A Phase II, Open-label, Multicentre Study to Evaluate the Long-term Safety and Efficacy of MT-1303 in Subjects with Moderate to Severe Active Crohn*s Disease who have Completed the MT-1303-E13 Study

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Primary Objective:* To evaluate the long-term safety and tolerability of MT-1303 in subjects with moderate to severe active CDSecondary Objectives:* To evaluate the long-term effects of MT-1303 on clinical outcomes in subjects with moderate to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON44363

Source
ToetsingOnline

Brief title
Mitsubishi MT-1303-E14

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohns disease

Research involving

Human

Sponsors and support

Primary sponsor: Mitsubishi Tanabe Pharma Europe Ltd (MTPE)
Source(s) of monetary or material Support: The pharmaceutical industry

Intervention

Keyword: Extension safety study, Moderate/Severe Active Crohn's Disease, MT-1303, Phase II

Outcome measures

Primary outcome

Primary Endpoint:

Safety, assessed by:

* AEs

* Vital signs

* 12-lead ECG

* Holter ECG monitoring

* Routine safety laboratory assessments

* Physical examination (including skin assessment)

* Optical coherence tomography (OCT).

Secondary outcome

Secondary Endpoints:

Efficacy

* Proportion of subjects who achieve a 70-point decrease from MT-1303-E13

baseline in CDAI score (i.e., CDAI 70) at Protocol-scheduled visits

* Proportion of subjects who achieve a 100-point decrease from MT-1303-E13

baseline in CDAI score (i.e., CDAI 100) at Protocol-scheduled visits

* Proportion of subjects who achieve clinical remission (i.e., CDAI score of

<150) at Protocol-scheduled visits

* CDAI score and change from MT-1303-E13 baseline in CDAI score at

Protocol-scheduled visits

* Proportion of subjects in corticosteroid-free remission at EOT

Phamacodynamics

* Lymphocyte count and lymphocyte subsets, their change from MT-1303-E13

baseline, and percentage of MT-1303-E13 baseline at Protocol-scheduled visits

* C-reactive protein (CRP) and faecal calprotectin value and their change from

MT-1303-E13 baseline at Protocol-scheduled visits.

Study description

Background summary

Sphingosine-1-phosphate (S1P), a multi-functional phospholipid mediator, is generated from sphingosine by sphingosine kinases and binds five types of G protein-coupled S1P receptors (S1P1, S1P2, S1P3, S1P4 and S1P5 receptors). It has been well documented that S1P and the S1P1 receptor play an essential role in lymphocyte egress from secondary lymphoid organs because it has been demonstrated that lymphocytes are unable to exit from secondary lymphoid organs to the periphery in mice lacking lymphocytic S1P1.

Fingolimod (FTY720), the first-in-class S1P receptor modulator, has been marketed widely and has demonstrated good efficacy in relapsing-remitting multiple sclerosis (RRMS) patientsThe active metabolite, fingolimod-phosphate, strongly internalises S1P1 receptors and acts as a functional antagonist at lymphocytic S1P1 receptors. Consequently, fingolimod inhibits S1P1-dependent lymphocyte egress from secondary lymphoid organs to the periphery, decreases circulating lymphocytes including autoreactive T cells, and exhibits immunomodulating effects . Fingolimod however is reported to cause a transient and mild reduction in heart rate , which is possibly associated with agonistic activity at S1P1 and S1P3 receptors on atrial myocytes]. According the Summary of Product Characteristics (SmPC) for fingolimod, time to reach peak plasma concentration (tmax) of fingolimod is approximately 12-16 hours (h) and hence

there is no obvious correlation between tmax and the timing of bradycardia . The reason for this discrepancy is not yet fully understood, however, it is considered due to different kinetics of receptor occupancy and receptor internalisation; the most plausible explanation is that internalisation of S1P1/3 receptors on atrial myocytes would occur more rapidly (i.e., within 6 h after the initial dose) than those on lymphocytes. The internalised receptors on atrial myocytes would no longer respond to a further exposure of fingolimod and therefore more severe bradycardia is unlikely to occur after 6-h post-dose

MT-1303, discovered by MTPC, was designed to be a selective S1P receptor compound, in the hope that it would have fewer adverse effects than fingolimod. MT-1303 is effectively converted to its active metabolite, (S)-MT-1303-P in vivo. In humans, (S)-MT-1303-P shows greater selectivity for the S1P1 receptors and shows no clear affinity to human S1P2/3 receptors. The long half-life (approximately 380-400 h in humans) of MT-1303 and MT-1303-P indicates that both will slowly accumulate to steady state over a period of about 10 weeks [19]. (Accumulation ratios were 16-29 and 7-10 for MT-1303 and MT-1303-P, respectively.) This pharmacokinetic (PK) profile therefore may be advantageous in initiating MT-1303 treatment, as initial low doses of MT-1303 will have little effect on heart rate and desensitisation can be expected to occur gradually over several weeks of accumulation, rendering dose titration unnecessary.

