# Pharmacokinetics and Pharmacodynamic Biomarkers of Janus Kinase Inhibitor Therapy in Patients With Ulcerative Colitis (PROPHETIC Study)

Published: 21-02-2020
Last updated: 08-04-2024

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Gastrointestinal conditions NEC |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON54935

**Source**
ToetsingOnline

**Brief title**
PROPHETIC Study

### Condition

- Gastrointestinal conditions NEC

**Synonym**
inflammatory bowel disease, Ulcerative colitis

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Alimentiv B.V.

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

## Intervention

**Keyword:** Inflammatoire bowel disease, PD biomarkers, PK biomarkers, Ulcerative Colitis

## Outcome measures

### Primary outcome

See objectives

### Secondary outcome

Not applicable

# Study description

### Background summary

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by inappropriate mucosal immune responses. Janus kinase (JAK) proteins (JAK1, JAK2, JAK3) and tyrosine kinase 2 (Tyk2) are implicated in inflammatory pathways through associations with intracellular domains of surface cytokine receptors. JAK1 and JAK3 are associated with many T cell-derived cytokines and have been linked to IBD. JAKs phosphorylate the signal transducers and activators of transcription (STATs) to modulate gene expression. At least 7 different STATs are involved in the JAK-STAT pathway, but STAT3 appears to be the most strongly phosphorylated in IBD, based on studies in a murine model and patients with IBD

Janus kinase inhibitors (JAKi) are a new class of small molecule drugs that act on 1 or more JAK receptors and disrupt phosphorylation-mediated activation of STAT proteins, ultimately disrupting gene expression that drive immune cell activation and proinflammatory cytokine response (including interleukin [IL]-6, IL-23, IL-13, IL-15, and interferon [IFN]*). Therefore, JAKi disruption of immune pathways can potentially lead to higher risk of toxicity and/or adverse events (AEs) as evidenced by an increased risk of infections among patients with rheumatoid arthritis or psoriasis treated with JAKi.6
Currently, the only JAKi approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with active UC is tofacitinib. Other small molecules such as the JAK1 selective inhibitors (filgotinib, upadacitinib) and the pan-JAK inhibitor (TD-1473) are currently

under development for UC.

## Study objective

The objectives of this study, in patients with moderately to severely active UC who are administered JAKi SOC therapy are to evaluate the following (ranked according to priority), both for JAKi as a class of drugs and for each individual JAKi:
1. Identify predictive fecal, blood, and tissue biomarkers (at baseline) associated with change from baseline in Ulcerative Colitis 100 Index (UC-100) score following SOC induction therapy and at Week 24.
2. Identify PD fecal, blood, and tissue biomarkers (change in variables from baseline to Weeks 4 and/or end of SOC induction therapy) associated with change from baseline in UC-100 score following SOC induction therapy and at Week 24.
3. Identify a fecal, blood, and tissue biomarker signature as a surrogate measure for change from baseline in UC-100 score following SOC induction therapy and at Week 24.
4. Identify whether colonic tissue pSTAT following SOC induction therapy and/or at Week 24, correlates with change from baseline in UC-100 score following SOC induction therapy and/or at Week 24, respectively.
5. Determine the time-concentration profile of JAKi at steady state in stool, serum, and tissue samples.
6. Evaluate correlation of exposure of JAKi between stool, serum, and tissue samples following SOC induction therapy and at Week 24.
7. Explore the exposure-response relationship of JAKi with exposure measured in stool, serum, and tissue samples and response defined as tissue PD biomarkers following SOC induction therapy and at Week 24.
8. Develop an exposure-response model of JAKi to characterize the relationships between local and systemic drug exposure and clinical, endoscopic, histologic, or biologic response to therapy.
9. Identify potential demographic and disease factors affecting the most relevant JAKi exposure-response relationships and determine target threshold of systemic exposure associated with relevant clinical, endoscopic, histologic, and/or biologic outcomes following
SOC induction therapy and at Week 24.
10. Evaluate long-term hospitalization rates, surgery rates, and corticosteroid use up to 2 years after initiation of JAKi therapy and identify baseline or early biomarker signatures associated with these long-term healthcare resource use (HRU) outcomes.
11. Measure ADRs, and clinical, endoscopic, and histologic response and remission rates to JAKi in a *real-world* population.

## Study design

This is an open-label prospective cohort study of JAKi therapy responsiveness in patients with moderately to severely active UC. A convenience sample of

approximately 40 subjects per JAKi therapy will be enrolled across study centers in North America and Europe. This study will consist of 2 parts, including an initial 24-week SOC treatment period with fecal, blood, and tissue sampling (Part 1) and a longer-term observational follow-up period for up to 2 years (Part 2)

**Study burden and risks**

This study will investigate how the JAKi therapy works in the body in patients with ulcerative colitis. We also would like to increase the general knowledge of the drug and the disease. Biopsies, blood and stools will be collected to investigate whether the biomarkers will change or are affected by JAKi. All this information will contribute to the development for the treatment of patients with ulcerative colitis.

# 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

1. 18 years of age or older.
2. Male or nonpregnant, nonlactating females.
3. Diagnosis of UC for at least 3 months prior to screening.
4. Moderately to severely active UC (total MCS * 6), with objective evidence of inflammation defined by a Mayo endoscopic subscore (MES) * 2 and disease extending > 15 cm from the anal verge.
5. Physician plans to administer JAKi for at least 8 weeks of induction therapy as part of SOC.
6. Documentation of a negative test result for latent tuberculosis within the last 12 months, or according to routine clinical practice.
7. Able to participate fully in all aspects of this clinical trial, including collection of tissue biopsies.
8. Written informed consent must be obtained and documented.

## Exclusion criteria

1. Diagnosis of CD or indeterminate colitis.
2. An active, serious infection, including localized infections.
3. Concomitant administration of biological therapies for UC or potent immunosuppressants,
such as azathioprine and cyclosporine. Subjects with previous exposure to these treatments
should undergo an appropriate washout period according to local practice prior to starting
JAKi, in keeping with routine clinical practice.
4. Hematology laboratory results (e.g., absolute lymphocyte count, absolute neutrophil count, and
hemoglobin levels) that contraindicate the product label.
5. Interval between live vaccinations and initiation of JAKi therapy should be in accordance with
current vaccination guidelines regarding immunosuppressive agents.
6. Serious underlying disease other than UC that in the opinion of the investigator may interfere
with the subject*s ability to participate fully in the study.

# Study design

## Design

**Study type:** Observational invasive

| | |
|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 25-08-2020 |
| Enrollment: | 13 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Jyseleca |
| Generic name: | Filgotinib |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Rinvoq |
| Generic name: | Upadacitinib |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Xeljanz |
| Generic name: | Tofacitinib |
| Registration: | Yes - NL intended use |

# Ethics review

Approved WMO

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|---|---|
| Date: | 21-02-2020 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |

Approved WMO

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|---|---|
| Date: | 04-05-2020 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 28-07-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 17-08-2021 |
| 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 | EUCTR2019-003780-21-NL |
| ClinicalTrials.gov | NCT04576000 |
| CCMO | NL71601.018.20 |