A Phase II, Multicentre, Randomised, Double-Blind, Parallel Group, Placebo Controlled Study to Evaluate Safety, Tolerability and Clinical Efficacy of MT 1303 in Subjects with Moderate to Severe Active Crohn*s Disease

Published: 03-11-2014
Last updated: 21-04-2024

Primary Objectives* To evaluate the safety and tolerability of MT-1303 in subjects with moderate to severe active CD* To evaluate the clinical efficacy of MT-1303 in subjects with moderate to severe active CD.Secondary Objectives* To explore the PK...

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

Summary

ID

NL-OMON44387

Source
ToetsingOnline

Brief title
Mitsubishi MT-1303-E13

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: Moderate/Severe Active Crohn's Disease, MT-1303, Phase II

Outcome measures

Primary outcome

Primary Efficacy Endpoint:

* The proportion of subjects who achieve a 100-point decrease from Baseline in CDAI score (i.e., CDAI 100) at Visit 6 (Week 12)

Secondary outcome

Secondary Endpoints:

Efficacy

* Proportion of subjects who achieve a 70-point decrease from Baseline in CDAI score (i.e., CDAI 70) at Protocol-scheduled visits.
* Proportion of subjects who achieve a 100-point decrease from Baseline in CDAI score (i.e., CDAI 100) at other 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 Baseline in CDAI score at Protocol-scheduled visits.

Pharmacodynamics

* Lymphocyte count and lymphocyte subsets, their change from Baseline, and

percentage of Baseline at Protocol-scheduled visits.

Pharmacokinetics

* PK concentration of MT-1303 and its active metabolite MT-1303-P 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 Objectives

* To evaluate the safety and tolerability of MT-1303 in subjects with moderate to severe active CD
* To evaluate the clinical efficacy of MT-1303 in subjects with moderate to severe active CD.

Secondary Objectives

* To explore the PK of MT-1303 in subjects with moderate to severe active CD
* To explore the PD effect of MT-1303 in subjects with moderate to severe active CD.

Study design

This is a phase IIa, multicentre, randomised, double-blind, parallel group, placebo-controlled study to evaluate safety, tolerability and clinical efficacy

of MT-1303 in subjects with moderate to severe active CD.

The study will consist of a Screening Period of up to 4 weeks, a 14-week Treatment Period and a 12-week Follow-up Period, during which there will be 10 scheduled visits. Following screening, 80 eligible subjects will be randomly assigned to receive either MT-1303 0.4 mg or matching placebo in a 1:1 ratio. Study medication should be taken in the morning, at approximately the same time each day, except at Visit 2 (first day of treatment) during which subjects will receive study medication at the clinical unit and at least a 48-hour (h) period of Holter electrocardiogram (ECG) monitoring (which includes 1 h pre-dose) with at least the first 6 h post-dose completed within the clinic (Visit 2). A 24-h post-dose period of Holter ECG monitoring will be performed at Visits 4 and 7 (Weeks 4 and 14, respectively).

Subjects who complete the 14-week placebo-controlled Treatment Period may have the option of immediately entering the 48-week open-label extension study (MT-1303-E14) after the Treatment Period. During the extension study, all subjects will receive MT-1303 0.4 mg for up to 36 weeks regardless of treatment received in MT-1403-E13. Those subjects not eligible to enter the extension study will be required to complete a 12-week safety Follow-up Period in MT-1303-E13.

Routine safety assessments (12-lead ECG, vital signs, clinical safety laboratory and physical examination) 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.

Concomitant use of oral 5-aminosalicylic acid (5-ASA), limited dose of oral corticosteroids, antibiotics use and non-parenteral nutrition therapy are permitted at stable doses for treatment of CD.

Intervention

Treatment Period:
Eligible subjects will be randomly assigned to receive a 14-week treatment with
- once daily an oral capsule of 0,4 mg MT-1303 or
- once daily its matching placebo

Study burden and risks

The study has been carefully designed to minimise the identified and potential risks to subjects; all subjects will undergo screening procedures aimed at minimising the likelihood and impact of any such risks. In addition, regular safety monitoring during the treatment and safety Follow-up Periods for all subjects 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 the extended monitoring (Section 4.5.1) and the permanent discontinuation of study medication (Section 4.5). 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-E13 study will be terminated.
Given that this is a proof-of-concept study, there are no guaranteed benefits for subjects; however, there is an expectation that subjects treated with MT-1303 will experience a selective reduction in lymphocytes which may be translated into clinical benefit. All subjects may have an option of entering the 48-week open-label extension study (MT-1303-E14) directly after the 14-week Treatment Period, if both the Investigators and subjects agree to do so (Section 5.2.3.4). Those subjects will be required to sign a separate Informed Consent Form (ICF) to document their wish to participate in the extension study. During the extension period, the subjects will receive MT-1303 0.4 mg once daily for 36 weeks. In order to ensure the subject*s safety, the rigorous withdrawal criteria (Section 4.5.3) will also continue to be applied to the MT-1303-E14 study. Subjects who enter MT-1303-E14 after completion of the Visit 7 (Week 14/EOT [End of Treatment]) assessments will not be required to complete the 12-week safety Follow-up Period (Visits 8-10) of this study (MT-1303-E13).
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

