A Double-Blind, Randomized, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

Published: 01-05-2014
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The objective is to evaluate safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active Ulcerative Colitis (UC).

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

Summary

ID

NL-OMON47464

Source
ToetsingOnline

Brief title
M14-033

Condition

- Gastrointestinal ulceration and perforation

Synonym
inflammatory bowel disease (IBD), Ulcerative colitis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Active Ulcerative Colitis, Adalimumab, M14-033, Phase 3

Outcome measures

Primary outcome

Efficacy:

The primary efficacy endpoint for the Induction Study is:

• Proportion of subjects achieving clinical remission (defined as a Full Mayo score <= 2 with no subscore > 1) at Week 8.

The primary efficacy endpoint for the Maintenance Study is:

• Proportion of Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of >= 3 points and >= 30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] >= 1 or an absolute RBS of 0 or 1) achieving clinical remission (per Full Mayo score) at Week 52.

Pharmacokinetics:

Blood samples will be collected for the measurement of serum adalimumab concentrations just prior to dosing at Baseline and Weeks 2, 4, 8, 10, 12, 16, 22, 24, 29, 35, 37, 42, 48, 52 (or at the PD visit if the subject discontinues prior to Week 52), and unscheduled visits. Pre-dosing serum samples for HACAs and infliximab concentrations will be collected at Week 0.

Blood samples will be collected for the measurement of AAA just prior to dosing

at Baseline and Weeks 4, 8, 12, 24, 37, 52 (or at the PD visit if the subject discontinues prior to Week 52), and unscheduled visits.

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 efficacy variables (ranked hierarchically in decreasing order) for the Induction Study are:

1. Proportion of subjects achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 8.

2. Proportion of subjects with fecal calprotectin below 150 mg/kg at Week 8.

3. Proportion of subjects with IBDQ response (increase of IBDQ >= 16 from Baseline) at Week 8.

4. Proportion of subjects achieving clinical response (per Full Mayo score) at Week 8.

5. Proportion of subjects achieving endoscopic subscore of 0 at Week 8.

Additional pre-specified endpoints in the Induction Study include but are not limited to the following:

• Assessment of the relationship between adalimumab serum concentrations and efficacy during the Induction Study

• All-cause and UC-related hospitalization and surgery rates during Weeks 0 - 8.

• Change from Baseline in histologic score at Week 8.

• Proportion of subjects achieving clinical remission per Adapted Mayo Score (defined as stool frequency subscore <= 1, rectal bleeding subscore of 0, and endoscopic subscore <= 1) at Week 8.

• Proportion of subjects achieving Full Mayo score, excluding the PGA subscore, <= 2 with no subscore > 1 at Week 8.

• Relationship between histologic scores and endoscopic improvement (endoscopy subscore of 0 or 1) at Week 8.

• Relationship between histologic scores and endoscopic subscore of 0 at Week 8.

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) for the Maintenance Study are:

1. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.

2. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid free for at least 90 days at Week 52.

3. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.

4. Proportion of Week 8 remitters (per Full Mayo score) achieving clinical remission (per Full Mayo score) at Week 52.

Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.

6. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at

Baseline who are steroid-free for at least 90 days at Week 52.

7. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.

8. Proportion of Week 8 responders (per Full Mayo score) with IBDQ response (increase of IBDQ >= 16 from Baseline) at Week 52.

9. Proportion of Week 8 non-responders (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.

10. Proportion of Week 8 non-remitters (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.

11. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.

12. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.

Additional pre-specified endpoints in the Maintenance Study include but are not limited to the following:

• Assessment of the relationship between adalimumab serum concentrations and efficacy during the Maintenance Study by Week 8 response status.

• Proportion of Week 8 responders (per Full Mayo score) with clinical response at Week 52.

• Proportion of Week 8 non-responders (per Full Mayo score) with clinical response at Week 52.

• Proportion of Week 8 non-responders (per Full Mayo score) with endoscopic

improvement at Week 52.

• All cause and UC-related hospitalization and surgery rates during Weeks 8 - 52.

• Change from Baseline in histologic score at Week 52.

• Proportion of Week 8 responders per Adapted Mayo Score (defined as decrease from Baseline in the Adapted Mayo Score >= 2 points and >= 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) >= 1 or an absolute RBS <= 1) achieving clinical remission per Adapted Mayo Scores at Week 52.

