A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of ABT-494 for the Induction of Symptomatic and Endoscopic Remission in Subjects with Moderately to Severely Active Crohn's Disease who have Inadequately Responded to or are Intolerant to Immunomodulators or Anti-TNF Therapy

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

Summary

ID

NL-OMON44996

Source
ToetsingOnline

Brief title
M13-740

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn syndrome, regional enteritis

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie Deutschland GmbH & Co. KG
Source(s) of monetary or material Support: Industry

Intervention

Keyword: ABT-494, Crohn's Disease, M13-740, Phase II

Outcome measures

Primary outcome

Endpoint Definitions:

The following definitions apply to the efficacy variables described below:

• Remission: Endoscopic remission AND Clinical remission

• Response: Endoscopic response AND Clinical response

• Endoscopic remission: SES-CD <= 4 and at least two point reduction versus baseline and no subscore > 1 in any individual variable

• Endoscopic response: SES-CD at least 25% reduction from baseline

• Clinical remission: average daily stool frequency <= 1.5 and not worse than baseline AND average daily abdominal pain <= 1.0 and not worse than baseline

• Clinical response: average daily stool frequency at least 30% reduction from baseline and average daily abdominal pain not worse than baseline OR average daily abdominal pain at least 30% reduction from baseline and average daily

stool frequency not worse than baseline

Secondary outcome

The co-primary endpoints are:

• Proportion of subjects who achieve endoscopic remission at Week 12/16.

• Proportion of subjects who achieve clinical remission at Week 16.

The secondary endpoints (Double-Blind Induction Treatment Period) include:

• Proportion of subjects who achieve CDAI < 150 at Week 16.

• Proportion of subjects with decrease in CDAI >= 70 points from Baseline at Week 16.

• Proportion of subjects who achieve clinical remission at Week 12.

• Proportion of subjects who achieve remission at Week 16 (endoscopic remission at Week 12/16 and clinical remission at Week 16).

• Proportion of subjects who achieve response at Week 16 (endoscopic response at Week 12/16 and clinical response at Week 16).

• Proportion of subjects with endoscopic response at Week 12/16.

• Proportion of subjects who achieve clinical response at Week 16.

• Proportion of subjects with an average daily SF >= 2.5 AND average daily AP >= 2.0 at Baseline who achieve clinical remission at Week 16.

• Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve CDAI < 150 at Week 16.

• Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve endoscopic remission at Week 12/16 and clinical remission at Week 16.

• Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve clinical remission at Week 16.

• Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve endoscopic remission at Week 12/16.

• Change from Baseline in fecal calprotectin level at Week 16.

• Change from Baseline in hs-CRP at Week 16.

• Change in IBDQ from Baseline at Week 16.

• Proportion of subjects with isolated ileal Crohn's disease who achieve remission at Week 16.

The secondary endpoints (Double-Blind Extension Phase) include:

• Proportion of subject who achieve remission at Week 52.

• Proportion of subjects who achieve endoscopic remission at Week 52.

• Proportion of subjects who achieve clinical remission at Week 52.

• Proportion of subject who achieve response at Week 52.

• Proportion of subjects who achieve endoscopic response at Week 52.

• Proportion of subjects who achieve clinical response at Week 52.

• Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieved CDAI < 150 at Week 52.

• Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve remission at Week 52.

• Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve clinical remission at Week 52.

• Proportion of subjects taking corticosteroids at Baseline who discontinued

corticosteroid use and achieve endoscopic remission at Week 52.

• Proportion of subjects who achieve CDAI < 150 at Week 52.

• Proportion of subjects with decrease in CDAI >= 70 points from Baseline at

Week 52.

• Change from Baseline in fecal calprotectin level at Week 52.

• Change from Baseline in hs-CRP at Week 52.

• Change in IBDQ from Baseline at Week 52.

• Proportion of subjects with isolated ileal Crohn's disease who achieve

remission at Week 52.

• Change in EIMs from Baseline at Week 52.

Additional endpoints include assessment of the above endpoints over time.

Study description

Background summary

Crohn*s disease is a chronic inflammatory condition involving the gastrointestinal tract. In Europe the prevalence of Crohn*s disease is estimated up to 214 cases per 100,000 persons. Approximately 80% of patients with Crohn*s disease will require at least one surgery related to the disease at some point in time. Newer treatments for Crohn*s disease, such as anti-TNF antibodies, have improved standard of care for patients however there remains a significant unmet medical need for patients who do not respond well to these.

This clinical study with ABT-494 is for patients who are unable to tolerate antiTNF therapies and/or have had an insufficient response to treatment with an antiTMF therapy. These patients currently have limited options for treatment, and may be subjected to repeated courses of corticosteroids, which are associated with a wide range of toxic effects affecting multiple organs.

Study objective

The objectives of this study are to determine the efficacy and safety of multiple doses of ABT-494 versus placebo and to assess the pharmacokinetics (PK) of ABT-494 following oral administration in subjects with moderately to severely active Crohn's Disease with a history of inadequate response to or intolerance to Immunomodulators or anti-TNF therapy.

