A Multicenter, Randomized, Double-Blind Study to Evaluate Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease and Evidence of Mucosal Ulceration.

Published: 22-04-2014
Last updated: 31-12-2024

The objective of Study M14-115 is to evaluate efficacy and safety of higher induction and maintenance dosing regimens in subjects with moderately to severely active Crohn's disease.

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

Summary

ID

NL-OMON47833

Source
ToetsingOnline

Brief title
M14-115

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's disease / 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: Adalimumab, Crohn's disease, M14-115, Phase 3

Outcome measures

Primary outcome

Efficacy Endpoints:

Subjects participating in the Induction Study randomized to the higher adalimumab induction dose regimen will be compared to those subjects randomized to the standard adalimumab induction regimen. Subject data from the Maintenance Study will be used for exploratory analyses.

Co-Primary Induction Study Efficacy Endpoints:

- Proportion of subjects who achieve a CDAI < 150 at Week 4.

- Proportion of subjects with endoscopic response (decrease > 50% SESCD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) at Week 12.

Pharmacokinetic:

Blood samples will be collected for measurement of serum adalimumab concentration just prior to dosing at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/Premature Discontinuation and

anti-adalimumab antibody (AAA) just prior to dosing at Baseline, Week 4, Week 12, Week 26, Week 40, and Week 56PD.

Blood samples will also be collected for measurement of infliximab serum levels and Human Anti Chimeric Antibodies (HACA) just prior to dosing at Baseline.

Exploratory Research Using Intestinal Mucosal Biopsy Samples (Optional):

Optional intestinal biopsies will be collected with consent at Screening, Week 12, and Week 56 or at premature discontinuation. The purpose of these samples is to test potential biomarker signatures and new drug targets for IBD. Assessments will include but may not be limited to nucleic acids, proteins, metabolites or lipids.

Safety:

Safety analyses will be performed on all subjects who receive at least one dose of study drug. Incidence of adverse events, changes in vital signs, physical examination results, and clinical laboratory data will be assessed.

Secondary outcome

Ranked Secondary Endpoints:

1. Proportion of subjects with sustained clinical remission (CDAI < 150) at both Weeks 4 and 12.

2. Proportion of subjects with CDAI < 150 at Week 4 and endoscopic response at Week 12

3. Proportion of subjects with clinical remission (CDAI < 150) at Week 12.

4. Proportion of subjects who discontinued corticosteroid use and achieved

clinical remission (CDAI < 150) at Week 12 among subjects taking corticosteroids at Baseline.

5.Proportion of subjects with endoscopic remission (SES-CD <= 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 12

6. Change from Baseline in fecal calprotectin level at Week 4.

7. Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 µg/g at Week 4.

8. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 µg/g at Week 4.

9. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD <= 4and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, and fecal calprotectin < 250 µg/g at Week 12.

10. Proportion of subjects who achieve an SES-CED <= 2 at Week 12.

11. Proportion of subjects with clinical response (decrease in CDAI >= 70 points from Baseline) at Week 4.

12. Proportion of subjects with clinical response (decrease in CDAI >= 70points from Baseline) at Week 12.

13. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score >= 8) at Week 4.

14. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score >= 8) at Week 12.

15. Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score >= 1) at Week 12.

Endpoints for Exploratory Maintenance Study:

• Proportion of subjects who achieve endoscopic improvement (SES-CD <= 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 56 among subjects with endoscopic improvement at Week 12.

• Proportion of subjects who achieve a CDAI < 150 at Week 56 among subjects who achieve CDAI < 150 at Week 12.

All other efficacy and exploratory endpoints will be non-ranked.

Additional analyses are outlined in the protocol.

Study description

Background summary

Crohn's disease encompasses a spectrum of clinical and pathological processes manifested by focal asymmetric, transmural, and occasionally granulomatous inflammation that can affect any segment of the gastrointestinal tract. Traditionally, therapy has been focused on symptomatic improvement and achievement of clinical remission.
It has been shown that patients with endoscopic evidence of ulceration of the gastrointestinal mucosa are at increased risk of experiencing a complicated disease course. Therefore, it is reasonable that another goal of therapy be improvement of the intestinal mucosal as visualized on endoscopy; as this has been found to be associated with positive clinical benefits, including higher rates of clinical remission, fewer hospitalizations, and fewer abdominal surgeries.