• Proportion of Week 8 responders (per Full Mayo score) achieving Full Mayo score, excluding the PGA subscore, <= 2 with no subscore > 1 at Week 52.

• Relationship between histologic scores and endoscopic improvement (endoscopy subscore of 0 or 1) at Week 52.

• Relationship between histologic scores and endoscopic subscore of 0 at Week 52.

• Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid free for at least 180 days and in clinical remission (per Full Mayo score) at Week 52.

The following additional pre-specified endpoints will also be analyzed in both the Induction Study and the Maintenance Study.

• Analysis of the impact of immunogenicity on safety, pharmacokinetics, and efficacy.

• Proportion of subjects who are taking corticosteroids at Baseline and are steroid-free over time.

• Evaluation of adalimumab concentrations and immunogenicity at the time of loss of clinical remission.

• Proportion of subjects achieving clinical remission per Partial Mayo (defined as a Partial Mayo score <= 2 with no subscore > 1) score over time.

• Proportion of subjects achieving clinical response per Partial Mayo score (defined as a decrease in Partial Mayo score of >= 2 points and >= 30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] >= 1 or an absolute RBS of 0 or 1) over time.

• Change from Baseline in hs-CRP over time.

• Change from Baseline in corticosteroid dose over time.

• Change from Baseline in IBDQ score over time.

• Change from Baseline in Mayo score, Partial Mayo score and Mayo subscores over time.

• Change from Baseline in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight).

• Change from Baseline in subject-reported stool frequency (absolute values).

• Change from Baseline in work productivity and impairment questionnaire (WPAI) scores over time.

• Change from Baseline in SF-36 score over time.

• Change from Baseline in fecal calprotectin over time.

• Time to achievement of remission (per Partial Mayo score).

• Time to achievement of response (per Partial Mayo score).

• Time to loss of response and factors associated with loss of response.

• Change in presence of extraintestinal manifestations over time.

Study description

Background summary

Ulcerative colitis (UC) is a chronic, relapsing inflammatory disease of the large intestine characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. The clinical course is marked by exacerbation and remission. The most severe intestinal manifestations of UC are toxic megacolon and perforation.
Extraintestinal complications include arthritis (sacroiliitis and ankylosing spondylitis), dermatological conditions (erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum), inflammation of the eye (uveitis), and liver dysfunction (primary sclerosing cholangitis). 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 have significant adverse effects.

The safety and efficacy of adalimumab for the induction and maintenance of clinical remission in adult subjects with moderately to severely active UC has been studied in two completed clinical trials (Study M06-826 and Study M06-827) and an ongoing open-label study (Study M10-223).
The purpose of this study is to evaluate a higher induction and maintenance regimen, including an exploratory arm evaluating a therapeutic drug monitoring strategy in adult patients with moderately to severely active UC.

Study objective

The objective is to evaluate safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active Ulcerative Colitis (UC).

Study design

This Phase 3 study design includes the Screening Period followed by an 8-Week double blind Induction Study and a 44-Week double blind Maintenance Study.
The Induction Study: will evaluate the efficacy and safety of a higher induction dosing regimen of adalimumab versus standard induction dosing in inducing clinical remission at Week 8 in subjects with moderately to severely

active UC.
The Maintenance Study: will evaluate the safety and efficacy of 44 weeks of three maintenance dosing regimens of adalimumab in achieving clinical remission at Week 52 (from the Induction Study Baseline) in subjects with moderately to severely active UC who achieved clinical response at Week 8 of the Induction Study.
During both the Induction Study and the Maintenance Study, visit week designations will represent weeks since first dose in the Induction Study. Week 0 (Baseline) will reflect the date of first adalimumab dosing in the Induction Study. Week 8 will represent the final assessment in the Induction Study. Week 52 will represent the final assessment in the Maintenance Study (representing 44 weeks of maintenance treatment in the Maintenance Study).
Subjects will have moderately to severely active UC as defined by a Mayo Score of 6 to 12 points with an endoscopy subscore of 2 or 3, confirmed by a central reader. For all Mayo Score evaluations throughout the entire study, the stool frequency and the rectal bleeding subscores will be calculated based on entries recorded into the subject's diary.
Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the Induction Study. During the Induction Study, subjects will be randomized at Baseline to one of 2 double-blinded adalimumab induction regimens (higher dose or standard dose) in a 3:2 ratio, as shown in the following figure. Use of the 3:2 randomization scheme allows for collection of additional safety data with the higher induction dose regimen.The randomization will be stratified by previous infliximab use and Baseline corticosteroid use.

