A phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-finding trial to evaluate the efficacy and safety of IMU-838 for treatment of patients with active Crohn*s disease with an option for open-label treatment extension (CALDOSE-2)

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Primary objective• To determine the optimal dose of IMU-838 to induce symptomatic remission (based on stool frequency [SF] and abdominal pain [AP], as assessed in the Crohn*s Disease Activity Index [CDAI] patient reported outcome [PRO]-2) in...

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

Summary

ID

NL-OMON48184

Source
ToetsingOnline

Brief title
CALDOSE-2 (CD)

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Immunic AG
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Crohn's Disease, IMU-838 (vidofludimus calcium)

Outcome measures

Primary outcome

Efficacy

Induction treatment phase (BT period)

• Proportion of patients with symptomatic remission at Week 14 i.e. fulfilling

the following criteria:

o Remission in AP-CDAI, defined as AP-CDAI score <=1 and not worse than at

Baseline,

and

o Remission in SF-CDAI, defined as SF-CDAI score <=2.8 and not worse than at

Baseline

For the primary analysis, the 45 mg/day IMU-838 will be compared to placebo

Secondary outcome

Efficacy

Induction treatment phase (BT period)

• Proportion of patients achieving endoscopic improvement at Week 14:

o Reduction of the SES-CD by >=50% versus Baseline, or SES-CD score <=4 (or in

patients with isolated ileitis an SES CD score <=2), a reduction of >=2 points

from Baseline, and no ulcer sub-score >1 in any of the 5 segments (ileum, right/transverse/left colon, and rectum)

For the analysis of the key secondary endpoint, the 45 mg/day IMU-838 dose will be compared to placebo.

The primary endpoint and the key secondary endpoint will be tested hierarchically. If a statistically significant difference between the treatment groups is found for the primary endpoint, the analysis of the key secondary endpoint will be considered confirmative. Otherwise the analysis of the key secondary endpoint is considered exploratory.

Study description

Background summary

Crohn*s disease (CD) is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract, the cause of which remains unknown. The disease affects the gastrointestinal tract discontinuously from mouth to anus, but most commonly the disease is located both in ileum and colon (40%), followed by a disease in the small bowel only (30%), and in the colon only (25%). This disorder leads to severe disability and a significant reduction in quality of life.
CD is characterized by uncontrolled mucosal inflammation as a result of a dysregulated immune system involving an excessive T helper 1 (Th1) response. Activated Th1 cells produce classical pro-inflammatory cytokines such as interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα), and interleukin (IL)-2. In addition, Th17 cells seem to be involved leading to enhanced synthesis of Th17 typical cytokines such as IL-23 and IL-17.
Several treatment options are currently available including anti-inflammatory drugs, immunosuppressive drugs, biologics and other drugs to manage specific symptoms. However, some patients respond only poorly to established treatment options or, after an initial response, experience flare-ups, and/or develop intolerable side effects.
The IMP IMU-838 (vidofludimus calcium) is a new compound that selectively inhibits the human enzyme dihydroorotate dehydrogenase (DHODH).

DHODH plays a major role in the de-novo pyrimidine synthesis and is specifically expressed at high levels in proliferating or activated lymphocytes. IMU-838 selectively inhibits pyrimidine synthesis in activated cells. The inhibition of nucleotide synthesis seems to be a promising approach to treat IBD. Purine synthesis inhibitors are established products for the long-term treatment of IBD. The DHODH inhibitor leflunomide, currently approved for RA, was efficacious in small studies investigating Crohn*s Disease, but was associated with diarrhea limiting its use in an IBD patient population.
Based on these data and the pharmacodynamics of vidofludimus, IMU-838 may represent a novel and efficacious oral treatment option for IBD patients. Previous clinical studies with the predecessor drug 4SC-101 confirmed that vidofludimus may be beneficial in patients with steroid-dependent IBD. Trial P2 IMU 838 CD evaluates the efficacy and safety of the formulation IMU 838 in patients with active CD.

Study objective

Primary objective
• To determine the optimal dose of IMU-838 to induce symptomatic remission (based on stool frequency [SF] and abdominal pain [AP], as assessed in the Crohn*s Disease Activity Index [CDAI] patient reported outcome [PRO]-2) in patients with active Crohn*s disease (CD)

Key secondary objective
• To determine the optimal dose of IMU-838 to induce endoscopic improvement in patients with active CD

Study design

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in patients with active CD with an option for open-label treatment extension. The trial includes a screening period, a blinded treatment (BT) period and an optional open-label extension (OLE) period.
Patients will undergo 2 Screening visits for enrollment criteria.
The BT period will be a multicenter, randomized, double-blind, placebo-controlled trial. It comprises an induction treatment phase of 14 weeks and an extended treatment phase of 24 weeks (total 38 weeks BT).
A total of approximately 258 eligible patients with active CD will be randomized 2:1:2 to placebo, 30 mg/day IMU-838, and 45 mg/day IMU-838.

