

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125289Orig1s157

Trade Name: SIMPONI

Generic or Proper Name: golimumab

Sponsor: Janssen Biotech, Inc.

Approval Date: October 7, 2025

Indication:

SIMPONI is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

- adult patients with moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate
- adult patients with active psoriatic arthritis (PsA) alone, or in combination with methotrexate
- adult patients with active ankylosing spondylitis (AS)
- adult and pediatric patients weighing at least 15 kg with moderate to severely active ulcerative colitis (UC)

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APPROVAL LETTER

BLA 125289/s-157

**SUPPLEMENT APPROVAL
FULLFILLMENT OF POSTMARKETING COMMITMENT**

Janssen Biotech, Inc.
Attention: Michelle Godin, MS, RAC
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Michelle Godin:

Please refer to your supplemental biologics license application (sBLA) received December 12, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for Simponi (golimumab) injection.

This Prior Approval supplemental biologics license application provides for the treatment of pediatric patients weighing at least 15 kg with moderately to severely active ulcerative colitis.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions listed below and reflected in the enclosed labeling:

- Updated the revision date to the approval month at the end of the Medication Guide and Instructions for Use for the prefilled syringe.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,¹ that is identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your supplement application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING COMMITMENT

We have received your submission dated December 12, 2024, containing the final report for the following postmarketing commitment listed in the May 15, 2013, approval letter for BLA 125289 supplements 77, 78 and 79.

- 2909-5 Conduct a study to evaluate the effectiveness and safety of Simponi (golimumab) in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis. The study should be designed to establish that the dose regimen(s) of Simponi (golimumab) identified in PMC#4 is (are) effective and safe for induction treatment, as well as for continued treatment after induction. Pharmacokinetic measurements should be conducted for exposure-response analysis. Collect serum samples for immunogenicity testing and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy and safety.

We have reviewed your submission and conclude that the above commitment was fulfilled.

We remind you that there is a postmarketing requirement listed in the May 15, 2013, approval letter that is still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 601.12(f)(4)]. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

If you have any questions, contact Andrew Chi, PharmD, Regulatory Project Manager, at (301) 796-8597 or email at andrew.chi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tara A. Altepeter, MD
Associate Director for Therapeutic Review
Division of Gastroenterology
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

³ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Medication Guide
 - Instructions for Use

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TARA A ALTEPETER
10/07/2025 11:27:19 AM

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SIMPONI safely and effectively. See full prescribing information for SIMPONI.

SIMPONI® (golimumab) injection, for subcutaneous use
Initial U.S. Approval: 2009

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal (such as histoplasmosis), and other opportunistic infections have occurred in patients receiving SIMPONI (5.1)
- Discontinue SIMPONI if a patient develops a serious infection or sepsis (5.1)
- Perform test for latent TB; if positive, start treatment for TB prior to starting SIMPONI (5.1)
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1)
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI is a member (5.2)

RECENT MAJOR CHANGES	
Indications and Usage (1.4)	10/2025
Dosage and Administration (2.1, 2.3, 2.4)	10/2025
Warnings and Precautions (5.11)	10/2025

- INDICATIONS AND USAGE**
- SIMPONI is a tumor necrosis factor (TNF) blocker indicated for the treatment of:
- adult patients with moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate (1.1)
 - adult patients with active psoriatic arthritis (PsA) alone, or in combination with methotrexate (1.2)
 - adult patients with active ankylosing spondylitis (AS) (1.3)
 - adult and pediatric patients weighing at least 15 kg with moderate to severely active ulcerative colitis (UC) (1.4)

- DOSAGE AND ADMINISTRATION**
- **RA, PsA, and AS:** 50 mg administered by subcutaneous injection once a month (2.2)
 - **UC:** The recommended dosage and administration by subcutaneous injection in adults and pediatric patients weighing at least 15 kg is shown in the table (2.3)

Recommended Dosage			
Weight for Patients with UC	Week 0	Week 2	Week 6 and every 4 weeks thereafter
Adults and pediatric patients 40 kg and greater	200 mg	100 mg	100 mg
Pediatric patients at least 15 kg to less than 40 kg	100 mg	50 mg	50 mg

- DOSAGE FORMS AND STRENGTHS**
- Injection (3):
- 50 mg/0.5 mL in a single-dose prefilled syringe or single-dose prefilled SmartJect® autoinjector
 - 100 mg/mL in a single-dose prefilled syringe or single-dose prefilled SmartJect® autoinjector

CONTRAINDICATIONS

None (4)

- WARNINGS AND PRECAUTIONS**
- Serious Infections: Do not start SIMPONI during an active infection. If an infection develops, monitor carefully, and stop SIMPONI if infection becomes serious (5.1)
 - Invasive Fungal Infections: For patients who develop a systemic illness on SIMPONI, consider empiric antifungal therapy for those who reside in or travel to regions where mycoses are endemic (5.1)
 - Malignancies: Incidence of lymphoma was greater than in the general U.S. population. Cases of other malignancies have been observed among patients receiving TNF blockers (5.2)
 - Congestive Heart Failure: Worsening, or new onset, may occur. Stop SIMPONI if new or worsening symptoms occur (5.3)
 - Demyelinating Disorders: Exacerbation or new onset may occur (5.4)
 - Hepatitis B Reactivation: Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop SIMPONI and begin antiviral therapy (5.5)
 - Lupus-like Syndrome: Discontinue SIMPONI if symptoms develop (5.6)
 - Hypersensitivity Reactions: Serious systemic hypersensitivity reactions including anaphylaxis may occur (5.12)