Public
Mitsubishi Tanabe Pharma Europe Ltd (MTPE)

Dashwood House 69 Old Broad Street
London EC2M 1QS
GB
Scientific
Mitsubishi Tanabe Pharma Europe Ltd (MTPE)

Dashwood House 69 Old Broad Street
London EC2M 1QS
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Able to provide written informed consent and to comply with the requirements of the Protocol;2. Male or female subjects aged between 18 and 65 years (inclusive). 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. ;3. Diagnosis of CD (involving small intestine and/or colon), confirmed at the time by endoscopy and histology at least 3 months prior to Visit 1 (Screening);4. Previous use of corticosteroids or immunosuppressants (such as azathioprine [AZA]/ 6-mercaptopurine [6-MP] or methotrexate [MTX]) or anti-TNF-alpha agents (such as infliximab, adalimumab or certolizumab pegol) for the treatment of CD;5. Moderate to severe active CD defined by a CDAI score of >=220 to <=450 points at Visit 1 ;6. C-reactive protein (CRP) >=5 mg per litre (/L) and/or faecal calprotectin >=250 µg/g;7. A negative stool test result for Clostridium difficile (C. difficile) toxin at Visit 1 ;8. Negative results for both QuantiFERON-TB Gold (or T-SPOT) test and chest x-ray (i.e., no evidence of tuberculosis [TB]) at Visit 1;For detailed information, please refer to the Protocol.

Exclusion criteria

1. Diagnosis of ulcerative colitis, indeterminate colitis, pseudomembranous colitis or coeliac disease ;2. Enterocutaneous, abdominal or pelvic active fistulae, abscesses or fistulae likely to require surgery during the study;3. Gastrointestinal (GI) surgery (including appendectomy) within 12 weeks prior to Visit 2 (Baseline) or has surgery planned or deemed likely to require surgery for CD during the study;4. History or evidence of ileostomy, colostomy, rectal pouch, significant stenosis or extensive resection in GI tract that could impair the drug absorption or interfere with the objectives of the study, as judged by the Investigator ;5. History or evidence of unresected adenomatous colonic polyps or colonic mucosal dysplasia;6. Chronic use of opioid for chronic pain which, in the opinion of the Investigator, would influence the subject reported CDAI parameters. ;7. Use of concomitant medications as described in the

protocol. ;8. Presence or history of clinically significant disease (except CD) that could interfere with the objectives of the study or the safety of the subject, as judged by the Investigator ;9. Body weight <=35 kg at Visit 1;10. Presence or history of any of cardiovascular diseases as decsribed in the protocol.;11. Need for, or likely need for treatment with Class I or Class III anti-arrhythmic drugs, or with beta-blockers or heart-rate-lowering calcium-channel blockers, or with any other drugs which can reduce the heart rate ;12. Known high risk for QT/QTc prolongation such as a family history of long QT syndrome or sudden death;13. History or known presence of cerebrovascular diseases ;14. Presence or history (within 5 years prior to initial screening) of malignancy, except for successfully treated basal cell and in situ squamous cell carcinomas of the skin;15. Known history of recurrent or chronic infection such as TB, hepatitis B, hepatitis C or human immunodeficiency virus (HIV);16. Receipt of live vaccine within 4 weeks prior to Visit 2;17. Diagnosis of diabetes mellitus (Type I or II);18. Presence or prior history of macular oedema, uveitis or evolutive retinopathy, or any other condition that could increase the risk of macular oedema in the opinion of the Investigator;19. History of substance abuse (drug or alcohol) or any other factor that limits the subject*s ability to cooperate with the study procedures.;20. Known history of allergy, hypersensitivity or any serious reaction to any component of the study medication ;21. Previous treatment with any investigational agent within 12 weeks prior to Visit 1 OR five half-lives of the investigational product, whichever is the longer.;22. WBC count <3,500/µL at Visit 1;23. Lymphocyte count <800/µL at Visit 1;24. LFT (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) >=2 x ULN at Visit 1;25. HbA1c >6.5% at Visit 1;26. Negative or indeterminate results for antibodies (IgG) to Varicella Zoster virus (VZV) at Visit 1;27. [For female subjects only] A positive pregnancy test at Visit 1 (serum beta-human chorionic gonadotropin [hCG] level or urine dipstick) or Visit 2 (urine dipstick);28. Low heart rate (<50 beats per minute [bpm]) in 12-lead ECG at Visit 1 or Visit 2 (pre-dose);29. QTcF interval >=450 milliseconds (msec) in 12-lead ECG at Visit 1 or Visit 2 (pre-dose);30. Clinically significant abnormal findings in 12-lead ECG (at Visit 1 or Visit 2 [pre-dose]) and/or in Holter ECG (at Visit 1) that the Investigator considers may jeopardise the subject's health ;For detailed information, please refer to the Protocol.

Study design

Design

Study phase:	2
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):	16-09-2015
Enrollment:	4
Type:	Actual

Ethics review

Approved WMO Date:	03-11-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2016
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	EUCTR2014-002556-77-NL
CCMO	NL50831.018.14