After completion of the BT period, patients with no major protocol deviation that in the investigator*s assessment may be relevant to patient compliance in the OLE period, no medically relevant safety issues (as assessed by the investigator) related to the IMP or the trial procedure, and no significant non-compliance (as assessed by the investigator) will have the

option to enter the OLE period. Patients who discontinue the BT period prematurely may also continue with open-label treatment, if they are eligible based on the additional inclusion and exclusion criteria for the OLE period. During the OLE, all patients will receive 30 mg/day IMU-838. Blinding of the randomized treatment assignment during the BT period will be maintained for patients entering the OLE period. The OLE period is optional.

Intervention

Blinded treatment (BT) period:
On Day 0, approximately 258 eligible patients will be randomized 2:1:2 to placebo, 30 mg/day IMU 838, and 45 mg/day IMU 838. Randomization will be stratified by prior use of biologics and current use of corticosteroids. The proportion of patients who previously received biologics will be limited to approximately 80% of all included patients.

All patients will receive only half of their assigned dose (1 tablet/day) during the 1st week and continue with the full dose starting on Day 7 (2 tablets/day once daily). Clinic visits during the BT period will be scheduled at Day 0, Day 7 (Week 1), at Week 2, and then every 28 days (every 4 weeks) until Week 38.

The extended treatment phase will start after Week 14 and will continue for 24 weeks. At Week 38 (end of BT period, EoBT), patients who completed all Week 38 assessments, including an ileocolonoscopy, will have the option to continue into the OLE period subject to additional inclusion and exclusion criteria.

Open-label extension period:
Patients may enter the OLE period if they either completed the BT period (and performed EoI and EoBT ileocolonoscopies), or, if they discontinued the BT period prematurely, who will have completed at least 10 weeks of blinded treatment, have at least 2 valid full CDAI, CDAI PRO-2 assessments, and completed the EoI ileocolonoscopy (and an additional EoBT ileocolonoscopy, if the EoI ileocolonoscopy was performed more than 14 weeks before the time of discontinuation).

Study burden and risks

IMU-838 can reduce the tubular uptake of uric acid in the kidneys, leading to an increase in urinary urinary acid excretion. Increased uric acid can in turn result in microcrystallization of uric acid in acid urine and can lead to the appearance of red blood cells in the urine. Various risk mitigation measures for urinary events have been implemented in this study.
There is potential for the colonoscope to injure the intestinal wall, causing perforation, infection or bleeding.

Side effects of IMU-838:
To date, around 300 patients have received a drug that is very similar to IMU-838 and that contains the same active substance as IMU-838 (vidofludimus). The most frequent adverse reaction reported by these patients was headache. Other commonly reported illnesses or side effects were: nasopharyngitis (common cold), urinary tract infection, diarrhea, upper abdominal pain and nausea. Preliminary results from 2 studies in which 52 healthy individuals were treated with IMU-838 are also available and the most frequently reported disease / side effect was a cold. Other reported illnesses / side effects were flatulence, increased red blood cell protein in urine, headache, soft stools, fatigue, increased lipase (protein involved in fat metabolism) and flank pain. It is not yet known whether these diseases and side effects are all related to the use of IMU-838 or whether they occurred after placebo.
At high doses of IMU-838, much higher than those used in this study, cases of increased numbers of red blood cells in urine were observed. However, this unpleasant effect is not expected at doses used in this study. The urine will be closely monitored for the presence of red blood cells.

