

# Efficacy of AlbenDazole to inDUce mUcosal healing in Patients with Crohn's disease

## on anti-TNF monotherapy:

### ADD UP trial

No registrations found.

|                              |                |
|------------------------------|----------------|
| <b>Ethical review</b>        | Not applicable |
| <b>Status</b>                | Pending        |
| <b>Health condition type</b> | -              |
| <b>Study type</b>            | Interventional |

## Summary

### ID

NL-OMON20630

### Source

Nationaal Trial Register

### Brief title

ADD UP trial

### Health condition

Crohn's disease

## Sponsors and support

**Primary sponsor:** Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands

**Source(s) of monetary or material Support:** ZonMW

## Intervention

## Outcome measures

### Primary outcome

- Proportion of patients with absence of ulcers on centrally read endoscopies after 12 weeks of albendazole and anti-TNF combination treatment compared to placebo

### Secondary outcome

#### Key secondary endpoints

- Proportion of patients with endoscopic response on centrally read endoscopies defined as a reduction in the Simple Endoscopic Severity index (SES-CD) score by  $\geq 50\%$  compared to baseline
- Proportion of patients with endoscopic remission on centrally read endoscopies defined as a SES-CD score  $< 3$  in general or  $< 2$  in case of L1 (ileal) disease

- Clinical endpoints:

- o Change in CDAI from baseline to W12

- Clinical remission: CDAI  $< 150$

- Clinical (partial) response: decrease in CDAI  $\geq 70$  points [CR-70])

- o General and change in quality of life, as measured by the IBDQ, SF-12 and EQ-5D-5L at baseline, week 12 and 36

- o Patient Reported Outcome Measure (PROM): assessment of the general and change in functional status and well-being measured from the patients' perspective by the IBD-CONTROL questionnaire [25], at baseline, week 12 and 36

#### Other secondary endpoints

- Change in Anti-TNF serum concentration and anti-drug-antibodies from baseline to W12
- Proportion of patients with hs-CRP  $< 5\text{mg/L}$  at W12
- Proportion of patients with fecal calprotectin  $< 250\text{ }\mu\text{g/g}$  at W12
- Proportion of patients with fecal calprotectin  $< 100\text{ }\mu\text{g/g}$  at W12
- Change in Anti-TNF serum concentration and anti-drug-antibodies from baseline to W12
- Histological changes from baseline to W12 based on centrally read scanned biopsies using

the colonic and ileal global histologic disease activity scoring system (CGHAS/IGHAS, appendix 14.2) and the Robarts histology index (RHI, appendix 14.3).

- Presence of type 2 regulatory wound-healing macrophages (CD14+CD68+CD206+) by immunohistochemical staining and fluorescence-activated cell sorting on intestinal biopsies
- Occurrence of (serious) adverse events
- Quality Adjusted Life Years (QALYs)
- Costs
- Identification of baseline predictive genetic marker for therapy response to albendazole

## Study description

### Background summary

Rationale: Crohn's disease (CD) is a chronic inflammatory bowel disorder (IBD) with a major impact on quality of life. Mucosal healing is an important treatment outcome to prevent long term complications of the disease. Regulatory M2 type macrophages play a key role in wound healing and were shown to be induced by anti-TNF treatment in vitro and in vivo. Moreover, thiopurines promote anti-TNF induced mucosal healing and enhance the generation of anti-TNF induced M2 macrophages, which might be a key underlying mechanism of action. The use of thiopurines however, is accompanied by evident downsides. In up to 25% thiopurines need to be discontinued due to intolerance or side effects. We aimed to find an alternative and initiated a drug screen in collaboration with the target Discovery Institute at the University of Oxford.

A library of 1600 FDA approved compounds was screened for the capacity to potentiate anti-TNF mediated induction of M2 macrophages in vitro using a human mixed lymphocyte reaction. During this screen, several benzimidazoles, including albendazole and mebendazole, were identified. Our preclinical work at the Tytgat Institute at the AMC confirmed that albendazole potentiates the efficacy of anti-TNF $\alpha$  therapy both in vitro and in an IBD mouse model. Albendazole is an antihelminthic agent with a well described safety profile. Potentially it could be a novel therapeutic agent for anti-TNF- $\alpha$  combination therapy in patients with Crohn's disease.

Objective: To evaluate the safety and efficacy of 12 weeks albendazole treatment added to anti-TNF monotherapy in adult patients with Crohn's disease with incomplete mucosal healing.

