# A Randomized, Placebo-controlled, Double-blind, Parallel-group, Exploratory, Phase 2 Study of the Efficacy and Safety of Oral AMT-101 in Combination with Adalimumab in Subjects with Moderate to Severe Ulcerative Colitis

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To evaluate the effects of AMT-101 in combination with adalimumab on UC disease activity as measured by symptoms, endoscopy, histology, and biomarkers. To evaluate the safety and tolerability of oral AMT-101 over 8 weeksTo assess the PK parameters...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Gastrointestinal inflammatory conditions |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON51097

**Source**
ToetsingOnline

**Brief title**
AMT-101-203

### Condition

- Gastrointestinal inflammatory conditions

**Synonym**
Inflammatory Bowel Disease, Ulcerative Colitis

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Applied Molecular Tranport Inc.
**Source(s) of monetary or material Support:** Applied Molecular Transport Inc.

## Intervention

**Keyword:** AMT-101 in combination with adalimumab, Biologics, Oral GI-selective IL-10, Ulcerative Colitis

## Outcome measures

### Primary outcome

• Mean change in UC-100 score from baseline

Mean change in Robarts Histopathology Index (RHI) from baseline

• Mean change in total Mayo Clinic Score (MCS) and component scores (Mayo

Endoscopic Subscore [MES], partial MCS, rectal bleeding, and stool frequency)

from baseline

• Mean change in faecal calprotectin from baseline

• Mean change in highly sensitive C-reactive protein value (hs-CRP) from

baseline

• Endoscopic remission rate (defined as an MES of 0 or 1)

• Endoscopic response rate (defined as a decrease in MES of at least 1 point

from baseline)

• Mucosal healing (defined as MES of 0 or 1 and a Geboes histological index

score of <= 3.1)

• Histological remission rate (defined as Geboes histological index score of <=

2B.0; or Robart's histopathology index [RHI] <= 3 with a subscore of 0 for

lamina propria neutrophils and 0 for neutrophils in the epithelium)

• Percentage of subjects with a 50% decrease in RHI • Clinical remission rate (defined as total MCS <= 2 with all subscores <= 1)

• Clinical response rate (defined as a decrease in MCS of at least 3 points and at least 30% from baseline, with a decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1)

• Clinical remission rate (alternate definition of the Mayo subscore for bowel movement frequency of 0 or 1 and Mayo subscore for rectal bleeding of 0 and MES of 0 or 1)

Security endpoints

• Frequency and severity of side effects

• Changes from baseline in clinical chemistry and hematology

• Changes from baseline in vital signs and physical exams

• Electrocardiogram (ECG) findings

**Secondary outcome**

Exploratory endpoints

• Levels of AMT-101, AMT-101 anti-drug antibodies (ADAs), total interleukin-10 (IL-10), adalimumab, and adalimumab ADAs in serum

• Concentrations of AMT-101, AMT-101 ADAs and total IL-10 in mucosal tissue biopsies

• Mean change on the Symptoms and Impact questionnaire for UC (SIQ-UC) from baseline

• Mean change in inflammatory bowel disease questionnaire score from baseline

• Change in the number of white blood cells

• Change in faecal matrix metalloproteinase 9 (MMP-9)

• Change in faecal lactoferrin

• Change in interleukin-1 receptor antagonist (IL-1Ra)

• Change in protein content in serum and mucosal tissue • Change in gene

expression in the mucosa

• Change in cell populations in the mucosa

• Change in the faecal microbiome

# Study description

**Background summary**

Disease Background:
Inflammatory Bowel Disease (IBD) is an autoimmune disease of the gastrointestinal (GI) tract with unknown etiology that encompasses 2 primary clinical manifestations: ulcerative colitis (UC) and Crohn*s disease (CD). IBD affects over 1.5 million people in North America and as many as 2.5 million in Europe, with a growing global spread and a prevalence of up to 0.5% of the population in most impacted regions.