Study design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and PK of ABT-494 as induction therapy in subjects with moderately to severely active Crohn's disease with a history of inadequate response to or intolerance to anti-TNF therapy. The study will allow enrollment of up to 35% of subjects with primary non-response to prior anti-TNF treatment. Approximately 210 adult subjects with moderately to severely active Crohn's disease, with evidence of mucosal inflammation, defined by:
• SES-CD >= 6, (or SES-CD >= 4 for patients with disease limited to the ileum), and
• CDAI >= 220 and <= 450, and
• Average daily liquid/soft stool frequency >= 2.5 or average daily abdominal pain score >= 2.0.
Will be enrolled at approximately 125 sites worldwide. SES-CD score will be confirmed by a central reader. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study.

Intervention

Subjects will be randomized in a 1:1:1:1:1:1 ratio to receive one of the six treatment groups (double-blind ABT-494 induction doses or matching placebo).

Double-Blind Induction Doses (week 1-16, see protocol figure 1 study design schemetic):
Group 1: ABT-494 3 mg BID
Group 2: ABT-494 6 mg BID
Group 3: ABT-494 12 mg BID
Group 4: ABT-494 24 mg BID
Group 5: ABT-494 24 mg QD
Group 6: Placebo

Double-Blind Extension Period Doses (re-randomization, Week 16- 52, see protocol figure 1 study design schemetic):
Group 1: ABT-494 3 mg BID
Group 2: ABT-494 12 mg BID
Group 3: ABT-494 24 mg QD

Subjects who are considered by the investigator to have not achieved meaningful symptomatic relief and meet the criteria for inadequate response at or after Week 20 will be eligible to receive the open-label therapy

Open-Label Extension Period Doses (Week 20-52, see protocol figure 2 study design schemetic for OLE):
Group 1: ABT-494 24 mg QD
Group 2: ABT-494 24 mg BID

Mode of Administration: Oral

Study burden and risks

Patients may or may not receive any direct medical benefit from being in this study. Their condition may get better, it may get worse, or it may stay the same. Information learned from this study may help in the future to better treat patients

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 >= 18 and <= 75 years of age at Baseline.
2. Diagnosis of ileal, colonic, or ileocolonic Crohn's disease for >= 3 months prior to Baseline and confirmed by endoscopy during the Screening Period or endoscopy performed within 15 days of the Screening Visit. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Average daily liquid/very soft stool frequency score >= 2.5 or average daily abdominal pain score >= 2.0.
4. CDAI >= 220 and <= 450.
5. Simplified Endoscopic Score for Crohn's disease (SES-CD) >= 6 (or >= 4 for subjects with disease limited to the ileum), confirmed by a central reader.
• A video-recorded ileocolonoscopy performed within 15 days prior to Screening can be used for the local and central reader assessment.
6. Subject has inadequately responded to or experienced intolerance to previous treatment with immunomodulators (e.g., azathioprine, 6-mercaptopurine, or methotrexate) and/or an anti-TNF agent (e.g., infliximab, adalimumab, or certolizumab pegol). The clinical measures that defined inadequate response should be based on the physician/investigator clinical assessment.
Note: Criteria for inadequate response to or experienced intolerance to previous treatment with immunomodulator or an anti-TNF agent defined as:
• Signs and symptoms of persistently active disease despite a history induction regimen with one of the following agents:
o At least a consecutive 90-day course of azathioprine, 6-mercaptopurine or injectable MTX prior to Baseline, with a stable dose for at least 28 days prior to Baseline of azathioprine >= 1.5 mg/kg/day or 6-MP >= 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation or a documented 6-TGN level of at least 230 pmol/8 × 108 RBC or higher on the current dosing regimen) or MTX >= 15 mg/week (subcutaneous [SC]/Intramuscular [IM]), or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.
At least one 6-week induction with Infliximab: 5 mg/kg IV, 3 doses at least 2 weeks apart
o At least one 4-week induction with Adalimumab: one 160 mg SC dose (or 80 mg SC dose in approved countries) followed by one 80 mg SC dose (or 40 mg SC dose in approved countries) followed by one 40 mg dose at least 2 weeks apart
o At least one 4-week induction with Certolizumab pegol: 400 mg SC, 2 doses at least 2 weeks apart OR
• Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) OR
• History of intolerance of at least one TNF antagonist (including, but not limited to infusion

related reaction, demyelination, congestive heart failure and infection)
7. Subject has a negative tuberculosis (TB) Screening Assessment. If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis or have documented completion of a full course of anti-TB prophylaxis, prior to Baseline.