Oral administration of MT-1303 inhibited the development of colitis induced by adoptive transfer of CD4+CD45RBhigh T cells in severe combined immunodeficiency (SCID) mice, an animal model of inflammatory bowel disease (IBD) [19]. Moreover, MT-1303 is effective in animal models of multiple sclerosis, psoriasis and systemic lupus erythematosus (SLE). These results indicate that MT-1303 may have a therapeutic potential for IBD, RRMS, psoriasis and SLE, while its effect on heart rate is anticipated to be less than that of fingolimod.

The mechanism of action of MT-1303, its potential modulation of physiological and pathological pathways and its safety profile warrant further investigation of MT-1303 in inflammatory and autoimmune diseases in humans.

Study objective

Primary Objective:
* To evaluate the long-term safety and tolerability of MT-1303 in subjects with moderate to severe active CD
Secondary Objectives:
* To evaluate the long-term effects of MT-1303 on clinical outcomes in subjects with moderate to severe active CD
* To explore the pharmacodynamic (PD) effects of MT-1303 in subjects with moderate to severe active CD

Study design

This is a phase II, multicentre, open-label extension study to evaluate safety, tolerability and efficacy of MT-1303 administered orally once daily (o.d.) for up to 36 weeks in subjects with moderate to severe active CD who satisfactorily complete the 14-week Treatment Period of the MT-1303-E13 study.
Subject eligibility will be confirmed at Visit 7 (Week 14) in MT-1303-E13 and eligible subjects who wish to continue in the open-label extension will be entered at Visit 1 (Week 0) in MT-1303-E14. There will be no interruption in treatment between completion of Visit 7 (EOT; End of Treatment) in MT-1303-E13 and initiation of treatment in MT-1303-E14. All subjects will receive MT-1303 0.4 mg regardless of treatment received in MT-1303-E13 (i.e., MT-1303 or placebo). Except for the first day of treatment, study medication should be taken in the morning at approximately the same time each day; the first dose will be administered at the clinical unit and will be followed by a 24-hour (h) period of Holter ECG monitoring with at least the first 6 h completed within the clinic.
Routine safety assessments (12-lead electrocardiogram [ECG], vital signs, clinical safety laboratory and physical examination, including skin assessment) and adverse events (AEs) will be documented at regular intervals during the Treatment Period. In addition the Crohn*s Disease Activity Index (CDAI) scoring system will be used to assess, clinical response and of clinical remission following treatment.
Permitted medication for the treatment of CD during the study will include oral 5-ASA, limited dose of oral corticosteroid, antibiotics (i.e., metronidazole or ciprofloxacin) and non-parenteral nutrition therapy.
Following completion of open-label treatment, all subjects will enter a 12-week safety Follow-up Period.

Intervention

Treatment Period:
Eligible subjects will be receive a 36-week treatment with
- once daily an oral capsule of 0,4 mg MT-1303

Study burden and risks

Although at the time of entering the MT-1303-E14 study there will be no documented benefits for subjects, there is an expectation that subjects treated with MT-1303 will experience a selective reduction in lymphocytes which may be translated into clinical benefit. Following completion and reporting of MT-1303-E13 study, it may be possible to outline any specific benefits of long-term treatment with MT-1303.

The MT-1303-E14 study closely follows the design of the MT-1303-E13 study which is carefully designed to minimise the identified and potential risks to

subjects. The screening procedure mandated in the MT-1303-E13 study excludes all subjects for whom the MT-1303-E14 study is considered to pose an unacceptable risk. Regular safety monitoring during the treatment and safety Follow-up Periods for all subjects in MT-1303-E14 will ensure that any unanticipated effects of study participation are identified promptly and managed appropriately.

At the level of the individual subject, the Protocol states well-defined criteria for intensive Cardiovascular Safety Monitoring, including extended monitoring (Section 4.5.1) and the permanent discontinuation of study medication (Section 4.5.3). In addition, an independent Data and Safety Monitoring Board (DSMB) will continue to review selected data across the study at regular, predefined intervals. The DSMB is empowered to make recommendations regarding continuation, termination or modification of the study, as appropriate (Section 11.3).

In particular, if it becomes clear that continuing treatment with MT-1303 is not clinically or ethically justified, the MT-1303-E14 study will be terminated. Overall, based on data from non-clinical and clinical studies of MT-1303 and the risk-minimisation strategies discussed above, the risk/benefit profile of this study is considered acceptable.

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. The subject completed the 14 week Treatment Period in the double-blind MT-1303-E13 study as per Protocol.;2. The subject is able to provide written informed consent and to comply with the requirements of the MT-1303-E14 Protocol during the study.;3. For subjects of reproductive potential, two methods of contraception must be used throughout the study and for 12 weeks after cessation of study medication. At least one of the methods of contraception must be a barrier method. ;For detailed information, please refer to the Protocol.

Exclusion criteria

1. Permanent discontinuation of study medication prior to the EOT Visit in MT-1303-E13;2. Newly diagnosed diabetes mellitus during the double blind MT-1303-E13 study.;For detailed information, please refer to the Protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status:	Recruitment stopped
Start date (anticipated):	24-02-2016

Enrollment:	4
Type:	Actual

Ethics review

Approved WMO Date:	03-11-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2014-002557-19-NL
CCMO	NL50865.018.14