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

INDUCTION TREATMENT PHASE
1 Male or female patient, aged 18-80 years
2 Confirmed diagnosis of active luminal CD, at least 3 months before Screening Visit S1
3 SES-CD score of at least 6, or of at least 4 in patients with isolated ileitis (screening ileocolonoscopy and SES-CD score assessed by an in-dependent central reader blinded to center and patient information)
4 At least one aphthous ulcerative lesion or more severe ulcer accessible by ileocolonoscopy (as confirmed by an independent central blinded reader from screening ileocolonoscopy)
5 Full CDAI score >=220 and <=450 at Screening Visit S1
6 Average daily very soft or liquid stool frequency score (based on the BSFS) >=4.0 and/or AP-CDAI score >=2.0 at Screening Visit S1 (according to retrospective data of the preceding 7 days)
7 Previous treatment failure defined as:
a Patient had an inadequate response with, lost response to, or was in-tolerant to approved or experimental immunomodulators or biologics. A maximum of 3 treatment failures with biologic drugs i.e. anti-tumor necrosis factor alpha antibodies, certolizumab pegol, vedolizumab, natalizumab, ustekinumab, or experimental antibodies, i.e. not approved for the use in CD or not approved but in development for CD, is allowed; or
b Patient had an inadequate response to corticosteroids (a corticosteroidrefractory patient is defined as having active disease despite prednisolone up to 1 mg/kg/day for a period of 4 weeks), was intolerant to corticosteroids, or is corticosteroid dependent (a corticosteroid-dependent patient is defined as i) unable to reduce steroids below the equivalent of prednisolone 10 mg/day [or budesonide be-low 3 mg/day] within 3 months of starting steroids, without recurrent active disease, or ii) who has a relapse within 3 months of stopping steroids.
8 Laboratory values: Neutrophil count >1500 cells/µL (>1.5 x 10^9 cells/L), platelet count
>=100 000/mm3 (>=100 x 10^9/L), serum creatinine <1.5 upper limit of normal (ULN), total bilirubin, alanine aminotransferase, and aspartate aminotransferase <1.5 ULN
9 Female patients
- must be of non-childbearing potential i.e. surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks

before Screening Visit S1) or postmenopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause), or
- if of childbearing potential, must have a negative pregnancy test at Screening Visit S1 (blood test) and at Day 0 before IMP administration (urine test). They must agree not to attempt to become pregnant, not to donate ova and to use a highly effective contraceptive method at the start of the trial (trial consent), during treatment with IMU 838, and for at least 30 days after the last intake of the IMP.
10 Male patients must agree not to father a child or to donate sperm starting at Screening Visit S1, throughout the clinical trial and for 30 days after the last intake of the IMP. Male patients must also
- abstain from sexual intercourse with a female partner (acceptable only if it is the patient*s usual form of birth control/lifestyle choice), or use adequate barrier contraception during treatment with the IMP and for at least 30 days after the last intake of the IMP, and
- if they have a female partner of childbearing potential, ensure that the partner uses a highly effective contraceptive method as outlined in inclusion criterion 9
- if they have a pregnant partner, use condoms while taking the IMP to avoid exposure of the fetus to the IMP
11 Ability to understand and comply with trial procedures and restrictions
12 Written informed consentEXTENDED TREATMENT PHASE
1 At least symptomatic response at Week 14, defined as improvement in AP-CDAI or SF CDAI scores of at least 30%, and both scores not worse than at Baseline
CRITERIA FOR SWITCHING FROM BLINDED TREATMENT TO OLE
1 Completion of at least 10 weeks of blinded treatment
2 Completion of a post-baseline ileocolonoscopy (either as EoI or EoBT ileocolonoscopy) in the last 14 weeks before switching to OLE
a if discontinuing the induction treatment phase at Week 10 or be-tween Week 10 and Week 14, a complete EoI visit must be per-formed at the time of discontinuation, including EoI ileocolonos-copy, or
b if discontinuing the extended treatment phase before Week 38, a complete EoBT examination must be performed; however, EoBT ileocolonoscopy will only be required if the EoI ileocolonoscopy was performed more than 14 weeks before the time of discontinuation
3 At least 2 valid assessments of the full CDAI, SF-CDAI and AP-CDAI scores post Baseline.sfSectie

Exclusion criteria

BT-period
GI CRITERIA
1 Diagnosis of ulcerative colitis, inflammatory bowel disease type unclassified, ischemic colitis, microscopic colitis, radiation colitis or diverticular disease-associated colitis

