# A Combined Phase 2/3 12-week, Randomized, Double-blind, Placebo-controlled Study Investigating the Efficacy of AMT-101 in Subjects with Chronic Antibiotic-resistant Pouchitis

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Phase 2:• To assess the safety, tolerability, systemic exposure, and efficacy of AMT-101 in subjects with chronic antibiotic-resistant pouchitis• To select an AMT-101 dose for Phase 3Phase 3:Co-primary Objectives:• To determine the effect of AMT-101…

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

## Summary

### ID

NL-OMON52357

**Source**
ToetsingOnline

**Brief title**
AMT-101-201

### Condition

- Gastrointestinal inflammatory conditions

**Synonym**
inflammatory bowel disease, Pouchitis

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** Biologics, IBD, oral GI-selective interleukin 10 (IL-10), Pouchitis

## Outcome measures

### Primary outcome

• Proportion of subjects with a stool frequency response at Week 12; defined as a reduction of >= 3 stools AND >= 30% reduction in number of stools from baseline, OR back to postoperative baseline number of stools

• Proportion of subjects with histologic healing at Week 12; defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue (Geboes score < 3.1)

### Secondary outcome

1. Proportion of subjects with histologic response at Week 12; defined as a reduction in Pouchitis Disease Activity Index (PDAI) histology subscore >= 2 points from baseline or a PDAI histology subscore of 0

2. Proportion of subjects with minimal histologic activity at Week 12; defined as PDAI neutrophil score <= 1 and ulcer score of 0

3. Mean change in PDAI histologic subscore at Week 12

Ranked efficacy endpoints:

4. Proportion of subjects with 50% reduction in Simple Endoscopic Score for Crohn*s Disease (SES-CD) score at Week 12 (area within 1 cm of the pouch suture line will not be included in the endoscopic evaluation)

5. Mean change in PDAI endoscopic subscore at Week 12

6. Proportion of subjects achieving mPDAI < 5 and a reduction of overall score by >= 2 points from baseline at Week 12

7. Proportion of subjects achieving PDAI < 7 and a reduction of overall score by >= 3 points from baseline at Week 12

8. Proportion of subjects achieving a partial response at Week 12; defined as reduction of mPDAI score by >= 2 points from baseline

9. Mean change in stool frequency at Weeks 2, 6, 8, 10, 12, and 4WPT

10. Proportion of subjects with Mayo stool frequency score of 0 or 1 at Weeks 2, 6, 8, 10, 12, and 4WPT

11. Mean change in urgency score at Week 12 and 4WPT

12. Mean change in incontinence score (St. Mark*s) at Week 12 and 4WPT

13. Mean change in rectal bleeding score at Weeks 2, 6, 8, 10, 12, and 4WPT

14. Mean change in total PDAI score at Week 12

Safety, HRQOL, and pharmacokinetic (PK) endpoints:

• Proportion of subjects with treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuation due to TEAEs

• Assessment of laboratory parameters

• Assessment of vital signs

• Mean change in Inflammatory Bowel Disease Questionnaire (IBDQ), 5-dimension EuroQoL questionnaire (EQ-5D), and 36-item Short-Form questionnaire (SF-36) at Week 12 and 4WPT

• Concentration of AMT-101, AMT-101 antidrug antibodies (ADAs), and total

interleukin-10 (IL-10) in serum at Week 12

# Study description

**Background summary**

Disease Background:
Inflammatory Bowel Disease (IBD) is an autoimmune disease of the gastrointestinal tract (GI) 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. Approximately 30% of patients with ulcerative colitis (UC) eventually require total proctocolectomy within 15 years of diagnosis and ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice. Unfortunately, up to 50% of patients experience pouchitis within 10 years of IPAA, with most patients experiencing their first episode within 12 months.
Pouchitis is characterized by clinical symptoms of crampy lower abdominal pain, pelvic discomfort, general malaise, stool frequency above post-IPAA normal, urgency, incontinence, and nocturnal seepage. Some patients also present with extraintestinal symptoms in the joints, liver, eyes, or skin.
The etiology of pouchitis is unknown, but it appears to involve multiple factors and is related to immune-mediated dysfunction in conjunction with an altered microbiotic environment. It is clear that pouchitis is more common in UC than other conditions that often lead to colectomy, such as familial adenomatous polyposis, suggesting that there are common pathogenetic mechanisms associated with UC and the development and progression of pouchitis.
Pouchitis can be classified based on the disease course (acute or chronic), underlying etiology (idiopathic or secondary), pattern of symptoms (infrequent or relapsing), or response to antibiotic therapy (responder or antibiotic-dependent, -resistant, or -refractory).
There are no approved therapies for pouchitis and treatment of chronic pouchitis is often challenging with modest remission rates ranging from 0% to 77%.