ADVERSE REACTIONS

Most common adverse reactions in adults (incidence > 5%) are upper respiratory tract infection, nasopharyngitis, injection site reactions (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- DRUG INTERACTIONS**
- Abatacept: Increased risk of serious infection (5.1, 5.7, 7.2)
 - Anakinra: Increased risk of serious infection (5.1, 5.8, 7.2)
 - Live vaccines/therapeutic infectious agents: Avoid use with SIMPONI (5.11, 7.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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 - 1.3 Ankylosing Spondylitis
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with SIMPONI are at increased risk for developing serious infections that may lead to hospitalization or death [see *Warnings and Precautions (5.1)*]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue SIMPONI if a patient develops a serious infection.

Reported infections with TNF blockers, of which SIMPONI is a member, include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Test patients for latent tuberculosis before SIMPONI use and during therapy. Initiate treatment for latent TB prior to SIMPONI use.
- Invasive fungal infections including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric antifungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.

Consider the risks and benefits of treatment with SIMPONI prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with SIMPONI, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy [see *Warnings and Precautions (5.1)*].

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI is a member [see *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

SIMPONI, in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis.

1.2 Psoriatic Arthritis

SIMPONI, alone or in combination with methotrexate, is indicated for the treatment of adult patients with active psoriatic arthritis.

1.3 Ankylosing Spondylitis

SIMPONI is indicated for the treatment of adult patients with active ankylosing spondylitis.

1.4 Ulcerative Colitis

SIMPONI is indicated for the treatment of adults and pediatric patients weighing at least 15 kg with moderately to severely active ulcerative colitis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Evaluations and Immunizations Before Initiating SIMPONI

Prior to initiating treatment with SIMPONI:

- Evaluate patients for active tuberculosis and test for latent infection [*see Warnings and Precautions (5.1)*].
- Test patients for hepatitis B viral infection.
- If possible, complete all age-appropriate vaccinations according to current immunization guidelines [*see Warnings and Precautions (5.11)*].

2.2 Recommended Dosage for Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis

The recommended SIMPONI dosage in adults is 50 mg administered by subcutaneous injection once a month.

For patients with rheumatoid arthritis (RA), SIMPONI should be given in combination with methotrexate and for patients with psoriatic arthritis (PsA) or ankylosing spondylitis (AS), SIMPONI may be given with or without methotrexate or other nonbiologic Disease-Modifying Antirheumatic Drugs (DMARDs). For patients with RA, PsA, or AS, corticosteroids, non-biologic DMARDs, and/or NSAIDs may be continued during treatment with SIMPONI.

2.3 Recommended Dosage for Moderately to Severely Active Ulcerative Colitis in Adults and Pediatric Patients Weighing at least 15 kg

The recommended dosage is shown in Table 1.

Table 1: Recommended Subcutaneous Dosage for Adults and Pediatric Patients Weighing at least 15 kg with Moderately to Severely Active Ulcerative Colitis

Weight for Patients with UC	Recommended Dosage of SIMPONI		
	Week 0	Week 2	Week 6 and every 4 weeks thereafter
Adults and pediatric patients 40 kg and greater	200 mg	100 mg	100 mg
Pediatric patients at least 15 kg to less than 40 kg	100 mg	50 mg	50 mg

2.4 Preparation and Administration Instructions

SIMPONI is intended for use under the guidance and supervision of a healthcare provider after proper training in subcutaneous injection technique. Patients may self-inject with SIMPONI if a physician determines that it is appropriate. Instruct patients to follow the directions provided in the Instructions for Use.

SIMPONI Prefilled Syringe

- Adult and pediatric patients 12 years of age and older may self-inject with SIMPONI prefilled syringe.

SIMPONI SmartJect® Autoinjector

- Adult patients may self-inject with SIMPONI SmartJect® autoinjector.
- Use of the SmartJect® autoinjector for pediatric self-administration has not been evaluated.
- To ensure proper use, allow the prefilled syringe or autoinjector to sit at room temperature outside the carton for at least 30 minutes prior to subcutaneous injection. Do not warm SIMPONI in any other way.
- Prior to administration, visually inspect the solution for particles and discoloration through the viewing window. SIMPONI is clear to slightly opalescent and colorless to light yellow. Do not use SIMPONI, if the solution is discolored, or cloudy, or if foreign particles are present.
- Do not use any leftover product remaining in the prefilled syringe or prefilled autoinjector.
- Instruct patients sensitive to latex not to handle the needle cover on the prefilled syringe or the needle cover of the prefilled syringe within the autoinjector cap because it contains dry natural rubber (a derivative of latex).
- At the time of dosing, if multiple injections are required, administer the injections at different sites on the body.
- Rotate injection sites and never give injections into areas where the skin is tender, bruised, red, or hard.
- If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/0.5 mL and 100 mg/mL clear to slightly opalescent, colorless to light yellow solution in a single-dose prefilled syringe or single-dose SmartJect® autoinjector.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with SIMPONI are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease. The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMPONI and these biologic products is not recommended [*see Warnings and Precautions (5.6, 5.7) and Drug Interactions (7.2)*].