The higher induction dose regimen of 160 mg at Weeks 0, 1, 2, and 3, followed by 40 mg at Weeks 4 and 6 leads to a total adalimumab dose over 8 weeks that is approximately twice that of the standard induction dose regimen (720 mg versus 320 mg).

At Week 4, all subjects who are taking oral corticosteroids from Baseline will have their corticosteroid therapy tapered according to the proposed tapering schedule specified in the protocol. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the Study Designated Physician (SDP) should be consulted for evaluation and approval.
At the conclusion of the 8-Week Induction Study, all subjects will be re-randomized into the 44-week Maintenance Study. Re-randomization into the Maintenance Study will be stratified by induction treatment regimen in the Induction Study and response status (per Full Mayo Score) at Week 8. Among the responders at Week 8, the re-randomization will be further stratified by remission status (per Full Mayo score) at Week 8. All subjects in the main study who complete the Induction Study) will be re-randomized into one of three blinded treatment groups in a 2:2:1 ratio:
• Adalimumab 40 mg every other week (eow)
• Adalimumab 40 mg every week (ew)

• Adalimumab Therapeutic Drug Monitoring (TDM) regimen (exploratory)

Intervention

Investigational Products: Adalimumab
Mode of administration: Subcutaneous injection (SC)

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

Doses:
Standard Induction Dose Regimen:
160 mg at Week 0 and matching placebo at Week 1.
Subjects will receive 80 mg at Week 2 and matching placebo at Week 3.
Subjects will receive 40 mg at Week 4 and Week 6.

Higher Induction Dose Regimen:
160 mg at Weeks 0, 1, 2, and 3.
Subjects will receive 40 mg at Week 4 and Week 6.

Maintenance Study: Double-Blind Maintenance Doses:
Subjects will be re-randomized to receive one of 3 double-blind adalimumab maintenance dosing regimens.
Adalimumab 40 mg eow Regimen:
40 mg every other week, starting at Week 8 until Week 50. Matching Placebo will be administered every other week, starting at Week 9 until Week 51. No dose will be administered at Week 52.

Adalimumab 40 mg ew Regimen:
40 mg every week, starting at Week 8 until Week 51. No dose will be administered at Week 52.

Adalimumab TDM Regimen:
40 mg eow at Week 8 and Week 10. Matching placebo at Week 9 and Week 11. At Weeks 12, 24 and 37, the regimen will be adjusted for subjects meeting specified criteria. Subjects receiving 40 mg eow and meeting the regimen adjustment criteria will escalate to 40 mg weekly. Subjects receiving 40 mg ew and meeting the regimen adjustment criteria will receive a one-time dose of 160 mg at the visit, followed by 40 mg ew starting the following week.
Subjects receiving 40 mg eow who do not meet the regimen adjustment criteria will receive adalimumab 40 mg eow and placebo at alternative weeks. No dose will be administered at Week 52.

NOTE: In order to retain blinding all subjects in the 40 mg eow and 40 mg ew regimen groups and subjects who do not meet the criteria for dose escalation in the TDM regimen group will receive matching placebo injections in addition to the adalimumab injection

(placebo reinduction) at Weeks 24 and 37.

Study burden and risks

Extensive clinical and postmarketing experience exists with adalimumab in a wide range of disease states, including Crohn's disease and 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 UC have not altered this safety profile and demonstrated a positive benefit/risk balance. Conditions which may present a risk specifically for patients with UC 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

Main Inclusion:
1. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol.;2. Male or female >= 18 and <= 75 years of age at the Baseline visit.;3. Subject with a diagnosis of UC for 90 days or greater prior to Baseline, confirmed by endoscopy (colonoscopy or flexible sigmoidoscopy) during the Screening Period, with exclusion of current infection, dysplasia and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the Investigator, must be available.;4. Active UC with a Mayo Score of 6 to 12 points and endoscopy subscore of 2 to 3 (confirmed by
central reader) despite concurrent treatment with at least one of the following oral corticosteroids or immunosuppressants as defined below:
- Subject taking oral corticosteroids, excluding budesonide or beclomethasone:
Oral corticosteroid dose must be <= 40 mg/day (prednisone or equivalent):
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.
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: Dose must not exceed 9 mg/day:
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.
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.;• Subject taking oral beclomethasone: dose must not exceed 5 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.;or,
At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP) or injectable methotrexate (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 x 108 RBC to clarify a therapeutic level was achieved 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 dosing and duration of use criteria. Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline), however prior or current 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 for their UC from infliximab and discontinued its use due to a subsequent loss of response (i.e., judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of UC related symptoms) or intolerance (i.e., in the opinion of the investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication). Confirmed documentation indicating loss of response or lack of tolerability will be required.;6. 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. ;7. If female, subject is not breast-feeding throughout the study and for 150 days after last dose.;8. 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 TB prophylaxis, prior to Baseline.;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, chest x-ray, 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