UC manifests through complex interactions between the gut microbiome, dysregulated immune responses, genetic mutations, diet, and other environmental factors. As a result, the precise etiology for disease initiation differs widely among patients with UC. The incidences of UC in European countries range from 0.9 to 24.3 per 100,000 person-years. The highest incidence rates are observed in Scandinavia and the United Kingdom, while the lowest rates are seen in Southern and Eastern Europe. Extrapolation of the incidence figures on the total European population (approximately 731 million in 2006) indicate a maximal estimate 178,000 cases of UC each year. The prevalence of UC in European countries varies from 2.4 to 294 cases per 100,000 persons; it is estimated that 2.1 million persons are in total are afflicted with UC in Europe.

Current therapies for UC are modestly successful and have significant adverse side effects including systemic immunosuppression, increased incidence of opportunistic and rare infections, and increased risk for cancer. Furthermore, approximately half of UC patients will relapse in any given year, including a minority with frequently relapsing or chronic, continuous disease. Prognosis in

UC remains generally optimistic, but 15.6 % will undergo surgery within 10 years of diagnosis, with 20% to 30% of patients ultimately proceeding to surgical colectomy. In addition, UC may have a profound effect on quality of life, including mental health consequences, and a significant minority become incapable of work due to disease. Thus, there remains a significant and unmet clinical need to better manage UC with safer and more effective oral therapies.

Study Drug Background:
AMT-101(cholix386-polyGlyser-rhIL-10) is a homodimeric fusion protein where each monomer consists of a cholix386 domain and a recombinant human interleukin (IL) -10 (rhIL-10) domain connected by a 14 amino acid polypeptide spacer of glycine and serine residues. The cholix386 domain of AMT-101 is a truncated form of cholix protein, a nontoxic mutant derived from Vibrio cholerae. The cholix386 domain facilitates active transport of AMT-101 across epithelial cells to the local GI submucosal tissue.

IL-10 is an immunomodulatory cytokine that inhibits effector functions of activated macrophages and monocytes in vitro, down-regulates the production of proinflammatory cytokines (e.g., tumor necrosis factor alpha [TNF-α], IL-1β and IL-6 from macrophages and interferon (IFN)-γ and IL-2 from T-cells) and cytokine receptor expression (e.g., TNF receptor [TNF-r]), and upregulates cytokine inhibitors (e.g., soluble TNF-r and IL-1Ra). IL-10 effects are mediated through activation of the januse kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling cascade, where phosphorylated STAT3 homodimers translocate to the nucleus to activate the expression of target genes. Activation of STAT3 in epithelial cells has been reported to promote cellular protection, survival and proliferation.
Parenterally-administered rhIL-10 has been evaluated in clinical trials conducted by other sponsors with IBD and while generally safe and well-tolerated did not result in significantly reduced remission rates or clinical improvements when compared to placebo.

AMT-101 is formulated as an enteric-coated tablet intended for oral administration, resulting in targeted, gut-restricted delivery and uptake, with low systemic exposure. Local delivery of IL-10 may bypass the side effects experienced with systemic administration and is expected to translate into higher mucosal concentrations and clinically meaningful reductions in inflammation and disease activity.

Rationale for the Study
Rationale for the use of AMT-101 in the treatment of IBD and UC is based on several studies in animal models and humans. Nonclinical studies with AMT-101 in rodents using oral gavage administration and monkeys using pan-colonic administration (via the rectum) have demonstrated both localization of AMT- 101 in intestinal submucosal tissue and activation of STAT3 by phosphorylation. Oral AMT-101 has shown evidence of anti-inflammatory activity in relevant animal models of IBD.

The rationale for evaluating the combination of AMT-101 with anti-TNF therapy is based on recent data suggesting that anti-TNF treatment response depends on IL-10 signaling pathways. In this series of experiments, the response to anti-TNF therapy in a mouse T-cell transfer model of colitis was reduced by pharmacological inhibition of IL 10, and this was found to be mediated by macrophages and not T-cells. Furthermore, in a small sample of patients with CD, different patterns of IL-10 production from human monocytes and mucosal mRNA expression of IL-10 and related cytokines were observed between responders and nonresponders to anti-TNF therapy. Therefore, it has been proposed that defects in IL-10 pathways may at least partially explain why some patients do not respond to anti-TNF therapy and that response to anti-TNF therapy may be partially IL-10 dependent. Approximately one-third of patients may exhibit nonresponse. It is hypothesized that addition of AMT-101 may improve response to anti-TNF therapy in patients with IBD through activation of IL-10 signaling pathways.

