who received at least one dose of study drug (i.e., participants who only took study drug in Stage 1 were also included). Participants were included in the treatment group corresponding to the study treatment they actually received, with active treatment taking precedence over placebo treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Rizatriptan

Reporting group description:

Participants who took any rizatriptan during the study (Stage 1 or 2)

Reporting group title	Placebo

Reporting group description:

Participants who took only placebo during the study

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events exceeded the 5% threshold for any treatment group.

Serious adverse events	Rizatriptan	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 462 (0.00%)	2 / 515 (0.39%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 462 (0.00%)	1 / 515 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Enterobacter bacteremia			
subjects affected / exposed	0 / 462 (0.00%)	1 / 515 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Rizatriptan	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 462 (0.00%)	0 / 515 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2010	Amendment 2: Primary reasons for amendment were (1) to indicate that approximately 900 participants between 12 and 17 years of age will be needed to enter the study in Stage 1 to yield approximately 548 evaluable adolescent participants in Stage 2 to demonstrate the primary hypothesis regarding pain freedom at 2 hours post Stage 2 dose; and (2) to indicate that text has been changed from a maximum of 362 participants aged 6 to 11 years will be enrolled in Stage 1 to state that a minimum of 135 participants to a maximum of 165 participants aged 6 to 11 years will be enrolled in Stage 1 which is expected to yield ~ 80 to 100 evaluable participants in Stage 2 under the same assumptions as the 12 – 17 year old group.
13 November 2010	Amendment 4: Primary reason for amendment was to indicate that approximately 265 participants aged 6 to 11 years old will be enrolled in Stage 1 which is expected to yield approximately 160 evaluable participants (80/arm) in Stage 2 under the same evaluability assumptions as for the 12-17 year olds.
24 January 2011	Amendment 6: Primary reason for amendment was to indicate that approximately 340 participants aged 6 to 11 years old will be enrolled in Stage 1 which is expected to yield approximately 160 evaluable participants (80 rizatriptan/80 placebo) in Stage 2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22711898