A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitnib (ABT-494) for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

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Main objective of SS1 (Ph2b induction) is to characterize dose-response, efficacy, and safety of upadacitinib compared to placebo in inducing clinical remission defined by Adapted Mayo score in subjects with moderately to severely active ulcerative...

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

Summary

ID

NL-OMON55646

Source
ToetsingOnline

Brief title
M14-234

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym

chronic bowel inflammation, Ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie B.V.
Source(s) of monetary or material Support: AbbVie

Intervention

Keyword: ABT-494, induction, ulcerative colitis, Upadacitinib

Outcome measures

Primary outcome

Substudy 1 and 2: The proportion of subjects who achieve clinical remission per

Adapted Mayo score at Week 8.

Substudy 3: The proportion of subjects who achieve clinical remission per

Adapted Mayo score at Week 52.

Secondary outcome

Substudy 1:

1. Proportion of subjects with endoscopic improvement (subscore = 1) at Week 8

2. Proportion of subjects achieving clinical remission per Full Mayo score at

Week 8

3. Proportion of subjects achieving clinical response per Adapted Mayo score at

Week 8

4. Proportion of subjects achieving clinical response per Partial Mayo score at

Week 2

5. Change in Full Mayo score from Baseline to Week 8 6. Proportion of subjects

with endoscopic remission (subscore of 0) at Week 8

7. Proportion of subjects who achieved histologic improvement (decrease from baseline in Geboes score) at Week 8

Substudy 2:

1. Proportion of subjects with endoscopic improvement at Week 8

2. Proportion of subjects with endoscopic remission at Week 8

3. Proportion of subjects achieving clinical response per Adapted Mayo Score at Week 8

4. Proportion of subjects achieving clinical response per Partial Adapted Mayo score at Week 2

5. Proportion of subjects achieving histologic-endoscopic mucosal improvement at Week 8

6. Proportion of subjects who reported no bowel urgency at Week 8

7. Proportion of subjects who reported no abdominal pain at Week 8

8. Proportion of subjects who achieved histologic improvement at Week

9. Change from Baseline in IBDQ total score at Week 8

10. Proportion of subjects with mucosal healing at Week 8

11. Change from Baseline in FACIT-F score at Week 8

Substudy 3:

1. Proportion of subjects with endoscopic improvement

2. Proportion of subjects who maintain clinical remission per Adapted Mayo score among subjects who achieved clinical remission per Adapted Mayo score in Study M14-234 (Substudy 1 or 2) or Study M14-675

3. Proportion of subjects who achieved clinical remission at Week 52 per adapted Mayo score and were corticosteroid free for = 90 days among subjects in clinical remission in the end of the induction treatment in Study M14-234 (Substudy 1 or 2) or Study M14-675.

4. Proportion of subjects with endoscopic improvement among subjects with endoscopic improvement in Study M14-234 (Substudy 1 or 2) or Study M14-675

5. Proportion of subjects with endoscopic remission

6. Proportion of subjects maintain clinical response per Adapted Mayo score

7. Proportion of subjects with histologic-endoscopic mucosal improvement

8. Change from Baseline in IBDQ total score

9. Proportion of subjects with mucosal healing

10. Proportion of subjects who reported no bowel urgency

11. Proportion of subjects who reported no abdominal pain

12. Change from Baseline in FACIT-F score

13. Incidence rate of UC-related hospitalizations

14. Incidence rate of UC-related surgeries

Study description

Background summary

Ulcerative colitis (UC) is a chronic, relapsing inflammatory disease of the large intestine characterized by inflammation and ulceration of mainly the mucosal and occasionally submucosal intestinal layers. The hallmark clinical symptoms include bloody diarrhea associated with rectal urgency and tenesmus. The most severe intestinal manifestations of UC are toxic megacolon and perforation. Patients with UC are at an increased risk for colon cancer, and the risk increases with the duration of disease as well as extent of colon affected by the disease.

The aim of medical treatment in UC is to control inflammation and reduce symptoms. Available pharmaceutical therapies are limited, do not always completely abate the inflammatory process, and may have significant adverse effects. Therapies for mild to moderate active UC include 5-aminosalicylic acid derivatives and immunosuppressants. Corticosteroids are used in patients with more severe symptoms but are not useful for longer term therapy. The frequency and severity of corticosteroid toxicities are significant, including infections, emotional and psychiatric disturbances, skin injury, and metabolic bone disease. Patients with moderate to severe symptoms may derive some benefits from immunomodulatory agents, however, the use of these agents is limited as induction treatment due to a slow onset of action (3 to 6 months) and as maintenance therapy due to adverse events (AEs), including bone marrow suppression, infections, hepatotoxicity, pancreatitis, and malignancies.

Biological agents targeting specific immunological pathways have been evaluated for their therapeutic effect in treating patients with UC as well, such as anti-tumor necrosis factor (TNF) agents. Anti-TNF therapies are an effective treatment for patients who are steroid refractory or steroid dependent, who had inadequate response to a thiopurine, or who are intolerant to these medications. Potential risks with anti-TNF therapies include infusion or injection site reactions, serious infections, lymphoma, heart failure, lupus-like syndromes, and demyelinating conditions. Despite the beneficial results achieved with the available biologic agents, only 17% to 45% of patients who receive them are able to achieve clinical remission. Thus, there remains a clear medical need for additional therapeutic options in UC for patients with inadequate response to or intolerance to conventional therapies and biologic therapies.

