A Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn`s Disease (CD) receiving ustekinumab induction treatment

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The main objectives Investigate a first signal of efficacy, safety and tolerability of BI 706321 in combination with ustekinumab treatment compared to placebo with ustekinumab treatment in patients with moderately to severely active CD at 12 weeks....

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

Summary

ID

NL-OMON53423

Source
ToetsingOnline

Brief title
1425-0003

Condition

- Gastrointestinal inflammatory conditions

Synonym
Inflammatory bowel disease / Crohn's

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: industry;Pharmaceutical company

Intervention

Keyword: BI 706321, Crohn's Disease, Ustekinumab

Outcome measures

Primary outcome

Absolute change from baseline in Simple Endoscopic Score for Crohns disease

(SES-CD) at week 12.

Secondary outcome

- Percent change in SES-CD from baseline at Week 12

- Endoscopic response (defined as >=50% SES-CD reduction from baseline) or for a

induction baseline SES-CD of 4, at least a 2 point reduction from induction

baseline)) at Week 12

- Endoscopic response (defined as >=50% SES-CD reduction from baseline)), or

for a induction baseline SES-CD of 4, at least a 2 point reduction from

induction baseline)) at Week 48

- Endoscopic remission (defined as SES-CD score of <=2) at week 12

- Endoscopic remission (defined as SES-CD score of <=2) at week 48.

- Biological remission, defined as C-reactive protein (CRP) <5 mg/L and faecal

calprotectin (FCP) < 250 ug/g at week 12

- Biological remission, defined as CRP < 5 mg/L and FCP <250 ug/g at week 48

- Clinical remission at week 12, defined as a Crohn's Disease Activity Index

(CDAI) score of <150

- Clinical remission at week 48, defined as a CDAI score of<150

- Clinical response at week 12, defined by a CDAI reduction from baseline of at

least 100 points, or a CDAI score of <150

- Number of patients with treatment-emergent adverse event(TEAE) through end of

treatment (EoT) and the residual effect period (REP) (i.e. through Visit 9)

Study description

Background summary

Crohn*s disease (CD) is characterized by transmural inflammation with ulcerative lesions affecting any site within the gastrointestinal tract, with most frequent involvement of the terminal ileum, often combined with inflammation in the colon. CD incidence and prevalence have been rising in all ethnic groups, the unmet medical need in patients with moderate to severe CD is the highest. The modest efficacy of the current drugs which address different components of the dysregulated inflammatory response in patients with CD suggests that multiple pathologic pathways need to be targeted in tandem to make major progress in treatment of this often severe and disabling disease. Combination treatments of established anti-inflammatory drugs with new medicines with a novel and differentiated mode of action might offer greater efficacy, in particular if such a combination partner would be orally available, safe and tolerable. BI 706321 may be such a candidate drug.

Study objective

The main objectives
Investigate a first signal of efficacy, safety and tolerability of BI 706321 in combination with ustekinumab treatment compared to placebo with ustekinumab treatment in patients with moderately to severely active CD at 12 weeks.

The primary objective
Estimate the difference in change from baseline in Simple Endoscopic Score for Crohn's disease (SES-CD) after 12 weeks. The primary treatment comparison will be between treatment groups while on treatment during the 12-week induction period.

Study design

This Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn`s Disease (CD) receiving ustekinumab induction treatment .
After the 12 week induction treatment period, patients will be treated with an additional 36 weeks of follow-on ustekinumab open label maintenance monotherapy. Ustekinumab therapy in both induction and maintenance will be administered in an open-label fashion. Both safety and efficacy data will be collected during the follow-up period.

The treatment duration with BI 706321 of 12 weeks is driven by the maximum treatment duration covered by current preclinical toxicology data. The overall trial duration with ustekinumab of 48 weeks followed by a final ileo-colonoscopy will allow assessment of the long-term effect of the initial 12-week period of BI 706321 add-on induction treatment on the endoscopic endpoints at the end of monotherapy maintenance.

Intervention

Patients will be randomised (1:1) to one of two arms.
Group 1:
BI 706321 8 mg p.o. QD for 12 weeks in conjunction with standard induction dosing of ustekinumab*, followed by ustekinumab maintenance dosing for an additional 36 weeks.

Group 2:
Placebo p.o. QD for 12 weeks in conjunction with standard induction dosing of ustekinumab*, followed by ustekinumab maintenance dosing for an additional 36 weeks.

After the 12 week induction treatment period, patients will be treated with an additional 36 weeks of follow-on ustekinumab open label maintenance monotherapy.

