A Six Month Phase II/III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety, Tolerability, and Efficacy of Telcagepant (MK-0974) for Prevention of Menstrually Related Migraine in Female Patients with Episodic Migraine

Published: 04-06-2010
Last updated: 30-04-2024

• Test the safety of the research drug, telcagepant (MK-0974)• Test the safety of the research study drug telcagepant (MK-0974) in the prevention of menstrually related migraines. • Compare the effectiveness of the research study drug telcagepant (...

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

Summary

ID

NL-OMON34533

Source
ToetsingOnline

Brief title
MK0974-065

Condition

- Headaches

Synonym
headache, migraine

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck;Sharp & Dohme B.V.

Intervention

Keyword: menses, migraine, MK0974-065, telcagepant

Outcome measures

Primary outcome

1. To evaluate the efficacy of telcagepant 140 mg once daily for 7-days per month compared to placebo for the prevention of migraine during the study period in female patients with menstrually related migraine or pure menstrual migraine.

2. To examine the tolerability and safety of telcagepant 140 mg once daily for 7-days per month for the prevention of migraine in female patients with episodic migraine

Secondary outcome

1. To evaluate the efficacy of telcagepant 140 mg, once daily, for 7-days per month, compared to placebo, for the prevention of migraine in female patients with menstrually related migraine.

Study description

Background summary

Calcitonin gene-related peptide (CGRP) is a potent neuropeptide that is believed to play a key role in the early stages of migraine pathogenesis. CGRP

levels in the cranial circulation are increased during a migraine attack and CGRP itself has been shown to trigger migraine headache. Telcagepant potassium (hereafter referred to as telcagepant) is a potent, selective competitive antagonist of the human CGRP receptor and is being developed for acute treatment of migraine.
Telcagepant has been studied in 5 completed double-blind, placebo-controlled acute migraine efficacy studies. In these studies, telcagepant has demonstrated effectiveness in relieving migraine pain and associated symptoms, and was generally well-tolerated. In three pivotal Phase III efficacy trials, both 140 mg and 280 mg showed superior efficacy over placebo as measured by 2 hour pain freedom, 2 hour pain relief, 2-24 sustained pain freedom, photophobia, phonophobia and nausea and was efficacious in patients who previously reported poor responses to triptans. In addition, telcagepant does not cause vasoconstriction and was not associated with the adverse events typically experienced by patients taking triptans, such as chest pain, chest pressure, paraesthesia, throat tightness and asthenia.

In 60% of female patients, migraine attacks increase during the perimenstrual period. Triptans have shown efficacy in short-term (mini-) prophylaxis of menstrual migraine when taken for 5-6 days perimenstrually. Reduction in migraine frequency in the range of 15-25% over placebo has been observed with triptans.
The first evidence that telcagepant may have prophylactic efficacy was seen in the acute efficacy studies. In the pivotal efficacy study for which zolmitriptan was used as an active control, telcagepant showed similar 2 hour pain freedom and pain relief as zolmitriptan. However, telcagepant appeared to have longer duration of action. In the long term safety study there was evidence that telcagepant decreased headache frequency. Among patients who experienced pain freedom at 2 hours after administration of the initial dose, migraine return within 24 hours (an exploratory endpoint) was less common with telcagepant than with rizatriptan. These finding, taken together, suggest that telcagepant may have potential to confer a prophylaxis against migraine even when taken for a short period of time each month.
Finally, in the migraine prophylaxis study, although the study was terminated early, both telcagepant 140 mg and 280 mg BID treatment groups showed a nominally significant ($p<0.02$) reduction in headache frequency after 1 month of treatment as compared to placebo.

During the clinical development program for telcagepant, elevations in aminotransferases were observed. The data suggest that the manner in which telcagepant is administered*how frequently and for how long*is a determinant of clinical risk. The current study is designed to obtain additional experience in a clinical trial setting when telcagepant is used at the anticipated maximum allowed frequency of dosing per month for the acute treatment of migraine. The large sample size in this study will help inform the risk of aminotransferase elevation relative to the background rate. For a more extensive explanation;

see section "burden and risks".