Study design: Multicentre randomised double-blind, placebo-controlled trial with 2 parallel groups (albendazole and placebo)

Study population: Adult Crohn's disease patients with incomplete mucosal healing (SES-CD > 6 or  $\geq 4$  for isolated ileal disease) on anti-TNF monotherapy (either infliximab or adalimumab) for  $\geq 4$  months. Only patients with therapeutic drug levels and no measurable anti-drug antibodies are eligible. Concomitant use of an immunomodulator (methotrexate, azathioprine, 6-mercaptopurine, 6-thioguanine) within three months before enrollment is an exclusion criterion. Patients who previously failed on combination therapy (anti-TNF + immunomodulator) – defined as discontinuation on this combination therapy due to refractory disease activity – are also not eligible for enrollment. A detailed overview of in- and exclusion criteria can be found at et section 4.1 and 4.1 (page 15 & 16).

Intervention: 110 subjects are randomly assigned to receive either albendazole or placebo (1:1) in combination with continued anti-TNF treatment at unchanged dose. Patients will receive oral albendazole treatment for 12 weeks in a weight adjusted dosage or placebo. Main study endpoints: Proportion of patients with absence of ulcers on centrally read endoscopies after 12 weeks of albendazole and anti-TNF combination treatment compared to placebo

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: It seems plausible that patients have benefit from the addition of albendazole to anti-TNF monotherapy. According to the extensive experience with albendazole (in similar dosage and duration) for other indications, the drug is known with a positive safety profile. In order to remain vigilant concerning possible side effects, several safety measures are in place. Firstly, an interim analysis will be performed after 15 patients in each arm have finished the intervention phase (week 12). Stopping rules, with emphasis primarily on patient safety and secondarily on efficacy, are in place which will guide the choice whether or not to continue. The interim analysis will be evaluated by a DSMB. Secondly, repeated blood samples are taken to monitor complete blood count and liver enzymes. Predefined criteria are in place concerning dose adjustments following liver enzyme elevation.

Peripheral blood is sampled 5 times on top of standard clinical care with a negligible risk and low burden. Subjects will be subjected to one additional (end of study) ileocolonoscopy on top of standard clinical care. This ileocolonoscopy is performed in order to assess endoscopic disease activity and evaluate the intervention's efficacy. Patients have established increased risk of persistent intestinal inflammation as determined by a repeated elevated faecal calprotectin. As part of standard clinical care patients will receive a screening colonoscopy to objectify refractory mucosal inflammation. During endoscopy biopsies are taken to determine histological disease activity. The procedure itself in combination with biopsy procurement include a minimal risk of complications, mainly bleeding or perforation (<1:10.000)[1]. In case a complication occurs, endoscopic treatment (clip placement to achieve hemostasis) is effective in most cases. Rarely, hospital admission with/without surgical intervention, antibiotic therapy and/or blood transfusion is required. Patients need to fill in 3 quality of life questionnaires and 1 'Patient Reported Outcome' questionnaire at three different timepoints. Moreover, 1 cost questionnaire required for the economic evaluation will be administered at week 12 and week 36.

## **Study objective**

Crohn's disease (CD) is a chronic inflammatory bowel disorder (IBD) with a major impact on quality of life. Mucosal healing is an important treatment outcome to prevent long term complications of the disease. Regulatory M2 type macrophages play a key role in wound healing and were shown to be induced by anti-TNF treatment in vitro and in vivo. Moreover, thiopurines promote anti-TNF induced mucosal healing and enhance the generation of anti-TNF induced M2 macrophages, which might be a key underlying mechanism of action. The use of thiopurines however, is accompanied by evident downsides. In up to 25% thiopurines need to be discontinued due to intolerance or side effects. We aimed to find an alternative and initiated a drug screen in collaboration with the target Discovery Institute at the University of Oxford.

A library of 1600 FDA approved compounds was screened for the capacity to potentiate anti-TNF mediated induction of M2 macrophages in vitro using a human mixed lymphocyte reaction. During this screen, several benzimidazoles, including albendazole and mebendazole, were identified. Our preclinical work at the Tytgat Institute at the AMC confirmed that albendazole potentiates the efficacy of anti-TNF $\alpha$  therapy both in vitro and in an IBD mouse model. Albendazole is an antihelminthic agent with a well described safety profile. Potentially it could be a novel therapeutic agent for anti-TNF- $\alpha$  combination therapy in patients with Crohn's disease.