The Janus kinases or JAKs are a family of intracellular tyrosinekinases that function as dimers in the signaling process of many cytokine receptors. The JAKs play a critical role in both innate and adaptive immunity, making them attractive targets for the treatment of inflammatory diseases. Targeting the Janus activated kinase (JAK) signaling pathway for autoimmune diseases is supported by the involvement of various pro-inflammatory cytokines that signal via JAK pathways in the pathogenesis of these immune-related disorders. Upadacitinib is a novel selective JAK1 inhibitor. JAK1 inhibition blocks the signaling of many important pro-inflammatory cytokines.

Study objective

Main objective of SS1 (Ph2b induction) is to characterize dose-response, efficacy, and safety of upadacitinib compared to placebo in inducing clinical remission defined by Adapted Mayo score in subjects with moderately to severely active ulcerative colitis (UC) in order to identify the induction dose of upadacitinib for further evaluation in Phase 3 studies, SS1 has closed enrollment and all subjects have completed the induction phase.

Main objective of SS2 (Ph3 induction) is to evaluate efficacy and safety of upadacitinib 45 mg once daily (QD) compared to placebo in inducing clinical remission in subjects with moderately to severely active UC.

Main objective of SS3 (Ph3 maintenance) is to evaluate efficacy and safety of upadacitinib 15 mg QD and 30 mg QD compared to placebo in achieving clinical remission in subjects with moderately to severely active UC who achieved clinical response following induction with upadacitinib in M14-234 SS1 or 2 or M14-675.

Study design

This is a Phase 2b/3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of upadacitinib as induction and maintenance therapy in adult subjects with moderately to severely active UC. The study comprises 3 substudies: a Phase 2b dose-ranging induction substudy (Substudy 1), a Phase 3 dose-confirming induction substudy (Substudy 2), and a Phase 3 maintenance substudy (Substudy 3).

Intervention

All subjects receive upadacitinib or placebo tablets (oral) once a day, until end of the study or discontinuation.

Study burden and risks

Upadacitinib is a novel JAK1 selective inhibitor with minimal inhibitory effects on JAK2 and JAK3, which could potentially minimize some of the reported safety concerns with non-selective JAK inhibition which are thought to be mediated by inhibition of JAK2 and JAK3 signaling pathways. upadacitinib was tested in two studies in patients with RA. upadacitinib was generally well-tolerated and the types and frequencies of side-effects were typical of patients treated with traditional RA medications. The most common reported AEs were: headache, upper chest infection, common cold, back pain, diarrhea, and cough. Study M14-234, a proposed phase 2b/3 double-blind randomized controlled study in UC subjects with multiple doses of upadacitinib is based on the following supportive findings: 1) demonstrated improved potency of upadacitinib versus tofacitinib in preclinical models of inflammation; 2) confirmed JAK1 selectivity of upadacitinib in both preclinical and clinical settings; 3) acceptable preclinical toxicological findings in chronic toxicity studies in two species; 4) acceptable safety and tolerability profile of upadacitinib in single ascending dose and multiple ascending dose studies in healthy volunteers; 5) evidence that JAK inhibition in inflammatory bowel disease results in clinical and endoscopic improvement; and 6) evidence of efficacy and safety in a different inflammatory disease (rheumatoid arthritis).

The possible clinical improvement outweighs the risks mentioned above as well as the limited additional study activities over a period of 77 weeks (doctor visits, blood drawings, questionnaires and medication diary). Additionally, subjects are closely monitored for any AEs and their relationship to the study drug will be evaluated by the investigator, documented and analyzed.

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 between 18 and 75 years of age at Baseline.
2. Diagnosis of ulcerative colitis for 90 days or greater prior to Baseline, confirmed by colonoscopy
3. Moderately to severely active ulcerative colitis
4. Demonstrated an inadequate response to, loss of response to, or

intolerance to immunosuppressants, corticosteroids or biologic therapies
5. Negative pregnancy test for female subjects of childbearing potential

Exclusion criteria

1. Subject with current diagnosis of Crohn's disease (CD) or diagnosis of indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subject with disease limited to the rectum (ulcerative proctitis) duringthe screening endoscopy.
4. Received cyclosporine, tacrolimus, mycophenolate mofetil, or thalidomide within 30 days prior to Baseline.
5. Subject who received azathioprine or 6-mercaptopurine within 10 days of Baseline.
6. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
7. Subject with previous exposure to JAK inhibitor.

Study design

Design

Study phase:	3
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):	09-03-2017
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo
Product type:	Medicine
Brand name:	Upadacitinib
Generic name:	nvt

Ethics review

Approved WMO Date:	08-08-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	03-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	09-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	02-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	23-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2021
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	EUCTR2016-000641-31-NL
ClinicalTrials.gov	NCT02819635
CCMO	NL56868.018.16

Study results

Date completed:	07-05-2021
Results posted:	17-08-2022
Actual enrolment:	25

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File