Study objective

• Test the safety of the research drug, telcagepant (MK-0974)
• Test the safety of the research study drug telcagepant (MK-0974) in the prevention of menstrually related migraines.
• Compare the effectiveness of the research study drug telcagepant (MK-0974) in the prevention of menstrually related migraines to placebo (look-alike drug with no active ingredients, sometimes called a "sugar pill").

Study design

This is a 6-month, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety, tolerability, and efficacy of telcagepant 140 mg for the prevention of menstrually related migraine. Patients who qualify at the screening visit (Visit 1) will be randomized in a 2:1 ratio to telcagepant 140 mg or placebo to be administered once a day at bedtime for 7 consecutive days starting at the beginning of each perimenstrual period. Patients will return to the clinic monthly as soon as possible (i.e. within 1 - 5 days) after completion of each 7-day dosing period for a follow-up visit. All follow-up procedures will be conducted according to the Study Flow Chart.

Intervention

Study drug supply will be provided as 140-mg tablets of telcagepant or matching placebo. Patients will administer a single daily dose of telcagepant 140 mg or placebo at bedtime for 7 consecutive days each month, beginning at the onset of menses, for up to 6 months. If a patient has prodromal symptoms that reliably predict the onset of menses, they may begin dosing up to 3 days prior to menses onset.

Study burden and risks

See E9.
During the clinical development program for telcagepant, elevations in aminotransferases greater than 3-fold above normal were observed. The majority of elevations were observed in a migraine prophylaxis study, which was terminated early due to concerns regarding aminotransferase elevations. The final analysis showed that these findings occurred at or after at least 2 weeks of treatment with telcagepant 280 mg or 140 mg twice daily. Two of these elevations were marked, and were associated with symptoms that could have represented an acute hepatitis. In each observed case, aminotransferase levels returned to normal after drug was discontinued, and clinical signs/symptoms dissapeared.
These findings occurred under treatment conditions that were qualitatively and

quantitatively different from those associated with the expected use of telcagepant for acute, intermittent migraine. Specifically, both duration of therapy and plasma drug exposures were greater during continuous daily dosing than during intermittent dosing (the expected treatment paradigm for acute intermittent migraine) with either 140 mg or 280 mg. Review of the telcagepant safety database suggests that there is no increased aminotransferase elevation beyond the expected background rate of other therapies when use is for less than 14 consecutive days of therapy.
The data suggest that the manner in which telcagepant is administered*how frequently and for how long*is a determinant of clinical risk. Plasma exposures during daily telcagepant administration are higher than exposures after the same dose administered once. Patients in the migraine prophylaxis study were exposed to sustained higher circulating concentrations of drug than those in the intermittently dosed studies, due to the twice daily dosing paradigm. It is possible, therefore, that circulating drug concentration and duration of treatment could have played a role in the development of aminotransferase elevations.
The current study is designed to obtain additional experience in a clinical trial setting when telcagepant is used at the anticipated maximum allowed frequency of dosing per month for the acute treatment of migraine. The present study will examine the safety of 140 mg dosing consecutively 7 days monthly. The large sample size in this study will help inform the risk of aminotransferase elevation relative to the background rate.

Since the elevation of aminotransferases could be a possible serious side effect in this study, the liver enzymes of patients will be monitored carefully if patients display the associated symptoms.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. patient is >=18 years of age at screening.
2. female who has regular menstrual cycles monthly (22 to 32 days) for at least the last 3 cycles.
3. history of migraine with or without aura for >=3 months and with >=2 migraine attacks per month in te 2 months prior to screening.
4. headache during menstrual period in at least 2 out of last 3 cycles.

Exclusion criteria

1. patient has basilar or hemiplegic migraine headache. 2. patient has taken medication for acute headache atttack on more than 15 days per month in any of the 3 months prior to screening. 3. patient is taking migraine prophylactic medication where the prescribed daily dose has changed during the 4 weeks prior to screening. 4. history of liver disease. 5. consumes 3 or more alcoholic drinks per day.

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:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-08-2010
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable
Generic name:	telcagepant

Ethics review

Approved WMO Date:	04-06-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-06-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-09-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-09-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Approved WMO Date:	18-11-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-02-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-05-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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
Other	begin juni op clinical trials.gov
EudraCT	EUCTR2010-019288-13-NL
CCMO	NL32161.058.10