Study burden and risks

Subject*s participation in this study will last 48 weeks and consists of a screening period, treatment period and a follow-up period. Subject will need to come to the hospital more often than they normally would and they undergo additional tests.

- During the treatment period, subjects will need to visit the study site every 7 times in 12 weeks. During the follow-up period, subjects will visit the site 8 times in 36 weeks.

- Participants will be subjected to the following tests: physical examinations;

electrocardiogram; questions about medical history (including pre-existing medical conditions, Crohn*s Disease history, previous therapy, concomitant therapy, and baseline conditions), and demographics (e.g., sex, age, ethnicity, race); urine sampling; stool sampling;
assessments about any new illnesses or symptoms; complete the Inflammatory Bowel Disease Questionnaire (IBDQ); vital signs.

-Subjects will be expected to come to some of their visits in fasted state, to not take part in other medical studies, keep their appointments for visits, follow instructions from the study team, keep a patient card with them at all times and to use appropriate forms of contraception.

-Subjects will also be asked to complete a diary and the Crohn*s Disease Activity Index (CDAI) questionnaire daily.

-The subjects will receive 13 times a venapunction, 1 intravenous injection, and 5 subcutaneous injections. The subjects will also undergo three times an ileocolonoscopy and biopsies will be taken during each ileocolonoscopy
So far, the trial drug has been studied in healthy volunteers and no side effects have yet been established. As with any drug, an allergic reaction can occur.

Safety monitoring for this Phase 2a trial will be robust, including a careful selection of experienced clinical trial sites and investigators. The Clinical Trial Protocol ensures that all patients are carefully selected, monitored, and discontinued if required. The Clinical Trial Team (including Trial Member Medicine) will also be informed immediately if any laboratory values are critically abnormal or ECG assessments show medically relevant abnormalities. Additionally, as part of BI standard PV processes there is a dedicated pharmacovigilance working group (PVWG) in place. Unblinded aggregated descriptive analyses of AEs and selected safety laboratory data will be made available to the Clinical Trial Team on a regular basis. In case there are observations noted in the unblinded aggregated descriptive analyses (e.g. imbalance in rates of infections) individual treatment allocation can be made immediately available for further evaluation. This close oversight allows flexible and rapid decision making in case of any observations. In addition, given the brief duration of exposure to BI 706321 (i.e. 12 weeks), and the small size of the trial (25 patients in the active treatment arm), BI considers the planned safety monitoring approach in this trial (defined by CTP, and central assessment of safety lab and ECG, and frequent internal unblinded aggregated descriptive safety analyses) 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. Male or female patients.

2. >= 18 - <= 75 years, at date of signing informed consent.

3. Diagnosis of CD for at least 3 months prior to visit 1 by endoscopic, radiology, and supported by histology.

4. Elevated CRP (>= 5 mg/L) OR elevated fecal calprotectin (>= 250 µg/g)

5. Moderate to severe active CD at visit 1 defined as CDAI >=220 and <=450 (one rescreening is allowed).

6. Presence of mucosal ulcers in at least one segment of the ileum or colon and a SESCD score >= 7 (for patients with isolated ileitis >=4), as assessed by ileo-colonoscopy and confirmed by central independent reviewer(s) before start

of study treatment.

7. Patients who are experienced to 1 or 2 TNF antagonists (i.e. biosimilars of a drug are counted as the originator drug, e.g. the switch from infliximab originator to CT-P13 will count as one TNF antagonist exposure) at a dose approved for CD. Patients may have stopped TNF antagonists treatment due to primary or secondary nonresponsiveness, intolerance, or for other reasons.

8. May be receiving a therapeutic dose of the following:
o Oral 5-ASA compounds must have been at a stable dose for at least 4 weeks prior to randomisation and must continue on this dose until week 12 and/or
o Oral corticosteroids if indicated for treatment of CD must be at a prednisone equivalent dose of <= 20 mg/day, or <= 9 mg/day of budesonide, and have been at a stable dose for at least 2 weeks
immediately prior to randomisation and must continue on this dose until week 12. [Allowed steroid treatments: Locally administered steroids as e.g. intra-articular, nasal inhalation or intra-ocular
administration are allowed.] and/or
o AZA, MP, 6-thioguanine (6-TG) or MTX, provided that dose has been stable for the 8 weeks immediately prior to randomisation and must continue on this dose until week 12.

9. Women of childbearing potential (WOCBP)1 must be ready and able to use highly effective methods of birth control per International Council a on Harmonisation (ICH) M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly.