Treatment with SIMPONI should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating SIMPONI in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with SIMPONI. Discontinue SIMPONI if a patient develops a serious infection, an opportunistic infection, or sepsis. For a patient who develops a new infection during treatment with SIMPONI, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, initiate appropriate antimicrobial therapy, and closely monitor them.

Serious Infection in Clinical Trials

In controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, serious infections were observed in 1.4% of SIMPONI-treated patients and 1.3% of control-treated patients. In the controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, the incidence of serious infections per 100 patient-years of follow-up was 5.7 (95% CI: 3.8, 8.2) for the SIMPONI group and 4.2 (95% CI: 1.8, 8.2) for the placebo group. In the controlled Phase 2/3 trial through Week 6 of SIMPONI induction in UC, the incidence of serious infections in SIMPONI 200/100 mg-treated patients was similar to the incidence of serious infections in placebo-treated patients. Through Week 60, the incidence of serious infections was similar in patients who received SIMPONI induction and 100 mg during maintenance compared with patients who received SIMPONI induction and placebo during the maintenance portion of the UC trial. Serious infections observed in SIMPONI-treated patients included sepsis, pneumonia, cellulitis, abscess, tuberculosis, invasive fungal infections, and hepatitis B infection.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF blockers, including patients who have previously received treatment for latent or active tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating SIMPONI and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blockers has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating SIMPONI, assess if treatment for latent tuberculosis is needed; an induration of 5 mm or greater is a positive tuberculin skin test, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of SIMPONI in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Cases of active tuberculosis have occurred in patients treated with SIMPONI during and after treatment for latent tuberculosis. Monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

Consider tuberculosis in the differential diagnosis in patients who develop a new infection during SIMPONI treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

In the controlled and uncontrolled portions of the Phase 2 RA and Phase 3 RA, PsA, and AS trials, the incidence of active TB was 0.23 and 0 per 100 patient-years in 2347 SIMPONI-treated patients and 674 placebo-treated patients, respectively. Cases of TB included pulmonary and extrapulmonary TB. The overwhelming majority of the TB cases occurred in countries with a high incidence rate of TB. In the controlled Phase 2/3 trial of SIMPONI induction through Week 6 in UC, no cases of TB were observed in SIMPONI 200/100 mg-treated patients or in placebo-treated patients. Through Week 60, the incidence per 100 patient-years of TB in patients who received SIMPONI induction and 100 mg during the maintenance portion of the UC trial was 0.52 (95% CI: 0.11, 1.53). One case of TB was observed in the placebo maintenance group in a patient who received SIMPONI intravenous (IV) induction.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Consider appropriate empiric antifungal therapy, and take into account both the risk for severe fungal infection and the risks of antifungal therapy while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

5.2 Malignancies

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy $\leq$ 18 years of age), of which SIMPONI is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression, and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF-blocker

therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

The risks and benefits of TNF-blocker treatment, including SIMPONI, should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated nonmelanoma skin cancer (NMSC) or when considering continuing a TNF-blocker in patients who develop a malignancy.

In the controlled portions of clinical trials of TNF blockers, including SIMPONI, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with patients in the control groups. During the controlled portions of the Phase 2 trials in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI group compared with an incidence of 0 (95% CI: 0, 0.96) in the placebo group. In the controlled and uncontrolled portions of these clinical trials in 2347 SIMPONI-treated patients with a median follow-up of 1.4 years, the incidence of lymphoma was 3.8-fold higher than expected in the general U.S. population according to the 1964-2004 data from SEER database (adjusted for age, gender, and race). Through Week 60 of the UC trials, there were no cases of lymphoma with SIMPONI. Patients with RA and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with TNF-blocker use, including SIMPONI, in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Rare postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blocking agents. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Nearly all of the reported TNF blocker associated cases have occurred in patients with Crohn's disease or ulcerative colitis. The majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine (AZA) or 6-mercaptopurine (6-MP) concomitantly with a TNF blocker at or prior to diagnosis. The potential risk with the combination of AZA or 6-MP and SIMPONI should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF blockers cannot be excluded.

During the controlled portions of the Phase 2 trial in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of malignancies other than lymphoma per 100 patient-years of follow-up was not elevated in the combined SIMPONI group compared with the placebo group. In the controlled and uncontrolled portions of these trials, the incidence of malignancies, other than lymphoma, in SIMPONI-treated patients was similar to that expected in the general U.S. population according to the 1969-2004 SEER database (adjusted for age, gender, and race). In the 6-week placebo-controlled portions of the SIMPONI Phase 2/3 clinical trials in UC, the incidence of non-lymphoma malignancies (excluding nonmelanoma skin cancer) was similar between the SIMPONI and the placebo group. Through Week 60, the incidence of non-lymphoma malignancies (excluding nonmelanoma skin cancer) was similar to the general U.S. population according to the 1969-2004 SEER database (adjusted for age, gender, and race). Short follow-up periods, such as those of one year or less in the studies above, may not adequately reflect the true incidence of malignancies.

