A Multicenter, Open-Label Study to Evaluate the Long Term Efficacy, Safety, and Tolerability of Repeated Administration of Adalimumab in Subjects with Crohn's Disease

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The primary objective of this study is to evaluate the long-term efficacy, safety, and tolerability of repeated administration of adalimumab in subjects with Crohn's disease (CD) who participated in and successfully completed Study M14-115.The...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal ulceration and perforation
Study type	Interventional

Summary

ID

NL-OMON44259

Source
ToetsingOnline

Brief title
M14-347

Condition

- Gastrointestinal ulceration and perforation

Synonym
Crohns Disease (also used in lay language)

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie Deutschland GmbH & Co. KG
Source(s) of monetary or material Support: For EU Countries: AbbVie Deutschland GmbH & Co. KG AbbVie Knollstrasse Ludwigshafen 67061 Germany

Intervention

Keyword: adalimumab, Crohn's Disease, HUMIRA, M14-347

Outcome measures

Primary outcome

Proportion of subjects with endoscopic improvement, defined as an SES-CD <= 4

and at least 2 point reduction versus baseline and no subscore greater than 1

in any individual variable, at Week 40 among subjects with endoscopic

improvement at Week 0 of Study M14-347.

Secondary outcome

For additional efficacy endpoints, the baseline is defined as the Baseline in

Study M14 115.

* Proportion of subjects with CDAI remission (CDAI < 150) over time among

subjects with CDAI remission at Week 0 of Study M14 347.

* Proportion of subjects with endoscopic improvement, defined as an SES-CD <= 4

and at least 2 point reduction versus baseline and no subscore greater than 1

in any individual variable at Week 40.

* Proportion of subjects with CDAI remission (CDAI < 150) over time.

* Proportion of subjects with CDAI < 150 at Week 40 and SES-CD <= 4 and at least

a 2 point reduction versus baseline and no subscore greater than 1 in any

individual variable at Week 40 among subjects with CDAI < 150 at Week 0 and

SES-CD <= 4 and at least a 2 point reduction versus baseline and no subscore

greater than 1 in any individual variable at Week 0 of Study M14 347.

* Proportion of subjects with CDAI < 150 at Week 40 and SES-CD <= 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 40

* Proportion of subjects with endoscopic response at Week 40 among subjects with endoscopic response at Week 0 of Study M13-740.

* Proportion of subjects with endoscopic response at Week 40.

* Change from Baseline in fecal calprotectin level over time.

* Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 µg/g over time among subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 µg/g at Week 0 of Study M14-347.

* Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 µg/g over time.

* Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 µg/g over time among subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 µg/g at Week 0 of Study M14-347

* Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 µg/g over time.

* Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD <= 4 and at least 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, and fecal calprotectin < 250 µg/g at Week 40 among subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD <= 4 and at least 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, and fecal calprotectin < 250 µg/g at Week 0 of Study M14-347.

* Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD <= 4 and at least 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, and fecal calprotectin < 250 µg/g at Week 40.

* Proportion of subjects with SES-CD <= 2 at Week 40 among subjects with SES-CD <= 2 at Week 0 of Study M14-347.

* Proportion of subjects with SES-CD <= 2 at Week 40.

* Proportion of subjects with CDAI response (decrease in CDAI >= 70 points from Baseline) over time among subjects with CDAI response at Week 0 of Study M14-347.

* Proportion of subjects with CDAI response (decrease in CDAI >= 70 points from Baseline) over time.

* Proportion of subjects with enhanced CDAI response (decrease in CDAI >= 100 points from Baseline) over time among subjects with enhanced CDAI response at Week 0 of Study M14-347.

* Proportion of subjects with enhanced CDAI response (decrease in CDAI >= 100 points from Baseline) over time.

* Change in IBDQ from Baseline over time.

* Proportion of subjects who discontinue corticosteroid use at each visit among subjects who used corticosteroids at Week 0 of Study M14-347.

* Proportion of subjects who achieve CDAI reemission and discontinue corticosteroid use at each visit among subjects who used corticosteroids at Week 0 of Study M14-347.

* Proportion of subjects with a SFPS remission (SFPS < 50) over time among subjects with SFPS remission at Week 0 of Study M14 347.