Exposure-response analyses based on adalimumab through serum concentration and Crohn's disease activity index (CDAI)-based efficacy at Week 4 conducted with data from previous adalimumab induction studies have shown that higher Week 4

efficacy rates corresponded to higher adalimumab. Therefore, to improve the likelihood of achieving more stringent efficacy endpoints, such as endoscopic improvement of the
intestinal mucosa, more intensive treatment with adalimumab may be required.

Study objective

The objective of Study M14-115 is to evaluate efficacy and safety of higher induction and maintenance dosing regimens in subjects with moderately to severely active Crohn's disease.

Study design

The duration of the study could be up to 60 weeks which includes a Screening Period (1 - 4 weeks), a 12 week double-blind Induction Study and a 44-week Maintenance Study. The Screening Period may be extended as necessary after consultation with and approval by the AbbVie Study Designated Physician (SDP) for subjects who require initiation of prophylactic anti-tuberculosis (TB) therapy, or in case of external, not subject-related circumstances (e.g., due to delay of availability of screening test results). There will also be a 70-day follow-up phone call for subjects who complete Week 56 or discontinue from the study prematurely.

Intervention

Investigational Products: Adalimumab (40 mg/0.8 mL)

Double-Blind Induction:
Subjects will be randomized to receive one of 2 double-blind adalimumab Induction Study regimens.

Doses:
(Higher Induction Regimen)
160 mg at Baseline, Weeks 1, 2, and 3, and 40 mg at Week 4, continuing at 40 mg every other week through Week 12.

Double-Blind Maintenance
Subjects will receive one of two double-blind adalimumab Maintenance Study regimens.
Clinically Adjusted (CA) Regimen:
Subjects randomized to the clinically adjusted regimen will receive 40 mg adalimumab every other week beginning at Week 12. The adalimumab dose will be escalated to every week starting at Week 14 if CDAI is >= 220 or hs-CRP >= 10 mg/L (using results from the prior or current visit) as shown by the dose adjustment criteria table. These subjects will also be allowed to escalate at unscheduled visits that may occur only on Weeks 16, 18, 22, 24, 30, 32, 36, 38,

44, 46, 50, 52 and 54. Once subjects in the clinically adjusted regimen are escalated, they will remain on 40 mg ew dosing.
Therapeutic Drug Monitoring (TDM) Regimen:
At Weeks 14, 28 and 42, the adalimumab dose for subjects randomized to the TDM regimen will be determined by the dose adjustment criteria table. Doses will be determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior visit. For subjects who meet criteria for dose escalation at Weeks 14, 28 or 42, subjects will receive 40 mg weekly.

Mode of Administration: Subcutaneous (SC)

Study burden and risks

Extensive clinical and post marketing experience exists with adalimumab in a wide range of disease states including Crohn's disease and ulcerative colitis (UC). The safety profile of adalimumab in those indications is well-established with more than 50,000 patient-years of adalimumab clinical trial experience. The clinical studies in adult CD have not altered this safety profile and demonstrated a positive benefit/risk balance. Conditions which may present a risk specifically for patients with CD are exclusion criteria in this study (e.g., evidence of colonic dysplasia or active infections).

Contacts

Public
AbbVie Deutschland GmbH & Co. KG

Knollstrasse 50
Ludwigshafen 67061
DE
Scientific
AbbVie Deutschland GmbH & Co. KG

Knollstrasse 50
Ludwigshafen 67061
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Males and females >= 18 and <= 75 years of age at Baseline.
2. Diagnosis of colonic, ileocolonic, or ileal Crohn's disease for >= 3 months prior to Baseline and
confirmed by endoscopy during the Screening period or endoscopy performed within 45 days before
Baseline, with exclusion of current infection, dysplasia, and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Simplified Endoscopic Score for Crohn's Disease (SES-CD) >= 6, excluding the presence of narrowing component, or SES-CD >= 4, excluding the presence of narrowing component, for patients
with disease limited to the ileum, on a screening endoscopy or endoscopy performed within 45 days
before Baseline, confirmed by a central reader.
4. Crohn's Disease Activity Index (CDAI) >= 220 and <= 450 at Baseline despite concurrent or prior
treatment with a full and adequate course, in the opinion of the Investigator, of at least one of the
following (oral corticosteroids and/or immunosuppressants or both as defined below):
* Subject taking oral corticosteroids, excluding budesonide:
o Oral corticosteroid dose must be <= 40 mg/day (prednisone or equivalent);
* For subjects with a dose > 10 and <= 40 mg/day, dose has been stable for at least 7 days prior to Baseline and the duration of the current steroid course has been at least 14 days prior to Baseline.
* For subjects with a dose <= 10 mg/day, dose has been stable for at least 10 days prior to Baseline and the duration of the current steroid course has been at least 14 days prior to Baseline.
* Subject taking oral budesonide:
o Dose must not exceed 9 mg/day;
* For subjects with a dose >= 6 mg/day, dose has been stable for at least 7 days prior to Baseline and the duration of the current steroid course has been at least 14 days prior to Baseline;