It is not known if SIMPONI treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In patients with newly diagnosed dysplasia treated with SIMPONI, the risks and benefits to the individual patient must be carefully reviewed and consideration should be given to whether therapy should be continued.

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocking agents, including SIMPONI. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

In controlled trials of other TNF blockers in patients at higher risk for malignancies (e.g., patients with chronic obstructive pulmonary disease [COPD], patients with Wegener's granulomatosis treated with concomitant cyclophosphamide) a greater portion of malignancies occurred in the TNF-blocker group compared to the controlled group. In an exploratory 1-year clinical trial evaluating the use of 50 mg, 100 mg, and 200 mg of SIMPONI in 309 patients with severe persistent asthma, 6 patients developed malignancies other than NMSC in the SIMPONI groups compared to none in the control group. Three of the 6 patients were in the 200 mg SIMPONI group.

5.3 Congestive Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including SIMPONI. Some cases had a fatal outcome. In several exploratory trials of other TNF blockers in the treatment of CHF, there were greater proportions of TNF-blocker-treated patients who had CHF exacerbations requiring hospitalization or increased mortality. SIMPONI has not been studied in patients with a history of CHF and SIMPONI should be used with caution in patients with CHF. If a decision is made to administer SIMPONI to patients with CHF, these patients should be closely monitored during therapy, and SIMPONI should be discontinued if new or worsening symptoms of CHF appear.

5.4 Demyelinating Disorders

Use of TNF blockers, of which SIMPONI is a member, has been associated with rare cases of new onset or exacerbation of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS) and peripheral demyelinating disorders, including Guillain-Barré syndrome. Cases of central demyelination, MS, optic neuritis, and peripheral demyelinating polyneuropathy have rarely been reported in patients treated with SIMPONI [see *Adverse Reactions (6.1)*]. Prescribers should exercise caution in considering the use of TNF blockers, including SIMPONI, in patients with central or peripheral nervous system demyelinating disorders. Discontinuation of SIMPONI should be considered if these disorders develop.

5.5 Hepatitis B Virus Reactivation

The use of TNF blockers including SIMPONI has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e., surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants.

All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF blockers, including SIMPONI, to patients who are carriers of HBV. Adequate data are not available on whether antiviral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF blockers. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blockers after HBV reactivation has been controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blockers in this situation and monitor patients closely.

5.6 Autoimmunity

Treatment with TNF blockers, including SIMPONI, may result in the formation of antinuclear antibodies (ANA) and, rarely, in the development of a lupus-like syndrome [*see Adverse Reactions (6.1)*]. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with SIMPONI, treatment should be discontinued.

5.7 Use with Abatacept

In controlled trials, the concurrent administration of another TNF blocker and abatacept was associated with a greater proportion of serious infections than the use of a TNF blocker alone; and the combination therapy, compared to the use of a TNF blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of TNF blockers, including SIMPONI, and abatacept is not recommended [*see Drug Interactions (7.2)*].

5.8 Use with Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF blocker was associated with a greater portion of serious infections and neutropenia and no additional benefits compared with the TNF-blocker alone. Therefore, the combination of anakinra with TNF blockers, including SIMPONI, is not recommended [*see Drug Interactions (7.2)*].

5.9 Switching Between Biological Disease-Modifying Antirheumatic Drugs

Care should be taken when switching from one biological product to another biological product since overlapping biological activity may further increase the risk of infection.

5.10 Hematologic Cytopenias

There have been reports of pancytopenia, leukopenia, neutropenia, agranulocytosis, aplastic anemia, and thrombocytopenia in patients receiving golimumab. Caution should be exercised when using TNF blockers, including SIMPONI, in patients who have or have had significant cytopenias.

5.11 Vaccinations/Therapeutic Infectious Agents

Live Vaccines

Patients treated with SIMPONI may receive vaccinations, except for live vaccines. In patients receiving anti-TNF therapy, limited data are available on the response to live vaccination, or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections.

If possible, it is recommended that prior to initiating therapy with SIMPONI, pediatric patients be brought up to date with all immunizations in agreement with current immunization guidelines.

Therapeutic Infectious Agents

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with SIMPONI.

Non-live Vaccines

In the Phase 3 PsA trial, after pneumococcal vaccination, a similar proportion of SIMPONI-treated and placebo-treated patients were able to mount an adequate immune response of at least a 2-fold increase in antibody titers to pneumococcal polysaccharide vaccine. In both SIMPONI-treated and placebo-treated patients, the proportions of patients with response to pneumococcal vaccine were lower among patients receiving MTX compared with patients not receiving MTX. The data suggest that SIMPONI does not suppress the humoral immune response to the pneumococcal vaccine.