* Proportion of subjects with a SFPS remission (SFPS < 50) over time.

* Time inProportion of subjects with a SFPS remission (SFPS < 50) over time among subjects with SFPS >= 100 at Week 0 of Study M14-347.

* Proportion of subjects with SES-CD <= 3 and at least 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 40 among subjects with SES-CD <= 3 and at least 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 0 of Study M14-347.

* Proportion of subjects with SES-CD <= 3 and at least 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 40

* Proportion of subjects with SES-CD = 0 at Week 40 among subjects with SES-CD = 0 at Week 0 of Study M14-347.

* Proportion of subjects with SES-CD = 0 at Week 40.

* Proportion of subjects with a decrease of SES-CD >= 3 points from Baseline of Study M14-115 at Week 40.

* Change from Baseline in hs-CRP level over time.

* Proportion of subjects with Inflammatory Bowel Disease Questionnaire (IBDQ) response (decrease >= 16 points from Baseline) over time among subjects with Inflammatory Bowel Disease Questionnaire (IBDQ) response (decrease >= 16 points from Baseline) at Week 0 of Study M14-347.

* Proportion of subjects with Inflammatory Bowel Disease Questionnaire (IBDQ) response (decrease >= 16 points from Baseline) over time.

* Proportion of subjects with IBDQ remission (IBDQ >= 170 points) over time among subjects with IBDQ remission (IBDQ >= 170 points) at Week 0 of Study

M14-347.

* Proportion of subjects with IBDQ remission (IBDQ >= 170 points) over time.

* Change in WPAI from Baseline over time.

* Change in European Quality of Life 5 Dimensions (EQ-5D) from Baseline over time.

* Change in CDAI from Baseline over time.

* Change in SFPS from Baseline over time.

* Change in Abdominal Pain Rating Scale score from Baseline over time.

* Change in Bristol Stool Scale score from Baseline over time.

* Change in each CDAI component subscore (number of liquid or very soft stools, abdominal pain rating, general well-being, CD related complications, anti-diarrhea use, abdominal mass, hematocrit, body weight) from Baseline over time.

* Time to first dose escalation.

* Proportion of subjects who require weekly dosing at Week 1 of Study M14 347.

* Proportion of subjects with major CD related event (e.g., hospitalization, bowel surgery, abscess drainage).

* Proportion of subjects requiring dose escalation to weekly dosing during this study.

* Proportion of subjects with no draining fistulas over time among subjects with draining fistula at Baseline of Study M14-115.

* Proportion of subjects in each treatment group with > 50% reduction from Baseline of Study M14-115 in the number of draining fistulas over time among subjects with draining fistula at Baseline of Study M14-115.

* Resolution of extraintestinal manifestations over time.

* Proportion of subjects who achieve symptomatic remission, defined as average daily stool frequency <= 1.5 (and not worse than baseline) and average daily abdominal pain <= 1.0 (and not worse than baseline) over time.

* Proportion of subjects who achieve symptomatic response, defined as 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 and average daily stool frequency not worse than baseline, over time.

Pharmacokinetic:

Blood samples for measurement of adalimumab concentrations will be obtained at Weeks 0 (from Week 12 of Study M14-115), 8, 16, 24, 32, 40/PD, and unscheduled visits if dose escalating or de escalating. AAA concentrations will be obtained at Weeks 0, 24, 40/PD, and unscheduled visits if dose escalating or de-escalating.

Safety:

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

Study description

Background summary

Crohn's disease (CD) 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 for CD has been focused on symptomatic improvement and achievement of clinical remission as measured using the Crohn's disease activity index (CDAI). In addition to improving symptoms, an emerging goal of therapy is to improve the condition of the intestinal mucosa. 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.
Study M14-115 assessed the efficacy and safety of two adalimumab induction regimens in achieving endoscopic improvement, (SES-CD <= 4 with an Ulcerated Surface sub-score no greater than 1 in any segment) at Week 12 and clinical remission (CDAI < 150) at Week 4 as well as the pharmacokinetics (PK) and immunogenicity of the two adalimumab induction regimens. This study is designed to investigate the long-term efficacy, safety, and tolerability of repeated administration of adalimumab in adult subjects with CD who participated and successfully completed Study M14-115.