Exclusion criteria

colitis.
2. Subject with previous exposure to JAK inhibitor (e.g., tofacitinib, baricitinib).
3. Subjects who discontinued biologic therapy such as Infliximab (REMICADE), Certolizumab pegol (CIMZIA), Adalimumab (HUMIRA), Vedolizumab (ENTYVIO), Natalizumab (TYSABRI) < 8 weeks prior to Baseline. Subjects who discontinued Ustekinumab (Stelara®) less than 12 weeks prior to Baseline.
4. Subject received azathioprine or 6-mercaptopurine (6-MP) within 10 days of Baseline.
5. Subject who previously or currently use oral aminosalicylates or MTX and meets one of the following criteria:
• Has not been on stable doses for at least 14 days prior to Baseline; or
• Has discontinued use of aminosalicylates or MTX within 14 days of Baseline.
6. Subject who previously or currently use oral corticosteroid and meets one of the following criteria:
• Is receiving prednisone or prednisone equivalent > 30 mg/day within 7 days of Baseline;
• Is receiving budesonide > 9 mg/day within 7 days of Baseline;
• Has discontinued use of corticosteroid within 7 days of Baseline;
• Has not been on stable doses of corticosteroid for at least 7 days prior to Baseline; or
• Has been taking both oral budesonide and prednisone (or equivalent) simultaneously.
7. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
8. Subject on probiotics who has not been on stable dose for at least 14 days prior to Baseline.
9. Subject who previously or currently use Crohn's disease related antibiotics and meets one of the following criteria:
• Has not been on stable doses for at least 14 days prior to Baseline;
• Has discontinued Crohn's disease related antibiotics within 14 days of Baseline.
10. Subject received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline.
11. Subject has received therapeutic enema or suppository, other than required for endoscopy, within 7 days prior to Screening and/or during the Screening Period.
12. Subject who has had surgical bowel resection within the past 6 months or is planning any resection while enrolled in the study.
13. Subject with an ostomy, ileoanal pouch or symptomatic bowel stricture.
14. Subject with an abdominal or peri-anal abscess.
15. Subject who has short bowel syndrome.
16. Subject who previously received stem cell transplantation or Subject who previously received fecal microbial transplantation in the past 1 month.

17. Subject who received non-steroidal anti-inflammatory drugs (NSAIDs) (except topical NSAIDs and the use of low dose aspirin for cardiovascular (CV) protection) within 14 days prior to Screening and during the Screening Visit.
18. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
19. Subject currently receiving total parenteral nutrition (TPN) or plan to receive TPN at any time during the course of the study.
20. Subject with positive Clostridium difficile (C. difficile) toxin stool assay during the Screening Period.
21. Screening laboratory and other analyses show any of the following abnormal results:
• Serum Aspartate Transaminase (AST) or Alanine transaminase (ALT) > 21.5 × upper limit of the reference range (ULN);
• Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73 m2;
• Total White Blood Cell (WBC) count < 3,000/µL;
• Absolute neutrophil count (ANC) < 1,200/µL;
• Platelet count < 100,000/µL;
• Absolute lymphocytes count < 750/µL;
• Hemoglobin < 9 g/dL.
22. Any active or recurrent viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study, including recurrent/disseminated herpes zoster or known history of human immunodeficiency virus (HIV).
22. Any active or recurrent viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study, including recurrent/disseminated herpes zoster or known history of human immunodeficiency virus (HIV).
23. Hepatitis B (HBs Ag positive [+] or detected sensitivity on the HBV DNA PCR qualitative test for HBc Ab positive subjects) or hepatitis C (HCV RNA detectable in any subject with anti-HCV Ab).
24. Subject with any active or chronic recurring infections or untreated latent TB.
25. History of moderate to severe congestive heart failure (NYHA class III or IV), cerebrovascular accident and any other condition within 6 months, which in the opinion of the Investigator, would put the subject at risk by participation in the study.
26. Use of known strong CYP3A inhibitors (e.g., clarithromycin, conivaptan, itraconazole, ketoconazole, posaconazole, telithromycin, voriconazole, grapefruit juice) or strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort) from Screening through the end of the study.
27. Receipt of any live vaccine within 1 month prior to the Screening Visit, or will require live vaccination during study participation including up to 1 month after the last dose of study drug.
28. Evidence of current colonic dysplasia, history of high grade colonic dysplasia, or history of malignancy (including of the gastrointestinal tract) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
29. Has had any uncontrolled and/or clinically significant (per Investigator's judgment) illness or has had any surgical procedure within 30 days prior to Screening.
30. Positive pregnancy test at Screening (serum) or Baseline (urine).
31. Female subjects who are breastfeeding or considering becoming pregnant during the

study.
32. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.
33. Subject who received any investigational agent or procedure within 30 days or 5 half-lives prior to Baseline, whichever is longer.
34. History of clinically significant drug or alcohol abuse in the last 12 months.

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):	06-01-2016
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ABT-494
Generic name:	ABT-494

Ethics review

Approved WMO

Date:	20-04-2015

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2017
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	EUCTR2014-003240-12-NL
ClinicalTrials.gov	NCT02365649
CCMO	NL51549.018.15