2 High likelihood of requiring bowel surgery during the 38 weeks of the BT period
3 Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
4 Ileorectal anastomosis or ileal-pouch anal anastomosis
5 Celiac disease
6 Presence of intra-abdominal or perianal abscess that is undrained
7 History of subtotal colectomy or imminent need for colectomy (i.e. colectomy is being planned)
8 Malabsorption or short-bowel syndrome
9 History of small bowel or colorectal cancer or gastrointestinal dysplasia (with the exception of dysplasia in polyps that have been removed)INFECTIOUS DISEASE
10 Clostridium difficile (C. difficile) infection
a Evidence of, or treatment for, C. difficile infection within 30 days before randomization
b Positive C. difficile toxin B stool assay at Screening Visit S1
11 Treatment for intestinal pathogens other than C. difficile within 30 days before randomization
12 Other chronic systemic infections
a History of chronic systemic infections including but not limited to tuberculosis, HIV, HBV, or HCV, within 6 months before Screening Visit S1
b Positive interferon-gamma release assay for Mycobacterium tuberculosis at Screening Visit S1
c Positive HBV surface antigen (HBsAg), hepatitis B core antibody (HBcAb), positive HCV and/or HIV-antigen-antibody (HIV-Ag/Ab) test at Screening Visit S1 (even without detectable virus load in blood)
13 Any live vaccinations within 30 days before randomization except for the influenza vaccineOTHER MEDICAL HISTORY AND CONCOMITANT DISEASE EXCLUSION CRITERIA
14 Known history of nephrolithiasis or underlying condition with a strong association o nephrolithiasis, including hereditary hyperoxaluria or hereditary hyperuricemia
15 Diagnosis or suspected liver function impairment which may cause, as assessed by the investigator, a potential for fluctuating liver function tests during this trial
16 Renal impairment i.e. eGFR <= 60 mL/min/1.73 m^2
17 Serum uric acid levels at Screening Visit S1 >=1.2 x ULN (for women > 6.8 mg/dL, for men > 8.4 mg/dL)
18 History or clinical diagnosis of gout
19 Known or suspected Gilbert syndrome
20 Indirect (unconjugated) bilirubin >=1.2 x ULN (i.e. >=1.1 mg/dL) at Screening Visit S1
21 Concurrent malignancy or prior malignancy within the previous 10 years except for the following: adequately-treated non-melanoma skin cancer and adequately-treated cervical cancerTHERAPY EXCLUSION CRITERIA
22 Use of any IMP within 8 weeks or 5 x the respective half-life before randomization, whichever is longer

23 Use of the following medications within 2 weeks before randomization:
a Tofacitinib
b Methotrexate,
c Mycophenolate mofetil
d Any calcineurin inhibitors (e.g. tacrolimus, cyclosporine, or pimecrolimus)
e Oral systemic corticosteroids >20 mg/day prednisolone equivalent including beclomethasone dipropionate (at >5 mg/day) and budesonide (at >9 mg/day)
f Oral aminosalicylates (e.g. mesalazines) >4 g/day
24 Use of the following medications within 4 weeks before randomization:
a Use of intravenous corticosteroids
b Use of thiopurines including azathioprine, 6-mercaptopurine and 6-thioguanine
c Use of any rectal or topical aminosalicylates and/or budesonide
25 Use of oral systemic corticosteroids <=20 mg/day prednisolone equivalent including beclomethasone dipropionate (at <=5 mg/day) and budesonide (at <=9 mg/day) unless they have been used at a stable dose for at least 2 weeks before randomization
26 Oral aminosalicylates (e.g. mesalazines) <=4 g/day unless they have been used at a stable dose for at least 3 weeks before randomization
27 Use of biologics as follows:
a anti-TNFα antibodies (infliximab, adalimumab, golimumab, certolizumab pegol, including their biosimilars, if available) within 4 weeks before randomization
b vedolizumab and ustekinumab within 8 weeks before randomization
28 Use of the DHODH inhibitors leflunomide or teriflunomide within 6 months before randomization
29 Any use of natalizumab (Tysabri*) within 12 months before randomization
30 Use of the following concomitant medications is prohibited at Screening Visit S1 and throughout the duration of the trial:
a any medication known to significantly increase urinary elimination of uric acid, in particular lesinurad (Zurampic*) as well as uricosuric drugs such as probenecid
b active treatments for any malignancy, in particular irinotecan, paclitaxel, tretinoin, bosutinib, sorafinib, enasidenib, erlotinib, regorafenib, pazopanib and nilotinib
c any drug significantly restricting water diuresis, in particular vasopressin and vasopressin analogs
d Rosuvastatin at doses >10 mg/dayPlease refer to protocol for information on general exclusion criteria and exclusion criteria during OLE period.laatste toed

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:	Recruiting
Start date (anticipated):	27-09-2019
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	IMU-838
Generic name:	vidofludimus

Ethics review

Approved WMO Date:	03-06-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2019
Application type:	First submission
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	EUCTR2018-001895-39-NL
CCMO	NL69011.018.19