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

Published: 09-12-2009
Last updated: 04-05-2024

The objective of this study is to test the safety of the research study drug, MK-0462 (rizatriptan) and to test the ability of study drug to relieve or reduce migraine for the study population.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Headaches
Study type	Interventional

Summary

ID

NL-OMON34773

Source
ToetsingOnline

Brief title
082- MAXALT

Condition

- Headaches

Synonym
migraine head ache

Research involving

Human

Sponsors and support

Primary sponsor: Merck & Co., Inc.
Source(s) of monetary or material Support: Merck & Co. Inc.

Intervention

Keyword: MAXALT, pedeatric migraine

Outcome measures

Primary outcome

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 NSAIDS or 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.

Secondary outcome

1. To evaluate the efficacy of rizatriptan compared to placebo in the treatment of acute migraine as measured by pain relief at 2 hours in pediatric migraineurs between 12 and 17 years of age who have not, historically, achieved a satisfactory response to treatment with NSAIDS or APAP.

2. 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 6 and 17 years of age who have not, historically, achieved a satisfactory response to treatment with NSAIDS or APAP.

3. To evaluate the efficacy of rizatriptan compared to placebo in the treatment of acute migraine as measured by pain relief at 2 hours in pediatric migraineurs between 6 and 17 years of age who have not, historically, achieved a satisfactory response to treatment with NSAIDS or APAP.

4. To evaluate the safety and tolerability of rizatriptan in pediatric migraineurs between 6 and 17 years of age who have not, historically, achieved a satisfactory response to treatment with NSAIDS or APAP.

Study description

Background summary

Migraine is a common neurological disorder afflicting children, adolescents and adults.
It contributes significantly to school absence, work loss, medication use, impaired quality of life, and health care visits. Rizatriptan (manufactured and marketed as MAXALTby Merck & Co, Inc., Whitehouse Station, NJ) is a 5-HT1B/1D agonist approved at a
therapeutic dose of 10 or 5 mg (up to 2-3 doses/24 hours depending on local product label; interdose interval of 2 or more hours) for the acute treatment of migraine in adults. 5-HT1B/1D agonists (triptans) are prescribed for and used by pediatric migraineurs with very limited systematically collected data on their safety and efficacy in this population. Two well-controlled trials conducted with rizatriptan 5 mg in adolescents aged 12 to 17 failed to demonstrate a statistically significant difference between the treatments on the primary endpoint (pain freedom at 2 hours post dose). However, a response

trend was observed in the rizatriptan group in the lower age stratum (12-14 years) compared to the higher age stratum (15-17 years), as well as by weight in that heavier children trended toward poorer outcomes. These findings suggest that the older and heavier children may have had insufficient exposures based on weight. A third controlled trial conducted by Ahonen et al applied a weight-based dosing strategy for pediatric migraineurs age 6 to 17, wherein patients weighing < 40 kg received rizatriptan 5 mg or placebo and patients weighing * 40 kg received rizatriptan 10 mg or placebo.

This study demonstrated a significant treatment effect for both doses of rizatriptan compared to placebo [1]. Data from a recently completed pharmacokinetic study (P083) demonstrated that exposures following single dose administration of 5 mg rizatriptan ODT to pediatric migraineurs weighing 20-39 kg or 10 mg rizatriptan ODT to pediatric migraineurs weighing * 40 kg were similar to those observed following single dose administration of 10 mg rizatriptan ODT to adults. This study plans to use a similar weight-based dosing strategy to further assess the efficacy and safety of rizatriptan in pediatric migraineurs age 6 to 17 years. Two oral formulations of rizatriptan are currently available: solid tablet and orally disintegrating tablet (ODT). The ODT formulation accounts for slightly more than half of the prescriptions in pediatric patients.

Study objective

The objective of this study is to test the safety of the research study drug, MK-0462 (rizatriptan) and to test the ability of study drug to relieve or reduce migraine for the study population.