* For subjects with a dose < 6 mg/day, dose has been stable for at least 10 days prior to Baseline and the duration of the current steroid course has been at least 14 days prior to Baseline;
or,
* At least a consecutive 42-day course of azathioprine, 6-MP 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 to clarify a therapeutic level was achived 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.
Note: If a subject is taking both an oral corticosteroid and an immunosuppressant listed above,
BOTH of the drugs need to meet the above criteria. Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline) however current or prior use of oral MTX is not sufficient for inclusion into the study.
or,
* Concurrent therapy with oral corticosteroids or immunosuppressants (azathioprine, 6-MP or SC/IM MTX) is not required for subjects not currently taking these medications who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability.
5. Subject may be included if they have previously experienced a benefit from infliximab and discontinued its use due to a subsequent loss of response (judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or
worsening of CD-related symptoms) or intolerance (in the opinion of the Investigator therapy was
discontinued as a result of a significant acute or delayed infusion/administration reaction to the
medication) to the agent. Confirmed documentation indicating loss of response or lack of tolerability
will be required.
6. Subject has a negative TB Screening Assessment (including a PPD test or QuantiFERON TB Gold test [or equivalent]) and negative chest x-ray (CXR - PA and lateral view) at Screening. If the
subject has evidence of a latent TB infection; the subject must initiate and complete a minimum of
2 weeks of an ongoing TB prophylaxis or have documented completion of a full course of anti-TB
prophylaxis, prior to Baseline.
7. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year
or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of
childbearing potential and is practicing an approved method of birth control throughout the

study and
for 150 days after last dose of study drug. Examples of approved methods of birth control which
result in a low failure rate (i.e., less than 1% per year) when used consistently are (see local informed consent for more detail):
* Implants, injectables, some intrauterine devices (IUDs), intrauterine hormone releasing system
(IUS)
* Sexual abstinence (when in line with preferred and usual lifestyle of the subject)
* Vasectomized partner
* Hormonal contraceptives for at least 90 days prior to study drug administration.
Note: low-dose progestin-only oral contraceptives such as norethindrone 0.35 mg and lynestenol
0.5 mg are not considered adequate.
8. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
9. Subject is judged to be in otherwise good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, CXR, and a 12-lead electrocardiogram (ECG) performed during Screening.
10. Subject must be able and willing to self-administer subcutaneous (SC) injections or have a qualified person available to administer SC injections.

Exclusion criteria

1. Subject with a current diagnosis of ulcerative colitis (UC) or indeterminate colitis.
2. Subject on azathioprine, 6-mercaptopurine (6-MP), methotrexate (MTX), or another immunosuppressant (e.g., thalidomide) who:
* Has not been on these medications for at least 42 days prior to Baseline; or
* Has not been on stable doses of these medications for at least 28 days prior to Baseline; or
* Has discontinued these medications within 14 days of Baseline.
3. Subject on oral aminosalicylates who:
* Has not been on stable doses of these medications for at least 28 days prior to Baseline; or
* Has discontinued use of aminosalicylates within 14 days of Baseline.
4. Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subjects on budesonide
> 9 mg/day; or
* Subject taking an oral corticosteroid (excluding budesonide):
o dose > 10 mg/day, but has not been on a stable dose for at least 7 days prior to Baseline; or
o dose > 10 mg/day, but has not been on a current steroid course for at least 14 days prior to Baseline; or
o dose <= 10 mg/day or equivalent, but has not been on a stable dose for at least 10 days prior
to Baseline; or
o dose <= 10 mg/day or equivalent but has not been on a current steroid course of at least