5.12 Hypersensitivity Reactions

In postmarketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following SIMPONI administration. Some of these reactions occurred after the first administration of SIMPONI. If an anaphylactic or other serious allergic reaction occurs, administration of SIMPONI should be discontinued immediately and appropriate therapy instituted.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections [*see Warnings and Precautions (5.1)*]
- Malignancies [*see Warnings and Precautions (5.2)*]
- Congestive Heart Failure [*see Warnings and Precautions (5.3)*]
- Demyelinating Disorders [*see Warnings and Precautions (5.4)*]
- Hepatitis B Reactivation [*see Warnings and Precautions (5.5)*]
- Autoimmunity [*see Warnings and Precautions (5.6)*]
- Hematologic Cytopenias [*see Warnings and Precautions (5.10)*]
- Hypersensitivity Reactions [*see Warnings and Precautions (5.12)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety data described below are based on:

- Five pooled, randomized, double-blind, controlled Phase 3 trials in patients with RA, PsA, and AS (Trials RA-1, RA-2, RA-3, PsA, and AS) [see *Clinical Studies (14.1, 14.2, and 14.3)*]. These 5 trials included 639 control-treated patients and 1659 SIMPONI-treated patients including 1089 with RA, 292 with PsA, and 278 with AS.
- Three pooled, randomized, double-blind, controlled Phase 2/3 in 1233 SIMPONI-treated adult patients with UC (Trials UC-1, UC-2, and UC-3 (NCT03596645)) [see *Clinical Studies (14.4)*].
- An open-label trial in 69 SIMPONI-treated pediatric patients weighing at least 15 kg with UC (Trial UC-3) (NCT03596645) [see *Clinical Studies (14.5)*].

The proportion of adult patients who discontinued treatment due to adverse reactions in the controlled Phase 3 trials through Week 16 in RA, PsA and AS was 2% for SIMPONI-treated patients and 3% for placebo-treated patients. The most common adverse reactions leading to discontinuation of SIMPONI in the controlled Phase 3 trials in RA, PsA and AS through Week 16 were sepsis (0.2%), alanine aminotransferase increased (0.2%), and aspartate aminotransferase increased (0.2%). The most common adverse drug reactions leading to discontinuation through Week 60 of the UC trials in adult patients who received SIMPONI induction and 100 mg during maintenance compared with patients who received SIMPONI induction and placebo during maintenance were tuberculosis (0.3% vs. 0.6%) and anemia (0.3% vs. 0%), respectively.

Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 RA, PsA and AS trials in adults through Week 16, occurring in 7% and 6% of SIMPONI-treated patients as compared with 6% and 5% of control-treated patients, respectively.

Infections

In adult controlled Phase 3 trials through Week 16 in RA, PsA, and AS, infections were observed in 28% of SIMPONI-treated patients compared to 25% of control-treated patients. For serious infections, see the Warnings and Precautions section [see *Warnings and Precautions (5.1)*]. In Trial UC-1, the rates of infections were similar in SIMPONI 200/100 mg-treated patients and placebo-treated patients, or approximately 12%. Through Week 60, the incidence per patient year of infections was similar in patients who received SIMPONI induction and 100 mg during maintenance compared with patients who received SIMPONI induction and placebo during the maintenance period Trial UC-2.

Demyelinating Disorders

In Trial UC-1 of SIMPONI induction through Week 6, no cases of demyelination were observed in SIMPONI 200/100 mg-treated patients or placebo-treated patients. Through Week 60 in Trial UC-2, there were no cases of demyelination in the SIMPONI 100 mg group during maintenance. One case of CNS demyelination was observed in the placebo maintenance group in a patient who received SIMPONI 400/200 mg during induction.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF blockers. In adult controlled Phase 3 trials of SIMPONI in patients with RA, PsA, and AS through Week 16, ALT elevations $\geq 5 \times \text{ULN}$ occurred in 0.2% of control-treated patients and 0.7% of SIMPONI-treated patients and ALT elevations $\geq 3 \times \text{ULN}$ occurred in 2% of control-treated patients and 2% of SIMPONI-treated patients. Since many of the patients in the Phase 3 trials for RA, PsA, and AS were also taking medications that cause liver enzyme elevations (e.g., NSAIDs, MTX), the relationship between SIMPONI and liver enzyme elevation is not clear.

In Trials UC-1, UC-2, and UC-3, the incidence of ALT elevations $\geq 5 \times \text{ULN}$ was similar in SIMPONI-treated patients and placebo-treated patients, or approximately 1%, with an average duration of follow-up of 46 weeks and 18 weeks, respectively. ALT elevations $\geq 3 \times \text{ULN}$ occurred in 2.0% of SIMPONI-treated patients compared with 1.5% of placebo-treated patients with an average duration of follow-up of 46 weeks and 18 weeks, respectively.

Autoimmune Disorders and Autoantibodies

In the adult controlled Phase 3 trials in patients with RA, PsA, and AS through Week 14, there was no association of SIMPONI treatment and the development of newly positive anti-dsDNA antibodies. In Phase 3 trials in RA, PsA, and AS through 1 year of follow-up, 4.0% of SIMPONI-treated patients and 2.6% of control patients were newly antinuclear antibody (ANA)-positive (at titers of 1:160 or greater). The frequency of anti-dsDNA antibodies at 1 year of follow-up was uncommon in patients who were anti-dsDNA negative at baseline. Through Week 60 of the UC trials (Trials UC-1, UC-2, and UC-3), 3.5% of patients who received SIMPONI induction and 100 mg during maintenance were newly ANA-positive (at titers of 1:160 or greater) compared with 3.5% of patients who received SIMPONI induction and placebo during the maintenance period in Trial UC-2. The frequency of anti-dsDNA antibodies at 1 year of follow-up in patients who were anti-dsDNA negative at baseline was 0.5% in patients receiving SIMPONI induction and 100 mg during maintenance compared with 0% in patients who received SIMPONI induction and placebo during maintenance [see *Warnings and Precautions* (5.6)].