Main Exclusion:
1. Subject with diagnosis and/or history 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) during the screening endoscopy.;4. Received therapeutic enema or suppository, other than required for endoscopy, within 7 days prior to the Screening endoscopy and during the remainder of the Screening Period.;5. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Kock pouch,
or ileostomy or is planning bowel surgery.;6. Received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline.
7. Positive pregnancy test at Screening (serum) or Baseline (urine).
8. Female who is breast-feeding or considering becoming pregnant during the study.
9. History of clinically significant drug or alcohol abuse in the last 12 months.
10. Subject on azathioprine, 6-MP, 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.

- 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.;11. Subject on oral aminosalicylates who:
- Has not been on stable doses of these medications for at least 14 days prior to Baseline; or
- Has discontinued use of aminosalicylates within 14 days of Baseline.;12. Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subject on oral budesonide > 9 mg/day; or subject on oral beclomethasone > 5 mg/day; or
- Subject taking an oral corticosteroid (excluding budesonide):
dose > 10 mg/day, but has not been on a stable dose for at least 7 days prior to Baseline; or
dose > 10 mg/day, but has not been on a current steroid course of at least 14 days in duration prior to Baseline; or
dose <= 10 mg/day or equivalent, but has not been on a stable dose for at least 10 days prior
to Baseline; or
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 oral budesonide:
dose >= 6 mg/day, but has not been on a stable dose for at least 7 days prior to Baseline; or
dose >= 6 mg/day, but has not been on a current steroid course of at least 14 days in duration
prior to Baseline; or
dose < 6 mg/day dose but has not been on a stable dose of at least 10 days prior to Baseline; or
dose < 6 mg/day but has not been a current steroid course of at least 14 days in duration prior to Baseline; or;Has been taking both oral budesonide (or oral becomethasone) and oral prednisone (or equivalent) simultaneously
and/or has discontinued use of corticosteroids within 14 days of Baseline.;13. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.;14. Positive Clostridium difficile (C. difficile) toxin stool assay during the Screening Period.;15. Currently receiving total parenteral nutrition (TPN).;16. Subject who received any investigational agent or procedure (including previous fecal microbial
transplantation) within 30 days or 5 half-lives prior to Week 0 (Baseline), whichever is longer.;17. 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.;18. Subject who has previously used infliximab:
and has 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.;19. 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 (i.e., natalizumab [Tysabri®], rituximab [Rituxan®], efalizumab
[Raptiva®]) or previous participation in an adalimumab clinical study. Prior exposure to any anti-tumor necrosis factor (TNF) agent other than infliximab (including but not limited to adalimumab [Humira®], etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol

[Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®) or vedolizumab
(Entyvio®).;20. Subject with known hypersensitivity to the excipients of adalimumab (see Protocol).;21. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of
demyelinating disease.;22. 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. If the Screening endoscopy shows evidence of dysplasia or malignancy, subject may not be enrolled in the study.;23. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency virus (HIV).;24. Subject with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.;25. 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 (+);26. Chronic recurring infections or active TB.;27. History of moderate to severe congestive heart failure (NYHA class III or IV), recent
cerebrovascular accident and/or any other condition which would put the subject at risk by participation in the study.;28. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.;29. 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.

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):	08-01-2015
Enrollment:	19
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:	01-05-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	28-11-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	06-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	09-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	16-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2016
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:	31-10-2017
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:	17-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	29-03-2019
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	EUCTR2013-001682-16-NL
ClinicalTrials.gov	NCT02065622
CCMO	NL48919.018.14

Study results

Date completed:	26-10-2018
Results posted:	30-03-2021

First publication
28-10-2020