14 days in duration prior to Baseline, or
* Subject taking budesonide:
o dose >= 6 mg/day, but has not been on a stable dose for at least 7 days prior to Baseline; or
o dose >= 6 mg/day, but has not been on a current steroid course for at least 14 days prior to
Baseline; or
o dose < 6 mg/day dose but has not been on a stable dose of at least 10 days prior to Baseline;
or
o dose < 6 mg/day but the current course has not been at least 14 days in duration prior to Baseline; or
Has been taking both oral budesonide and prednisone (or equivalent) simultaneously, with the
exception of inhalers.
5. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening
Period.
6. Subject who has had surgical bowel resections within the past 6 months or is planning any resection at any time point while enrolled in the study.
7. Subject with a symptomatic bowel stricture.
8. Subject with an abdominal or peri-anal abscess.
9. Subject with an ostomy or ileoanal pouch.
10. Subject who has short bowel syndrome.
11. Subject has received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to Screening and/or during the Screening period.
12. Subject with prior exposure to medications that have a potential or known association with
progressive multifocal leukoencephalopathy (PML) including participation in a clinical trial of investigational agents targeting white cell trafficking (e.g., natalizumab [Tysabri®], rituximab [Rituxan®], efalizumab [Raptiva®]). Prior exposure to any anti-tumor necrosis factor (TNF) agent
other than infliximab (including etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol
[Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®) or vedolizumab (Entyvio®).
13. Subject who received any investigational agent or procedure within 30 days or 5 half-lives prior to Baseline, whichever is longer.
14. Subject who previously received treatment with adalimumab or previously participated in an
adalimumab clinical study.
15. Subject received cyclosporine, tacrolimus, or mycophenolate mofetil within 60 days prior to
Baseline.
16. Subject who previously received stem cell transplantation.
17. Subject who previously received fecal microbial transplantation.
18. Subject that received non-steroidal anti-inflammatory drugs (NSAIDs) within 14 days prior

to
Screening and during the Screening Visit, except low-dose aspirin for prevention of heart attacks, unstable angina or transient ischemic attacks or topical NSAIDs.
19. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the
Baseline Visit or oral anti-infectives for non-Crohn's disease related infections within 14 days prior
to the Baseline Visit.
20. Subjects on Crohn's disease related antibiotics that have not been on stable doses for at least 28 days prior to Baseline. Subjects on Crohn's disease related antibiotics that have discontinued these medications within 28 days of Baseline are excluded.
21. Subject currently receiving total parenteral nutrition (TPN) or plan to receive TPN at any time during the course of the study.
22. Subject with positive Clostridium difficile (C. difficile) toxin stool assay during the Screening period.
23. Screening laboratory and other analyses show any of the following abnormal results:
* AST, ALT > 1.75 × upper limit of the reference range;
* WBC count < 3.0 × 109/L;
* Electrocardiogram (ECG) - with clinically significant abnormalities;
* Total bilirubin >= 3 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
* Serum creatinine > 1.6 mg/dL.
24. Known hypersensitivity to adalimumab or its excipients.
25. Subject who has previously used infliximab:
* and had not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction;
or
* who used infliximab within 56 days of Baseline.
26. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of
demyelinating disease.
27. History of invasive infection (e.g., listeriosis and histoplasmosis) or human immunodeficiency
syndrome (HIV).
28. Subject with an active systemic viral infection or any active viral infection that based on the
investigator's clinical assessment makes the subject an unsuitable candidate for the study.
29. Subjects with a positive result for the Hepatitis B surface antigen (HBs Ag) will be excluded.
Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Subjects with HBs Ag (-), HBs Ab (-), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection
sensitivity will be exclusionary.
Subjects with a negative HBs Ag test and tests showing the results below do not require HBV DNA
PCR qualitative testing:

* HBc Ab Total (-) and HBs Ab (-)
* HBc Ab Total (-) and HBs Ab (+)
* HBc Ab Total (+) and HBs Ab (+)
30. Chronic recurring infections.
31. Subject with active TB.
32. Subject with latent TB infection unless there is evidence the subject initiated and completed a
minimum of 2 weeks of an ongoing TB prophylaxis or have documented completion of a full course
of anti-TB prophylaxis, prior to Baseline.
33. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which, in the opinion of the Investigator, would put the subject at risk by participation in the study.
34. Subject with a previous history of dysplasia of the gastrointestinal tract, or found to have dysplasia in any biopsy performed during the Screening endoscopy or endoscopy performed within 45 days before Baseline.
35. Positive pregnancy test at Screening (serum) or Baseline (urine).
36. Female subjects who are breastfeeding or considering becoming pregnant during the study.
37. History of clinically significant drug or alcohol abuse in the last 12 months.
38. Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
39. Current evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other
than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or
localized carcinoma in situ of the cervix.
40. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	22-01-2015
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Humira
Generic name:	Adalimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-04-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	04-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	18-03-2019
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	EUCTR2013-001746-33-NL
ClinicalTrials.gov	NCT02065570
CCMO	NL47319.018.14

Study results

Date completed:	05-01-2018
Results posted:	21-01-2021

First publication
20-01-2021