Study design

This is a randomized, double-blind (with in-house blinding), placebo-controlled, parallelgroup study. Patients will treat a single migraine attack in two stages, with Stage 1 to identify placebo non-responders who will then enter into Stage 2. In Stage 1, patients will be randomized in a 20:1 ratio to placebo or rizatriptan, with randomization stratified based on age (6 to 11 years old vs. 12 to 17 years old). Patients will administer study medication within 30 minutes of onset of a qualifying migraine attack. After 15 minutes, patients will call into the Interactive Voice Response (IVR) system to report their pain intensity level. Patients who report mild pain or no pain (i.e., responders) will be instructed to take no further study medication. Patients who report moderate or severe pain (i.e., non-responders) will be instructed to take study medication in Stage 2. Nonresponders to placebo in Stage 1 will be randomized in a 1:1 ratio to rizatriptan or placebo, with randomization stratified based on age (6 to 11 years old vs. 12 to 17 years old) and migraine intensity reported at 15 minutes post Stage 1 dose (moderate versus severe). The migraine intensity reported at 15 minutes post Stage 1 dose

will be used as the Stage 2 baseline pain severity. Non-responders to rizatriptan in Stage 1 will be allocated to receive placebo in Stage 2.
A qualifying migraine is defined as a migraine of moderate or severe intensity and treatment with study medication is limited to settings where the study procedures may be followed (Please see section 3.2.3.6.1 Qualifying Migraine for further details). Patients will complete a paper migraine diary at prespecified time points to evaluate efficacy and tolerability.

Intervention

The study has two stages:
Stage 1 treatment is to be administered within 30 minutes following the onset of a qualifying migraine.
Stage 2 treatment is to be administered immediately after IVRS confirmation for Stage 2 (occurring just after the 15-minute post dose response for Stage 1).

Study burden and risks

Reported side effects for MK-0462 (rizatriptan) are:
Numbness, pain and/or pressure (chest, neck, throat and/or jaw region and general), dry, mouth, nausea, dizziness, headache, sleepiness, weakness/tiredness, seizures, anaphylactic reaction (a potentially life-threatening allergic reaction that requires immediate medical attention)

In addition, an uncommon but potentially life-threatening condition called serotonin syndrome can occur with rizatriptan or other medications in the triptan class particularly when taken together with certain types of antidepressant and mood disorder medications called selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, sertraline, olanzapine/fluoxetine, citalopram hydrobromide, escitalopram oxalate, and selective serotonin/norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, and duloxetine.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Patient is between 6 and 17 years of age inclusive at screening Visit 1.
2. Patient weighs * 20 kg.
3. Patient has a history of migraine as defined by International Headache Society [IHSAppendix
6.1, 6.3] migraine definitions and meets the following criteria:
a. Unilateral or bilateral migraine headache, with or without aura;
b. History of migraine attacks for more than 6 months;
c. Reports * 1 to * 8 moderate or severe migraine attacks per month in the 2 months prior to screening Visit 1. This also includes attacks which were treated early, while pain was mild, but which, in the patient*s judgment, would have progressed to moderate or severe if untreated.
d. Duration of a typical untreated migraine attack (excluding sleep) is * 3 hours.
4. Patient has had a history of migraine with or without aura for more than 6 months
5. Patient is either:
a. of reproductive potential and agrees to maintain true abstinence* or use (or have their partner use) one of the listed highly effective methods of birth control within the projected duration of the study: hormonal contraceptives, intrauterine device (IUD), condoms, diaphragm, vasectomy. The use of barrier contraceptive (condom or diaphragm) should always be supplemented with the use of a spermicide. Complete details regarding contraceptive requirements are specified in protocol Section 3.2.3.2.
OR
b. not of reproductive potential. For the purposes of this protocol, the following

definitions apply:
A female patient who is not of reproductive potential is defined as:
one who 1) has not reached menarche or 2) is 6 weeks post surgical bilateral oophorectomy, hysterectomy, or bilateral tubal ligation.
A male patient who is not of reproductive potential is defined as:
one who has undergone a successful vasectomy. A successful vasectomy is defined as: 1) microscopic documentation of azoospermia, or 2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post vasectomy.
* If abstinence is not a locally acceptable method of contraception, then another highly effective birth control method must be used.
6. Patient is willing to stay awake for at least 2 hours after administration of the first dose of study medication.
7. Patient has not experienced satisfactory relief from migraine pain with NSAIDs or APAP treatment, in the opinion of the investigator.
8. Patient is able to complete the migraine diary and is cooperative with completing the prestudy assessments. Patients who require help to read should be assisted by an adult; however, the patient will provide the actual written responses to the pain scale questions in the migraine diary.
9. The parent or guardian and patient agree to the patient*s participation in the study as indicated by parental/guardian signature on the consent form and patient assent.
10. For patients taking migraine prophylactic medication, treatment regimen is stable and has been taken for at least 3 months prior to Visit 1.