Injection Site Reactions

In adult controlled Phase 3 trials through Week 16 in RA, PsA and AS, 6% of SIMPONI-treated patients had injection site reactions compared with 2% of control-treated patients. The majority of the injection site reactions were mild and the most frequent manifestation was injection site erythema.

In Trial UC-1, 3.4% of SIMPONI-treated patients had injection site reactions compared with 1.5% in control-treated patients. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema.

In adult controlled Phase 2 and 3 trials in RA, PsA, AS, no patients treated with SIMPONI developed anaphylactic reactions.

Other Adverse Reactions

Table 2 summarizes the adverse drug reactions that occurred at a rate of at least 1% in the SIMPONI ± DMARD group and with a higher incidence than in the placebo ± DMARD group during the controlled period of the 5 pooled Phase 3 trials through Week 16 in adult patients with RA, PsA, and AS.

Table 2: Adverse Drug Reactions Reported by ≥ 1% of SIMPONI-Treated Patients and with a Higher Incidence Than Placebo-Treated Patients in the Adult Phase 3 Trials of RA, PsA, and AS through Week 16^a

	SIMPONI ± DMARDs	Placebo ± DMARDs
Patients treated	1659	639
Adverse Reaction		
Infections and infestations		
Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis, and rhinitis)	16%	13%
Viral infections (such as influenza and herpes)	5%	3%
Bronchitis	2%	1%
Superficial fungal infections	2%	1%
Sinusitis	2%	1%
General disorders and administration site conditions		
Injection site reaction (injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation, paresthesia)	6%	2%
Investigations		
Alanine aminotransferase increased	4%	3%
Aspartate aminotransferase increased	3%	2%
Vascular disorders		
Hypertension	3%	2%
Nervous system disorders		
Dizziness	2%	1%
Paresthesia	2%	1%
Gastrointestinal disorders		
Constipation	1%	<1%

^a Patients may have taken concomitant MTX, sulfasalazine, hydroxychloroquine, low dose corticosteroids (≤ 10 mg of prednisone/day or equivalent), and/or NSAIDs during the trials).

Less Common Clinical Trial Adverse Drug Reactions

Adverse drug reactions that occurred <1% in adult SIMPONI-treated patients in the RA, PsA and AS clinical trials that do not appear in the Warnings and Precautions section included the following events listed by system organ class:

Infections and infestations: Septic shock, atypical mycobacterial infection, pyelonephritis, arthritis bacterial, bursitis infective

Neoplasms benign, malignant and unspecified: Leukemia

Skin and subcutaneous tissue disorders: Psoriasis (new onset or worsening, palmar/plantar and pustular), vasculitis (cutaneous)

Vascular disorders: Vasculitis (systemic)

Adults and Pediatric Patients Weighing at least 15 kg with Ulcerative Colitis

In general, adverse reactions reported in adult patients with UC in Trials UC-1, UC-2, and UC-3 were similar to those reported in clinical trials of patients with RA, PsA, and AS. Adverse reactions reported in the clinical trial of pediatric patients weighing at least 15 kg with UC were also similar to those reported in clinical trials of adults with UC and the other indicated populations. Additional adverse reactions reported in at least 10% of pediatric patients in the trial were headache (17%) and pyrexia (10%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of golimumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to SIMPONI exposure.

Immune system disorders: Serious systemic hypersensitivity reactions (including anaphylactic reaction) [see *Warnings and Precautions* (5.12)], sarcoidosis

Neoplasms benign, malignant and unspecified: Melanoma, Merkel cell carcinoma [see *Warnings and Precautions* (5.2)]

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease

Skin and subcutaneous tissue disorders: Skin exfoliation, lichenoid reactions, rash, bullous skin reactions

7 DRUG INTERACTIONS

7.1 Methotrexate

For the treatment of RA, SIMPONI should be used with methotrexate (MTX) [see *Clinical Studies* (14.1)]. Since the presence or absence of concomitant MTX did not appear to influence the efficacy or safety of SIMPONI in the treatment of PsA or AS, SIMPONI can be used with or without MTX in the treatment of PsA and AS [see *Clinical Studies* (14.2, 14.3) and *Clinical Pharmacology* (12.3)].

7.2 Biological Products for RA, PsA, and/or AS

An increased risk of serious infections has been seen in clinical RA trials of other TNF blockers used in combination with anakinra or abatacept, with no added benefit; therefore, use of SIMPONI with abatacept or anakinra is not recommended [see *Warnings and Precautions* (5.7, 5.8)]. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. The concomitant use of SIMPONI with biologics approved to treat RA, PsA, or AS is not recommended because of the possibility of an increased risk of infection.

7.3 Live Vaccines/Therapeutic Infectious Agents

Live vaccines should not be given concurrently with SIMPONI [see *Warnings and Precautions* (5.11)].

Therapeutic infectious agents should not be given concurrently with SIMPONI [see *Warnings and Precautions* (5.11)].

Infants born to women treated with SIMPONI during their pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to SIMPONI *in utero* is not recommended for 6 months following the mother's last SIMPONI injection during pregnancy [see *Use in Specific Populations* (8.1)].