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) signalling 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.
Parentally-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 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 doses selected for this study (3 or 10 mg administered once daily) are expected to be safe, well tolerated, and result in pharmacological effects in intestinal tissue in subjects with pouchitis. The study is designed with a 12-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**

Phase 2:
• To assess the safety, tolerability, systemic exposure, and efficacy of AMT-101 in subjects with chronic antibiotic-resistant pouchitis
• To select an AMT-101 dose for Phase 3

Phase 3:
Co-primary Objectives:
• To determine the effect of AMT-101 on stool frequency in subjects with chronic antibiotic-resistant pouchitis
• To determine the effect of AMT-101 on histologic disease activity in subjects with chronic antibiotic-resistant pouchitis
Secondary Objectives:
• To assess the efficacy of AMT-101 on histologic, endoscopic, and other clinical signs and symptoms in subjects with chronic antibiotic-resistant pouchitis
• To assess the safety and tolerability of AMT-101 in chronic antibiotic-resistant pouchitis
• To assess the efficacy of AMT-101 to improve health-related quality of life (HRQOL)
• To determine the systemic exposure of subjects following dosing

Exploratory Objectives (both Phases):
• To assess the effect of AMT-101 to reduce time to rescue therapy
• To assess the pharmacodynamic (PD) effect of AMT-101 on endoscopic and histologic inflammation
• To determine the mucosal tissue exposure of subjects following dosing
• To assess the PD effect of AMT-101 on change in biomarkers
• To assess target engagement and mechanism of action
• To assess the effect of AMT-101 on work productivity

**Study design**

This is a combined Phase 2/3 trial to assess the efficacy and safety of AMT-101 in subjects with a prior history of ulcerative colitis (UC) who have undergone colectomy with subsequent ileal pouch-anal anastomosis (IPAA) formation and have a history of chronic antibiotic-resistant pouchitis. The study will be conducted in 2 parts in an operationally seamless manner. Both parts of the study will be conducted with a randomized, double-blind, multicenter design. The Phase 3 portion of the study will be placebo-controlled.

In the Phase 2 portion, 20 subjects will be randomized in a double-blind manner to either 3 mg once daily or 10 mg once daily of AMT-101 for 12 weeks in a 1:1 fashion. Data relating to key efficacy endpoints, safety, and dose selection will be analyzed upon completion of Phase 2 and prior to initiating Phase 3. Based upon available efficacy and safety data, either the 3 mg or the 10 mg dose will be selected for the Phase 3 portion. Dose selection will be conducted by the Data Monitoring Committee (DMC) in conjunction with the sponsor. If > 30% of subjects achieve a stool frequency response at Week 12 then the study will proceed to Phase 3. If <= 15% (3/20) or fewer subjects achieve a stool frequency response, the trial will be halted.

The Phase 3 portion of the study will enroll an additional 124 subjects

randomized 1:1 (AMT-101 [3 mg or 10 mg]: placebo) for 12 weeks. Evaluation of efficacy will be based on co-primary endpoints at Week 12 of the proportion of subjects with a stool frequency response (defined as a reduction of >= 3 stools AND >= 30% reduction in number of stools from baseline, OR back to postoperative baseline number of stools) and the proportion of subjects with histologic healing (Geboes score < 3.1). A 30% reduction in daily stool count is considered a meaningful and beneficial change for patients with pouchitis that is expected to improve quality of life.

**Intervention**

AMT-101: Once daily by mouth in the morning approximately 30 minutes before breakfast for 12 weeks.
Matching placebo: Once daily by mouth in the morning approximately 30 minutes before breakfast for 12 weeks.
The first dose of study treatment will be administered in clinic under the supervision of study personnel and all other doses will be self-administered at home, with details recorded in the subject diary.

**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 where the electrodes are applied 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)

## Inclusion criteria

The study will enroll male and female adult subjects with chronic antibiotic-resistant pouchitis. Inclusion criteria (subjects must meet the following criteria to be randomized into the study):
1. Male and female subjects aged 18 to 75 yrs, inclusive.
2. IPAA for UC completed at least 1 yr prior to screening.
3. Active signs and symptoms of pouchitis, as follows:
a. Modified Pouchitis Disease Activity Index (mPDAI) score >= 5, and,
b. Increased stool frequency, defined as 3 more stools per day above *normal* (after IPAA) and an absolute total of >= 6 stools per day.
*Increased stool frequency* is calculated as the difference between *Normal* and *Screening stool frequency.
*Normal* is the stool frequency achieved post-IPAA when the subject*s bowel function was most settled. This typically occurs approximately 1 year after IPAA and should be supported by documentation in the subject*s medical records. If stool frequency never normalized after IPAA, consult with the Medical Monitor to determine if pre-IPAA stool frequency is appropriate.
To be eligible for the study, subjects must experience 6 or more stools per day, and this value must be 3 or more stools per day greater than the *Normal* value, as defined above.
4. Chronic or recurrent pouchitis, defined by:
a. >= 2 episodes within 1 year prior to or including the screening period treated with antibiotic or other prescription therapy, or,
b. Maintenance antibiotic therapy taken continuously for >=4 weeks immediately prior to the screening endoscopy.
5. Antibiotic-resistant pouchitis, defined as disease remaining active despite at least 2 weeks of antibiotic therapy.
6. Histologic inflammation in the pouch, defined by a Geboes score of 3.1 or greater.
7. Unlikley to conceive.
8. 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.
9. Able to participate fully in all aspects of this clinical trial.

