# A randomized, double-blind, placebo-controlled, multicenter, phase 2a study to evaluate the safety, tolerability, and early proof of concept of TAK-018 for the prevention of postoperative Crohn*s disease recurrence.

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Primary Objective:to assess the safety and tolerability of TAK-018 in postoperative subjects with CD afterlaparoscopic ileocecal resection with primary anastomosis.Secondary Objectives:to evaluate the impact of TAK-018 on intestinal inflammation...

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| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Gastrointestinal inflammatory conditions |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON48150

**Source**
ToetsingOnline

**Brief title**
TAK-018-2001

### Condition

- Gastrointestinal inflammatory conditions

**Synonym**
Crohn's disease, Inflammatory bowel disease

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Takeda
**Source(s) of monetary or material Support:** Sponsor: Takeda

## Intervention

**Keyword:** Phase 2a study, postoperative Crohn's disease recurrence, TAK-018

## Outcome measures

### Primary outcome

Primary Objective: To assess the safety and tolerability of TAK-018 in postoperative subjects with CD after laparoscopic ileocecal resection with primary anastomosis.

### Secondary outcome

Secondary Objectives: To evaluate the impact of TAK-018 (ie, early proof of concept) on intestinal inflammation based on endoscopic recurrence and serial fecal calprotectin measurements. To characterize the PK of TAK-018 in postoperative subjects with CD after laparoscopic ileocecal resection with primary anastomosis.

# Study description

### Background summary

Crohn*s disease (CD) is a chronic, relapsing inflammatory disease of the gastrointestinal tract with no known cure. Its incidence globally is on the rise, reaching 20 per 100,000 person-years in Western countries. A third of patients with CD will require a major abdominal resection within 5 years after diagnosis, and up to 60% of patients within a decade. Up to 70% of patients who undergo resection develop postoperative endoscopic recurrence within 1 year, and one third need repeat surgery within 10 years. The

pathophysiology of CD relies on a complex interaction of host genetics, the microbiome and inflammatory responses. Significant human gut commensal community functional breakdown or dysbiosis is observed in CD. Genome-wide association study (GWAS) results in CD underscore the theme of aberrant host-microbiome interactions, pecifically ineffective pathogen clearance from the mucosa because of genetic defects in bacterial pattern recognition (Nod2) and in autophagy. Chronic immune stimulation by bacterial antigens is well established as patients with CD have detectable antibodies to bacterial cell constituents such
as OmpC and Flagellin, with higher titers of antibodies being associated with a more severe *complicated* disease phenotype. The question that arises is whether immune recognition of proteobacteria is causative for inflammation in CD or is it a secondary phenomenon due to mucosal barrier disruption? Recent evidence shows that antibacterial antibodies can be detected in serum of patients with CD several years before clinical symptoms and diagnosis, supporting the hypothesis of an initial bacterial insult that triggers inflammation. In addition, metagenomic approaches coupled with classic culture microbiology from mucosal biopsies from the terminal ileum of patients with Crohn*s ileitis support the case for proteobacteria as pathobionts in CD. The specific association of Escherichia coli with invasive properties, termed adherent-invasive Escherichia coli (AIEC), with CD was first reported by Darfeuille-Michaud et al. Since then, AIEC have been isolated from multiple independent studies involving adult and pediatric patients with CD. Using the multi-component definition of Darfeuille-Michaud et al, the reported prevalence of AIEC in the literature varies from approximately 36% to over 90% in patients with CD when evaluating mucosa-associated and intracellular E coli. AIEC are distinct from other strains of E coli because they show non-classic virulence factors of adherence and invasion. In particular, AIEC are able to survive and replicate in intestinal epithelial cells and macrophages, thereby stimulating the production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-*). The interaction between AIEC and the intestinal epithelial cells is primarily mediated by the FimH adhesin located at the tip of type 1 pili present on the bacterial surface. Although type 1 pili genes are present in the genomes of all E coli, AIEC strains specifically express FimH adhesin and variants that allow them to more efficiently bind to mannose. These mechanisms set the stage for a selective over-colonization of the epithelium by AIEC and subsequent biofilm formation. The type 1 pili interact with glycoproteins such as carcinoembryonic antigen-related cell-adhesion molecule 6 (CEACAM6) on intestinal epithelial cells, TLR4 on immune cells, and GP2 on intestinal M cells in a mannose-dependent manner. CEACAM6 and TLR4 receptors are upregulated by inflammatory cytokines in patients with CD with ileal disease. The binding of FimH to TLR4 induces the production of TNF-*, IL-6 and IL-8 in the gut, independently of LPS. Additionally, FimH binding
to GP2 on the surface of M cells in the Peyer*s patches allow AIEC to enter into the lamina propria. The subsequent phagocytosis of the AIEC by the macrophages further contributes to the chronic production of TNF-*. A vicious cycle of proinflammatory cytokine release is produced by the

TNF*-driven overexpression of CEACAM6 and increase in M-cell development. Thus, FimH appears as a critical factor both in the production of pro-inflammatory cytokines from the gut epithelium and in the invasion of the lamina propria.

**Study objective**

Primary Objective:

to assess the safety and tolerability of TAK-018 in postoperative subjects with CD after
laparoscopic ileocecal resection with primary anastomosis.

Secondary Objectives:

to evaluate the impact of TAK-018 on intestinal inflammation based on endoscopic recurrence and serial fecal calprotectin measures.
to characterize the pharmacokinetics (PK) of TAK-018 in postoperative subjects with CD
after laparoscopic ileocecal resection with primary anastomosis.