## Study design

W-2 - W0: Screening

W0 - W12: albendazol/placebo treatment

W12: primary endpoint assessment

W36: Follow up / close out visit

## Intervention

110 subjects are randomly assigned to receive either albendazole or placebo (1:1) in combination with continued anti-TNF treatment at unchanged dose. Patients will receive oral albendazole treatment for 12 weeks in a weight adjusted dosage or placebo

## Contacts

### Public

Academic Medical Center Amsterdam, Department of gastroenterology and hepatology, C2-231

Toer W. Stevens  
Meibergdreef 9

Amsterdam 1105 AZ  
The Netherlands  
(020-56)65584

**Scientific**

Academic Medical Center Amsterdam, Department of gastroenterology and hepatology,  
C2-231

Toer W. Stevens  
Meibergdreef 9

Amsterdam 1105 AZ  
The Netherlands  
(020-56)65584

## Eligibility criteria

### Inclusion criteria

- Patients  $\geq 18$  years and  $\leq 65$  years
- Diagnosis of CD, based on endoscopy and histopathologic examination of mucosal biopsies
- Written informed consent
- Active mucosal disease as defined by a repeated faecal calprotectine  $\geq 250$   $\mu\text{g/g}$  at 2 consecutive occasions ( $\geq 2$  weeks and  $\leq 3$  months interval) AND presence of mucosal lesions as defined by a SES-CD  $> 6$  ( $\geq 4$  for L1 (ileal) disease) on screening ileocolonoscopy
- On anti-TNF therapy (ADM at a dose of 40mg Subcutaneous (SC) every week (QW) or every other week (Q2W) and IFX at a dose of 5-10 mg/kg every 4-8 weeks) for a period of at least 4 months at stable dose.
- Therapeutic trough serum concentrations of anti-TNF at screening (for IFX  $\geq 3$   $\mu\text{g/ml}$  and for adalimumab (ADM)  $\geq 5$   $\mu\text{g/ml}$ ) and undetectable levels of anti-drug antibodies (ADA's) at baseline.

### Exclusion criteria

- Ulcerative colitis or indeterminate colitis
- Current malignancy

- Women: current pregnancy wish, pregnancy or lactation. Men: active child wish
  - Ongoing use of an immunomodulator (including azathioprine, methotrexate, 6-thioguanine, 6 mercaptopurine or mycophenolic acid).
  - Prior failure on anti-TNF and immunomodulator combination therapy due to refractory disease per treating physicians opinion.
- o NOTE: Patients with prior use of co-therapy who stopped the IMM due to stable disease (with continued anti-TNF treatment), prior IMM monotherapy and prior intolerance to IMM's are considered eligible for enrolment
- Elevated liver enzymes (ALAT, ASAT, LDH,  $\gamma$ -GT, AF) >1.5 times the upper limit of normal (ULN)
  - Current use of any CYP3A4 inducing or inhibiting agents (outlined in table 1, section 5.3, page 18)
  - Patients on prednisone >10mg/day or budesonide >6mg/day
  - Patients who require rescue therapy with corticosteroids during the screening phase
  - Leukopenia (neutrophil count <  $1.8 \times 10^9/L$ ) and/or thrombopenia <  $50 \times 10^9/L$
  - Other conditions which in the opinion of the investigator may interfere with the subject's ability to comply with the study procedure

## Study design

### Design

|                     |                               |
|---------------------|-------------------------------|
| Study type:         | Interventional                |
| Intervention model: | Parallel                      |
| Allocation:         | Randomized controlled trial   |
| Masking:            | Double blinded (masking used) |
| Control:            | Placebo                       |

### Recruitment

|                     |         |
|---------------------|---------|
| NL                  |         |
| Recruitment status: | Pending |

|                           |             |
|---------------------------|-------------|
| Start date (anticipated): | 01-08-2018  |
| Enrollment:               | 110         |
| Type:                     | Anticipated |

## Ethics review

|                   |                |
|-------------------|----------------|
| Not applicable    |                |
| Application type: | Not applicable |

## 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              |
|----------|-----------------|
| NTR-new  | NL7173          |
| NTR-old  | NTR7364         |
| Other    | : METC 2018_072 |

## Study results

### Summary results

NA