Based on the preliminary results of the Phase 1 study, the dose selected for this study (3 mg administered once daily) is expected to be safe, well tolerated, and result in pharmacological effects in intestinal tissue in subjects with UC. The study is designed with a 8-week induction period because this is typical for IBD treatments and is expected to be of adequate duration to demonstrate clinical effects; previous Phase 2 studies of other treatments have employed 8 to 12 weeks of induction. Nonclinical toxicology studies are currently ongoing to evaluate longer periods of AMT-101 administration, and potentially support maintenance dosing regimens in the future.

**Study objective**

To evaluate the effects of AMT-101 in combination with adalimumab on UC disease activity as measured by symptoms, endoscopy, histology, and biomarkers.
To evaluate the safety and tolerability of oral AMT-101 over 8 weeks
To assess the PK parameters of AMT-101 in combination with adalimumab
To assess health-related quality of life (HRQOL)
To assess the PD effect of AMT-101 on biomarkers
To assess target engagement and mechanism of action

**Study design**

This is a randomized, placebo-controlled, double-blind, parallel-group, multicenter study. As this is a proof-of-concept study, the objectives and endpoints are descriptive and designed to explore multiple types of outcomes, including clinical, endoscopic, histologic, PK, PD, and HRQOL.
Endoscopic assessments will be scored both locally and centrally and histologic assessments will be scored centrally. Study central readers will receive standardized training on Robarts* Central Image Management Solutions (CIMS) for assessment of endoscopy and histopathology (qualified gastroenterologists and

pathologists, respectively). Central readers will enter scores in a study database. For endoscopic assessments, central reader scores will be the primary scores for analyses and for confirming eligibility. In the case of adjudication for endoscopy, the second central reader (adjudicator) would select either the local reader or first central reader score to be used as the final score (forced adjudication). For histologic assessments, there will be a single central read.

A total of 30 subjects with moderate to severe UC (total MCS 6-12; MES >= 2) are planned to be enrolled in this study from approximately 4 centers in Europe. Eligible subjects will be randomized in a 1:1 ratio to receive adalimumab + placebo or adalimumab + AMT-101 (3 mg). Adalimumab will be administered by subcutaneous injection according to the induction regimen outlined on the product label. AMT-101 or matching placebo will be administered orally, once daily for 8 weeks.

**Intervention**

Both groups are treated with adalimumab for 8 weeks, per standard dose as prescribed
1 group takes 1 tablet of AMT-101 once a day. The other group takes 1 placebo tablet once a day

**Study burden and risks**

Nonclinical studies evaluating AMT-101 support the mechanism of action for targeted, intestinally restricted delivery of rhIL-10 via oral administration, while minimizing systemic IL-10 exposure. The nonclinical effects of AMT-101 have been studied in a comprehensive panel of studies that address pharmacology, pharmacodynamics, pharmacokinetics and toxicology, including evaluation of AMT-101 in two mouse models of disease. There were no adverse effects at the highest dose tested in repeat-dose toxicology studies up to 13 weeks. Results from the AMT-101 nonclinical program indicates a potential therapeutic benefit of an oral targeted delivery rhIL-10 in the management of ulcerative colitis, pouchitis and potentially other related diseases.

Initial clinical evaluation of oral AMT-101 in a first-in-human clinical study in healthy subjects and patients with active UC, suggests that AMT-101 is generally well tolerated, with all treatment emergent AEs being mild (Grade 1) to moderate (Grade 2) in severity. Preliminary data from this ongoing clinical study supports the hypothesis that AMT-101 treatment has potential for clinical activity in patients.