Exclusion criteria

1. Patient is pregnant (positive serum *-hCG test at screening) or breast-feeding, or is a female expecting to conceive within the projected duration of study participation.
2. Patient has a history of predominantly mild migraine attacks or migraines usually resolved spontaneously in less than 2 hours.
3. Patient has basilar or hemiplegic migraine headaches (For diagnostic criteria for basilar migraine, see Appendix 6.2)
4. Patient has >15 headache-days per month OR has taken medication for acute headache on more than 10 days per month in any of the 3 months prior to screening.
5. Patient has clinical, laboratory, or ECG evidence of uncontrolled hypertension, uncontrolled diabetes, HIV disease, any neoplastic disease, or other significant pulmonary, renal, hepatic, endocrine, neurological, or other systemic disease in the opinion of the investigator (e.g., epilepsy; systemic lupus erythematosus; Kawasaki disease; homozygous sickle cell anemia; recurrent syncope).
6. Patient has a history or clinical evidence of congenital heart disease suspected or confirmed; atherosclerotic disease; history of cerebrovascular pathology including stroke; Prinzmetal*s angina; cardiac arrhythmias requiring medication; or hypertension for age.
7. Patient has a history or current evidence of any clinically significant disease that according to the investigator might confound the results of the study [e.g., chronic

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pain syndromes (i.e., condition requiring daily use of opiates), major psychiatric diagnoses such as schizophrenia, bipolar disorder, or major depression] that complicate the interpretation of the study results, interfere with the patient*s participation for the full duration of the study, or pose an additional undue risk to the patient.
8. Patient has either demonstrated hypersensitivity to or experienced a serious adverse event in response to rizatriptan.
9. Patient has demonstrated hypersensitivity to or experienced a serious adverse event in response to 3 or more pharmacologic classes of drugs (over-the-counter and prescription).
10. Patient did not experience satisfactory relief from migraine pain to prior treatment with 2 or more adequate courses of 5HT1 agonists.
11. Patient has a recent history (within the past year) or current evidence of drug or alcohol abuse or is a
12. Patient is currently taking monoamine oxidase inhibitors, methysergide, or propranolol, and is unable to tolerate withdrawal of these medications for the intervals required.
13. Patient is currently participating or has participated in a study with an investigational compound or device within 30 days of screening. (This includes studies using commercially available compounds or devices for investigational purposes, e.g., new indications).
14. Patient has abnormal screening laboratory values as per the guidelines listed below or other clinically significant, unexplained laboratory abnormality, according to the investigator:
a. AST > 1.5 x upper limit of normal
b. ALT > 1.5 x upper limit of normal
c. Total bilirubin > 1.5 x upper limit of normal
d. Serum creatinine > 1.5 x upper limit of normal
15. Patient is legally or mentally incapacitated.
16. Patient has undergone major surgery (in the opinion of the investigator) within 30 days of screening or has donated blood products or has had phlebotomy of > 300 ml within 8 weeks of signing informed consent, or intends to donate blood products or receive blood products within 30 days of screening and throughout the study.
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17. Patient is unlikely to adhere to study procedures, keep appointments, or is planning to relocate during the study.

Study design

Design

Study phase: 3

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2010
Enrollment:	39
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Rizatriptan
Generic name:	MAXALT
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	09-12-2009
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)

Approved WMO

Date:	15-02-2010
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)

Approved WMO

Date:	13-07-2010
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Approved WMO

Date:	18-11-2010
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	24-01-2011
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-016374-32-NL
ClinicalTrials.gov	NCT01001234
CCMO	NL30596.075.09