10. Written informed consent must be obtained and fully documented.

## Exclusion criteria

Exclusion criteria (subjects who meet any of the following criteria are not eligible for participation in the study):
1. Known Crohn*s disease (CD) or suspected CD of the pouch, defined as complex perianal/pouch fistula and/or extensive length of pre-pouch ileitis with deep ulceration.
2. Diagnosed or suspected irritable pouch syndrome (IPS).
3. Isolated or predominant cuffitis.
4. Mechanical complications of the pouch such as stricture or fistula(e) that preclude evaluation of the pouch and terminal ileum.
5. Fecal incontinence due to anal sphincter dysfunction.
6. Pelvic sepsis within 12 months prior to screening.
7. Planned surgery for UC, or any other elective surgery within the time frame of the study.
8. Diverting stoma.
9. Current bacterial or parasitic pathogenic enteric infection, including Clostridium difficile; known infection with hepatitis B or C virus; known infection with human immunodeficiency virus; infection requiring hospitalization or intravenous 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.
10. A positive diagnostic tuberculosis (TB) test at screening (defined as a positive QuantiFERON test).
11. Prior biologic use restrictions and exclusions:
a. No more than 60% of enrolled subjects in Phase 2 and no more than 25% of enrolled subjects in Phase 3 may have prior failure of any biologics for pouchitis.
b. Subjects who have used prior biologic therapies must have discontinued within 12 weeks or 5 half-lives of screening (or within 4 weeks if drug levels are undetectable).
12. Use of any of the following prohibited therapies, except under the stated conditions (if applicable):
a. Opioids within 4 weeks prior to screening.
b. Chronic use (>4 weeks of continuous use prior to screening) of nonsteroidal anti-inflammatory drugs, except for chronic use of low-dose 81 mg aspirin.
c. Oral 5-aminosalicylate (5-ASA), unless the dose is <= 4.8 g/day and has been stable for at least 4 weeks prior to screening.
d. Oral budesonide within 6 weeks of screening.
e. Other oral corticosteroids at daily doses > 20 mg prednisone or equivalent, or who started oral corticosteroids within 6 weeks prior to screening; stable doses <= 20 mg prednisone or equivalent for at least 4 weeks prior to screening

are permitted.
f. Any rectal compounds.
g. Immunosuppresant therapy (azathioprine, 6-mercaptopurine, methotrexate, cyclosporin) within 8 weeks prior to screening.
h. Fecal transplant within 12 weeks prior to screening.
i. Live virus vaccination within 1 month prior to screening.
j. Any investigational therapy within 4 weeks prior to screening.
13. Diagnosed with any immune deficiency.
14. History of malignancy, except for basal cell carcinoma, nonmetastatic squamous cell carcinoma of the skin, or prior malignancy with curative therapy completed at least 5 years prior to screening and no recurrence.
15. Clinically meaningful laboratory abnormalities at screening that would affect subject safety, as judged by the investigator from local testing.
16. A concurrent, clinically significant, serious, unstable, or uncontrolled underlying cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitoruinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, might confound study results, pose additional risk to the subject, or interfere with the subject*s ability to participate fully in the study.
17. 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.
18. Pregnant or lactating females.
19. Any surgical procedure requiring general anesthesia within 1 month prior to screening, or planned elective surgery during the study.
20. 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.
21. Concurrent participation in any other interventional study or received any investigational therapy within 1 month prior to screening.
22. Previous exposure to AMT-101.
23. A known hypersensitivity to AMT-101 or its excipients.

# Study design

## Design

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

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

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 07-12-2021 |
| Enrollment: | 12 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | AMT-101 |
| Generic name: | AMT-101 |

## Ethics review

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|---|---|
| Approved WMO Date: | 08-10-2020 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 04-01-2021 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 10-05-2021 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 23-05-2021 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 24-06-2021 |

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|---|---|
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 29-06-2021 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 10-03-2022 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 21-03-2022 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |

# 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 | EUCTR2020-000048-73-NL |
| CCMO | NL75187.028.20 |