Taken together, the AMT-101 nonclinical program and clinical experience with oral AMT-101, supports a favorable projected risk-benefit profile for the continued clinical development of AMT-101 as a monotherapy and in combination

with other modalities of IBD treatment in Phase 2 trials for UC and pouchitis.

Clinical reproductive toxicity risk of AMT-101 is unknown. Nonclinical reproductive toxicity studies have not been completed and no clinical pregnancies have been observed. Histopathology of the reproductive tract was evaluated as part of repeat-dose toxicology testing and no test-article-related effects were observed. To minimize risk, women planning to become pregnant are not eligible for the study, study subjects must agree to use contraception, and pregnancy tests will be performed throughout the study.

Risks associated with study procedures/tests:
- Blood samples: Pain, bruising and/or bleeding where the needle enters the vein. Some people feel light-headed or faint. Rarely will this procedure lead to swelling and/or infection of the vein.
- Sigmoidoscopy: Cramping, pain, abdominal bloating (common). Peritonitis (inflammation of the lining of the abdominal cavity) (rare). Perforation (a hole) of the intestinal wall (rare). Surgery may be needed if a perforation occurs (rare).
- Video capture sigmoidoscopy: No discomfort/risk is expected from the video capture. Video images are identified by study identification number. There is a chance that the video images may accidentally lead to identification however, such disclosure is not planned or expected.
- Intestinal biopsy: Persistent bleeding after biopsy or polyp removal (if taken) can occur. Biopsy results can identify a cancer of the intestine (bowel).
- Stool sample: No discomfort/risk expected. Some may find stool collection unpleasant.
- Electrocardiogram: Minor skin irritation may occur at the site of the electrodes but will be resolved once the electrodes are removed from the skin.

## 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

The study will enroll male and female adult subjects with moderate to severe UC.
Inclusion criteria (subjects must meet the following criteria to be randomized into the study):
1. Male and female subjects aged 18 to 75 years, inclusive.
2. Diagnosis of UC for at least 3 months prior to screening.
3. Moderate to severe UC, as defined by a total MCS of 6 to 12 inclusive at baseline, with a MES >= 2 (confirmed by central reader).
4. Eligible for adalimumab (or adalimumab biosimilar) therapy.
5. Naïve to therapy with approved or investigational biologics/tofacitinib including any anti-tumor necrosis factor (TNF) therapy, vedolizumab, or ustekinumab.
6. If subjects are receiving the following treatments, they must be on a stable dose for at least 4 weeks prior to randomization:
a. 5-aminosalicylates (5-ASAs) (not exceeding 4.8 g per day).
b. Oral corticosteroids (not exceeding prednisone 20 mg, budesonide 9 mg, or equivalent).
c. 6-mercaptopurine (6-MP) (any stable dose).
d. Azathioprine (AZA) (any stable dose).
e. Methotrexate (MTX) (any stable dose).
Note: subjects may be using 5-ASA and only 1 of the other medications listed (oral corticosteroids/6 MP/AZA/MTX).
7. If subjects are receiving bile-salt sequestrant, they must be on a stable dose for at least 3 months prior to randomization.
8. If subjects are receiving any nonprohibited medications, they must agree to maintain stable doses of concomitant medications for UC until the end of the safety follow-up period.
9. Unlikely to conceive.
10. Women of childbearing potential (WOCBP) must have a negative pregnancy test

at screening and at the randomization visit prior to the first dose of study drug.
11. Able to participate fully in all aspects of this clinical trial.
12. Written informed consent must be obtained and documented.