Study objective

The primary objective of this study is to evaluate the long-term efficacy, safety, and tolerability of repeated administration of adalimumab in subjects with Crohn's disease (CD) who participated in and successfully completed Study M14-115.
The secondary objective is to assess pharmacokinetics (PK) and immunogenicity of adalimumab following subcutaneous (SC) administration.

Study design

This is an open-label extension (OLE) study which comprises a 40-week open-label period designed to evaluate the long-term efficacy, safety, and tolerability of adalimumab. Approximately 300 subjects with CD who participated in and successfully completed Study M14-115 will be enrolled. Subjects will be evaluated for entry into Study M14-347 at the final study visit (Week 12) of Study M14-115. Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in this study. The Week 12 visit of Study M14-115 will be considered Week 0 (Baseline) of Study M14-347.

There will be a 70-day follow-up Phone call for subjects who complete the study or discontinue from the study prematurely.

Intervention

All subjects will receive open-label adalimumab 40 mg every other week (eow) beginning at Week 0. Subjects may be escalated to adalimumab 40 mg every week (ew) at or after Week 2 should the subject meet the criteria for inadequate response:
Inadequate Response =
Crohn's disease activity index (CDAI) >= 200 for two consecutive visits that are at least fourteen (14) days apart, and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high sensitivity C reactive protein (hs-CRP) from Baseline or a hs-CRP >= 5 mg/L. Assessment of inadequate response should include consideration by the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation.
For subjects taking corticosteroids at Baseline of Study M14-115, adalimumab dose escalation should be considered in lieu of increases in steroid dose. Subjects who continue to experience inadequate response on 40 mg ew who were taking corticosteroids at Baseline may have their steroid dose increased, per the Investigator's discretion, in order to manage the subject's symptoms. Any subject who continues to experience inadequate response on 40 mg ew may be discontinued from the study at the investigator's discretion after discussion with the Study designated physician (SDP). Subjects who dose escalated to adalimumab 40 mg ew, have one opportunity to de-escalate adalimumab dose to 40 mg eow provided the following criteria have been met: CDAI < 200, and high-sensitivity C reactive protein (hs CRP) value equal to or lower than that observed at the time of dose escalation. Subjects who experience inadequate response after dose de-escalation (using the same criteria outlined above) may again be escalated to 40 mg ew. A subject has only one opportunity to dose-de-escalate and one opportunity to re-escalate to ew adalimumab dosing.

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 ulceralive 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
s pecificallyfor patients with CD are exclusion criteria in this study (e.g., evidence of colonic dysplasia or active
infections).

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. Subject must have successfully enrolled in and completed Study M14-115, including the Week 12 ileocolonoscopy.
2. 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)
• A 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
Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):
Main Inclusion (Continued):
3. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
4. Subject must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.

Exclusion criteria

1. For any reason subject is considered by the investigator to be an unsuitable candidate.
2. Known hypersensitivity to adalimumab or its excipients.
3. 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.
4. Positive pregnancy test at Baseline (Week 12 of Study M14-115).
5. Female subject who is considering becoming pregnant during the study.
6. History of malignancy other than a successfully treated non-metastatic cutaneous squamous cell, basal cell carcinoma and/or localized carcinoma in situ of the cervix. If the Week 12 (Study M14 115) colonoscopy shows evidence of dysplasia or a malignancy, subject must not be enrolled in the study.
7. Subject with a poorly controlled medical condition, such as uncontrolled diabetes, unstable ischemic heart disease, moderate or severe congestive heart failure, recent cerebrovascular accidents and any other condition which, in the opinion of the investigator or sponsor, would put the subject at risk by participation in this study.
8. Subject is not in compliance with prior and concomitant medication requirements throughout Study M14-115.
9. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
10. History of invasive infection (e.g., listeriosis and histoplasmosis) or human immunodeficiency syndrome (HIV).
11. Subject who developed active Tuberculosis (TB) during Study M14-115, or subject who is non compliant with prophylaxis for latent TB initiated per Study M14-115 procedures.

Study design

Design

Study phase: 3

Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-05-2015
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	27-11-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2015
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2017
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	EUCTR2013-004034-15-NL
ClinicalTrials.gov	NCT02185014
CCMO	NL49541.018.14