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF α) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of SIMPONI in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from postmarketing case reports with golimumab use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. An observational study of northern European births observed similar unadjusted rates of major birth defects in infants exposed *in utero* to golimumab compared to no treatment or non-biologic systemic therapy. However, this study had important limitations (*see Data*).

Monoclonal antibodies, such as golimumab, are transported across the placenta during the third trimester of pregnancy and may affect immune response in the *in utero* exposed infant (*see Clinical Considerations*). In an animal reproductive study, golimumab administered by the subcutaneous route to pregnant monkeys, during the period of organogenesis, at doses that produced exposures approximately 360 times the maximum recommended human dose (MRHD) had no adverse fetal effects (*see Data*). In a pre- and post-natal development study with pregnant monkeys, subcutaneous administration of golimumab, during the later gestational and lactation periods, at doses producing maximal maternal blood concentrations approximately 460 times those found with the MRHD had no adverse developmental effects on infants (*see Data*). Data suggest that there are risks to the mother and the fetus associated with rheumatoid arthritis and ulcerative colitis in pregnancy (*see Clinical Considerations*). All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and of miscarriage is 15-20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

Golimumab crosses the placenta during pregnancy. Another TNF-blocking monoclonal antibody administered during pregnancy was detected for up to 6 months in the serum of infants. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to SIMPONI *in utero* is not

recommended for 6 months following the mother's last SIMPONI injection during pregnancy [see *Warnings and Precautions* (5.11) and *Drug Interactions* (7.3)].

Data

Human Data

An observational, exposure-based, cohort study based on data from the Swedish, Danish, and Finnish Medical Birth Registers conducted between 2006-2020 (Sweden and Denmark) and 2006-2019 (Finland) compared the risk of major birth defects in 134 live-born infants exposed to golimumab (116 from women treated for rheumatic conditions, 18 from women treated for ulcerative colitis) to no treatment or non-biologic systemic therapy. The unadjusted rate of major birth defects in infants exposed *in utero* was similar across all groups. However, this study had important limitations such as a small number of pregnant women exposed to golimumab, a wide exposure ascertainment window, and incomplete risk adjustment for potential confounders.

Animal Data

In an embryofetal developmental toxicology study in which pregnant cynomolgus monkeys were treated with golimumab during the period organogenesis from gestation days (GD) 20 to 51, exposures up to 360 times greater than the exposure at the MRHD (on an area under the curve (AUC) basis with maternal subcutaneous doses up to 50 mg/kg twice weekly) produced no evidence of fetal malformations or embryotoxicity. There was no evidence of maternal toxicity. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation.

In a pre- and post-natal developmental study in which pregnant cynomolgus monkeys were treated with golimumab from gestation day 50 to postpartum day 33, maximal drug concentrations approximately 460 times greater than that found with the MRHD (on a maximum blood concentration (C_{max}) basis at steady state with maternal subcutaneous doses up to 50 mg/kg twice weekly) were not associated with any evidence of developmental defects in infants. There was no evidence of maternal toxicity. Golimumab was present in fetal serum at the end of the second trimester and in neonatal serum from the time of birth and for up to 6 months postpartum.

8.2 Lactation

Risk Summary

There is no information regarding the presence of SIMPONI in human milk, the effects on breastfed infants, or the effects on milk production. Maternal IgG is known to be present in human milk. Golimumab is present in the milk of lactating cynomolgus monkeys (*see Data*). If golimumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to golimumab are unknown. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for SIMPONI and any potential adverse effects on the breast-fed infants from SIMPONI, or from the underlying maternal condition.

Data

In the pre- and post-natal development study in cynomolgus monkeys in which golimumab was administered subcutaneously during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 400-fold lower than the maternal serum concentrations.

8.4 Pediatric Use

Ulcerative Colitis

The safety and effectiveness of SIMPONI for the treatment of moderately to severely active ulcerative colitis have been established in pediatric patients weighing at least 15 kg. Use of SIMPONI for this indication is supported by evidence from adequate and well-controlled studies in adults with additional safety and efficacy data from an open-label, study in 69 pediatric patients (4 to 17 years of age). The adverse reaction profile in these pediatric patients was similar to adults [see *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), and *Clinical Studies* (14.5)]. Additionally, headache (17%) and pyrexia (10%) were reported in at least 10% of pediatric patients in the trial.

The safety and effectiveness of SIMPONI for the treatment of moderately to severely active ulcerative colitis have not been established in pediatric patients weighing less than 15 kg.

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

The safety and efficacy of SIMPONI were evaluated in a multicenter, placebo-controlled, double-blind, randomized-withdrawal, parallel group study in 173 children (2 to 17 years of age) with active polyarticular juvenile idiopathic arthritis (pJIA) despite treatment with MTX for at least 3 months. Subjects were maintained on their stable dose of MTX at the same dose (mg/week) at study entry. Concurrent use of stable doses of oral corticosteroids (≤ 10 mg/day or 0.2 mg/kg/day prednisone or equivalent, whichever was less) and/or NSAIDs was permitted. In the 16 week open-label phase, all patients received MTX and SIMPONI 30 mg/m² (maximum 50 mg) subcutaneously every 4 weeks. Patients who achieved an ACR Ped 30 response at Week 16 entered the randomized-withdrawal phase of the study and received MTX and either SIMPONI 30 mg/m² (maximum 50 mg) or placebo every 4 weeks through Week 48.