## Exclusion criteria

1. A diagnosis of Crohn*s disease (CD), indeterminate colitis, or presence or history of fistula with CD.
2. Disease activity limited to distal 15 cm (proctitis).
3. Current evidence of toxic megacolon, abdominal abscess, symptomatic colonic stricture, or stoma.
4. History or current evidence of colonic dysplasia or adenomatous colonic polyps.
5. Current bacterial or parasitic pathogenic enteric infection, including Clostridium difficile;; known active cytomegalovirus infection; known infection with hepatitisB or C virus; known infection with human immunodeficiency virus; infection requiring hospitalization or intravenous (IV) antimicrobial therapy, or opportunistic infection within 6 months prior to screening; any infection requiring antimicrobial therapy within 2 weeks prior to screening; history of more than 1 episode of herpes zoster or any episode of disseminated zoster.
6. A positive diagnostic tuberculosis (TB) test at screening (defined as a positive QuantiFERON test). In cases where the QuantiFERON test is indeterminate, the participant may have the test repeated once and if their second test is negative, they will be eligible. In the event a second test is also indeterminate, or QuantiFERON is unavailable, the investigator has the option to perform a purified protein derivative (PPD) skin test. If the PPD reaction is < 5 mm, then the subject is eligible. If the reaction is >= 5 mm, or PPD testing is not done, the subject is not eligible. An exception is made for subjects with a history of latent TB who are currently receiving treatment for latent TB, will initiate treatment for latent TB before the first dose of study treatment, or have documentation of completing appropriate treatment for latent TB within 3 years prior to the first dose of study treatment.
7. Live virus vaccination within 1 month prior to screening.
8. Any prior treatment with an approved or investigational biologic/tofacitinib, including anti-TNF therapy, vedolizumab, or ustekinumab.
9. Treatment with sirolimus, cyclosporine, mycophenolate, or tacrolimus within 8 weeks prior to randomization.
10. Treatment with IV corticosteroids, rectal corticosteroids, or rectal 5-ASA within 4 weeks prior to randomization.
11. Fecal microbiota transplantation within 1 month prior to screening.
12. A concurrent clinically significant, serious, unstable, or uncontrolled underlying cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, might

confound the study results, pose additional risk to the subject, or interfere with the subject*s ability to participate fully in the study.
13. A diagnosis of multiple sclerosis or optic neuritis, or history of a demyelinating disorder.
14. Known primary or secondary immunodeficiency.
15. History of myocardial infarction, unstable angina, transient ischemic attack, decompensated heart failure requiring hospitalization, congestive heart failure (New York Heart Association Class 3 or 4), uncontrolled arrhythmias, cardiac revascularization, stroke, uncontrolled hypertension, or uncontrolled diabetes within 6 months of screening.
16. Clinically meaningful laboratory abnormalities at screening that would affect subject safety, as determined and documented by the investigator.
17. Pregnant or lactating females.
18. Any surgical procedure requiring general anesthesia within 1 month prior to screening, or planned elective surgery during the study.
19. History of malignant neoplasms or carcinoma in situ within 5 years prior to screening.
20. Current or recent history of alcohol dependence or illicit drug use that, in the opinion of the investigator, may interfere with the subject*s ability to comply with the study procedures.
21. Mental or legal incapacitation or a history of clinically significant psychiatric disorders at the time of the screening visit that would impact the ability to participate in the trial according to the investigator.
22. Unable to attend study visits or comply with procedures.
23. Concurrent participation in any other interventional study or received any investigational therapy within 1 month of randomization.
24. Previous exposure to AMT-101 or recombinant human interleukin-10 (rhIL-10).
25. A known hypersensitivity to AMT-101, adalimumab, or their respective excipients.
26. Current treatment with antimotility medications or antidiarrheals (except for bile-salt sequestrants).

# Study design

## Design

| | |
|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |

| | |
|---|---|
| Control: | Placebo |
| Primary purpose: | Treatment |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 30-06-2021 |
| Enrollment: | 4 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | AMT-101 |
| Generic name: | AMT-101 |
| Product type: | Medicine |
| Brand name: | Humira |
| Generic name: | Adalimumab |
| Registration: | Yes - NL intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 29-10-2020 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 05-02-2021 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 21-05-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 23-05-2021 |

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|---|---|
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 02-11-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 01-12-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 28-03-2022 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 25-04-2022 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 07-05-2022 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 16-05-2022 |
| 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 | EUCTR2020-002833-13-NL |
| CCMO | NL75240.018.20 |