**Study design**

This is a randomized, placebo-controlled, double-blind study of TAK-018 (previously known as EB8018) in a total of 45 to 75 postoperative subjects with Crohn*s disease (CD) after laparoscopic ileocecal resection with primary anastomosis. All eligible subjects will be randomized 1:1:1 to either TAK-018 low dose (0.30 g taken twice daily [BID]), TAK-018 high dose (1.5 g taken BID), or placebo (BID) for a 12-week treatment period. Subjects will receive the first dose of study drug on Day 1 (D1, within 72 hours after surgery) and take it twice daily immediately after a meal (ie, breakfast and dinner) with water, approximately 8 to12 hours apart. Subjects will have on-treatment clinic visits at Week 3 (W3), Week 6 (W6), and Week 12 (W12), and follow-up clinic visits (off-treatment) at Week 18 (W18) and Week 26 (W26), and a Week 30 (W30) phone call for safety follow-up. Blood samples will be collected presurgery and after first and multiple doses at all clinic visits during the treatment period to characterize disease progression, response to study drug, safety parameters, and the pharmacokinetics (PK) of TAK-018. Subjects will also collect stool samples before surgery during the screening period and at W3, W6, W12, W18, and W26. Fecal calprotectin will be measured before surgery during the screening period and in every stool collection. Endoscopic assessments will be performed at the end of the 12-week treatment period (W12) and repeated at W26. Intestinal resection tissue will be collected at surgery and biopsies will be performed at W12 and W26. Subjects who relapse clinically or endoscopically (Rutgeerts score *i2) during the study will discontinue study drug, receive institutional standard of care in use at their investigational site, attend an early termination visit 30 days after last dose of study drug, and be

discontinued from the study. The end of study will occur at W30, via telephone call, for safety follow-up.

### Intervention

As most patients with Crohn's Disease (CD) eventually require an intestinal resection, postoperative recurrence poses a significant burden to the CD population. Disease recurrence on the histological level is observed within days after ileocolonic anastomosis. Most CD therapies, such as probiotics, aminosalicylates, thiopurines, steroids, antibiotics, and biologics, have yielded either negative or equivocal results in terms of preventing relapse.

Because of its unique mechanism of action (MOA), TAK-018 blocks the pathobiont entry underlying chronic inflammation and bowel wall damage observed in patients with CD. This MOA is distinct from the conventional approach of neutralizing inflammatory mediators such as TNF-alpha and IL-23, thereby allowing patients with CD to maintain remission without lifelong immune suppression. The purpose of this phase 2a, randomized, multicenter, double-blind study is to evaluate the safety, tolerability, and early proof of concept of TAK-018 for the prevention of postoperative CD recurrence.

### Study burden and risks

Please see the schedule of events in the protocol for a detailed overview of visits, tests and examinations paragraph 9.3. The risks associated with this study are described in the ICF, paragraph 6.

## Contacts

**Public**
Takeda

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Male or female subjects aged *18 years or local legal age at signing of informed consent
2. Subject has a documented diagnosis of CD confirmed by endoscopic biopsy before resection or by tissue obtained
at resection.
3. Subject undergoes laparoscopic ileocecal resection with primary anastomosis within 72 hours before
randomization (D1). Confirmation that no active disease has been left behind after resection will be based on the
surgeon*s documentation in the operative report.
4. Postoperative discontinuation of all concomitant medications related specifically to the treatment of CD. This
includes anti-tumor necrosis factor and anti-integrin therapy, anti-IL 12/23, thiopurines and other
immunomodulators, steroids, 5-aminosalicylates, and antibiotics.
5. Subject has resumed oral intake and is capable of swallowing tablets within 72 hours after surgery.
6. If female of child-bearing potential, subject must agree to comply with the contraception requirements.
7. A male subject who is nonsterilized and sexually active with a female partner of child-bearing potential must
agree to comply with protocol-defined contraception requirements.

## Exclusion criteria

1. Subject has active perianal CD.
2. Subject has had >3 previous surgical procedures for CD.

3. Subject has macroscopically active CD not resected at the time of surgery.
4. The extent of small bowel resected exceeds 100 cm or the subject is considered at risk for short bowel syndrome.
5. Subject has any significant intraoperative or postoperative complications such as anastomotic leak, surgical site
infection, or inability to tolerate oral intake.
6. Subject is unable or unwilling to undergo or has contraindications to ileocolonoscopic procedures as assessed by
the investigator.
7. Subject has inadequate renal and hepatic function postsurgery and before the first dose of study drug on the basis
of laboratory parameters including: total bilirubin >1.5× the institutional upper limit of normal (ULN) unless
subject has known Gilbert*s syndrome that can explain the elevation of bilirubin, serum alanine aminotransferase
>3× the institutional ULN, creatinine >1.5× the institutional ULN or estimated creatinine clearance
<50 mL/minute/1.73 m2 for subjects with serum creatinine concentrations above institutional limits.

# 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) |
| Control: | Placebo |
| Primary purpose: | Prevention |

## Recruitment

NL

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|---|---|
| Recruitment status: | Will not start |
| Enrollment: | 3 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | TAK-018 |
| Generic name: | TAK-018 |

## Ethics review

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|---|---|
| Approved WMO Date: | 17-09-2019 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 06-03-2020 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 23-04-2020 |
| 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 | EUCTR2019-000886-19-NL |

| Register | ID |
| --- | --- |
| Other | IRAS nr: 266345 / NCT nr: NCT03943446 |
| CCMO | NL71098.018.19 |