10. Signed and dated written informed consent in accordance with ICH Good Clinical Practice (GCP) and local legislation prior to admission to the trial.

Exclusion criteria

1. Have any current or prior abscesses, unless they have been drained and treated at least 6 weeks prior to randomisation and are not anticipated to require surgery. Patients with active fistulas may be
included if there is no anticipation of a need for surgery and there are currently no abscesses present based on investigator`s judgement.

2. Have complications of CD such as strictures, stenosis, short bowel syndrome, or any other manifestation that might require surgery, or could preclude the use of SESCD/ CDAI to assess response to therapy, or would possibly confound the evaluation of benefit from treatment with
BI 706321 (based on investigator's judgement).

3. Patient with an inflammatory bowel disease (IBD) diagnosis other than CD.

4. Have had any kind of bowel resection or diversion within 4 months or any other intraabdominal surgery within 3 months prior to visit 1. Patients with current ileostomy, colostomy, or ileorectal anastomosis are excluded.

5. Treatment with:
- any non-biologic medication for IBD (e.g.tacrolimus or mycophenolate mofetil, systemic corticosteroids), other than those allowed per inclusion criteria, within 30 days prior to randomisation
- any biologic treatment with a TNF-alpha antagonist (adalimumab, infliximab, golimumab, certolizumab pegol) or vedolizumab (or a biosimilar) within 4 weeks prior to randomisation. (If drug level testing for previously used biologic treatment confirms no detectable drug level before randomisation, patient can be enrolled despite not having completed 4 week from last treatment.)
- any previous treatment with ustekinumab (or a biosimilar)
- any previous treatment with an investigational (or subsequently approved) non-biologic/biologic drug for CD (including but not limited to JAK inhibitors, [e.g. upadacitinib], S1P modulators, IL-23 inhibitors, [e.g. risankizumab], anti-integrins).
- any investigational drug for an indication other than CD during the course of the actual study and within 30 days or 5 half-lives (whichever is longer) prior to randomisation.
- any prior exposure to rituximab within 1 year prior to randomisation.

6. Positive stool examination for C difficile (toxin A/B - test positive) or other intestinal pathogens <30 days prior to randomisation. Rescreening can be undertaken following documented successful treatment, no sooner than 1 week after last intake of antimicrobial therapy.

7. Evidence of colonic moderate/severe mucosal dysplasia or colonic adenomas, unless properly removed.

8. Fecal transplant <= 30 days prior to randomisation.

9. Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency (e.g. Human immunodeficiency virus (HIV)), past organ or stem cell transplantation (with exception of a corneal transplant > 12 weeks prior to screening) or have ever received stem cell therapy (e.g., Prochymal). Prior treatment with a somatic cell therapy product (e.g., Alofisel) is not excluded, provided it was administered > 8 weeks prior to randomisation.

10. Live or attenuated vaccination within 4 weeks prior to randomisation.

11. Have received BCG vaccines <= 1 year prior to randomisation.

12. Active or latent TB:

- Patients with active tuberculosis are excluded.
- Patients will be screened with Interferon Gamma Release Assay (IGRA) such as QuantiFERON or T spot, the patient may also be evaluated for the presence of TB with any additional test required by
local practice. Patients with positive test results are excluded unless patient is known to have had a previous diagnosis of active or latent TB and has completed appropriate treatment per local practice/guidelines within the last 3 years and at least 6 months before first administration
of trial medication under this protocol (patients may be rescreened once to meet this specific criterion)
- Patients with indeterminate QuantiFERON or invalid/borderline T spot may be re-tested with IGRA (once), and if again inconclusive, should have a Purified Protein Derivative (PPD) skin test.
- If IGRA is not available or result remains indeterminate after repeat testing, tuberculin skin test (TST) should be performed: A tuberculin skin test positive reaction >=10mm (>=5mm if receiving >=15mg/d prednisone or its equivalent) is considered positive. Patients with a positive TST are excluded unless they have completed treatment as above.

13. Presence of clinically significant acute or chronic infections not otherwise listed, including viral hepatitis, COVID-19, or others based on investigator's judgement. A patient can be rescreened (up to two times) if the patient was treated and is cured from the acute infection.

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:	Completed
Start date (anticipated):	01-02-2024

Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not given
Generic name:	BI 706321

Ethics review

Approved WMO Date:	26-01-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-05-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-07-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-07-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-07-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-12-2023

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-03-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2020-004527-16-NL
ClinicalTrials.gov	NCT04978493
CCMO	NL82983.100.23