The primary endpoint of the study was the proportion of patients who did not experience a flare between Week 16 and Week 48, among all subjects who entered the randomized withdrawal phase. The efficacy of SIMPONI in the treatment of pJIA was not demonstrated in this study because there was no statistical evidence of differences in flare rate between SIMPONI-treated patients and placebo patients between Weeks 16 and 48.

In this study, the frequency and type of the adverse reactions seen in children were generally similar to those observed in adults.

8.5 Geriatric Use

In the Phase 3 trials in RA, PsA, and AS, there were no overall differences in SAEs, serious infections, and AEs in SIMPONI-treated patients ages 65 or older (N=155) compared with younger SIMPONI-treated patients. Clinical studies of SIMPONI in patients with moderately to severely active ulcerative colitis did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger adult patients. Because there is a higher incidence of infections in the geriatric population in general, caution should be used in treating geriatric patients with SIMPONI [see *Warnings and Precautions* (5.1, 5.5)].

11 DESCRIPTION

Golimumab is a human IgG1 κ monoclonal antibody specific for human tumor necrosis factor alpha (TNF α) that exhibits multiple glycoforms with molecular masses of approximately 150 to 151 kilodaltons. Golimumab was created using genetically engineered mice immunized with human TNF, resulting in an antibody with human-

derived antibody variable and constant regions. Golimumab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

SIMPONI® (golimumab) Injection is a preservative-free, sterile, clear to slightly opalescent, colorless to light yellow solution of the golimumab antibody supplied in a single-dose prefilled syringe (with a passive needle safety guard) or a single-dose prefilled autoinjector.

Each 0.5 mL prefilled syringe and autoinjector contains 50 mg golimumab, L-histidine and L-histidine monohydrochloride monohydrate (0.44 mg), polysorbate 80 (0.08 mg), sorbitol (20.5 mg) and Water for Injection. Each 1 mL prefilled syringe and autoinjector contains 100 mg golimumab, L-histidine and L-histidine monohydrochloride monohydrate (0.87 mg), polysorbate 80 (0.15 mg), sorbitol (41.0 mg) and Water for Injection. The pH is approximately 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNF α . This interaction prevents the binding of TNF α to its receptors, thereby inhibiting the biological activity of TNF α (a cytokine protein). There was no evidence of the golimumab antibody binding to other TNF superfamily ligands; in particular, the golimumab antibody did not bind or neutralize human lymphotoxin. Golimumab did not lyse human monocytes expressing transmembrane TNF in the presence of complement or effector cells.

Elevated TNF α levels in the blood, synovium, and joints have been implicated in the pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. TNF α is an important mediator of the articular inflammation that is characteristic of these diseases. The exact mechanism by which golimumab treats ulcerative colitis is unknown. Golimumab modulated the *in vitro* biological effects mediated by TNF in several bioassays, including the expression of adhesion proteins responsible for leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of proinflammatory cytokines (IL-6, IL-8, G-CSF and GM-CSF).

12.2 Pharmacodynamics

In clinical trials, decreases in C-reactive protein (CRP), interleukin (IL)-6, matrix metalloproteinase-3 (MMP-3), intercellular adhesion molecule (ICAM)-1 and vascular endothelial growth factor (VEGF) were observed following SIMPONI administration in patients with RA, PsA, and AS.

12.3 Pharmacokinetics

Absorption

Following subcutaneous administration of SIMPONI to healthy subjects and patients with active RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A subcutaneous injection of 50 mg SIMPONI to healthy subjects produced a mean $\pm$ standard deviation maximum serum concentration (C_{max}) of 3.2 $\pm$ 1.4 mcg/mL.

By cross-trial comparisons of mean AUC_{inf} values following an IV or subcutaneous administration of SIMPONI, the absolute bioavailability of subcutaneous SIMPONI was estimated to be approximately 53%.

Distribution

Following a single IV administration over the dose range of 0.1 to 10.0 mg/kg in patients with active RA, mean volume of distribution ranged from 58 to 126 mL/kg. The volume of distribution for golimumab indicates that golimumab is distributed primarily in the circulatory system with limited extravascular distribution.

Metabolism

The exact metabolic pathway of golimumab is unknown.

Elimination

Following a single IV administration over the dose range of 0.1 to 10.0 mg/kg in patients with active RA, mean systemic clearance of SIMPONI was estimated to be 4.9 to 6.7 mL/day/kg.

Median terminal half-life values were estimated to be approximately 2 weeks in healthy subjects and patients with active RA, PsA or AS.

Population PK analyses indicated that concomitant use of NSAIDs, oral corticosteroids, or sulfasalazine did not influence the apparent clearance of golimumab.

Patients who developed anti-golimumab antibodies generally had lower steady-state serum trough concentrations of golimumab.

Dose Linearity

Golimumab exhibited dose-proportional pharmacokinetics (PK) in patients with active RA over the dose range of 0.1 to 10 mg/kg following a single intravenous (IV) dose. Following a single SC dose in healthy subjects, dose proportional pharmacokinetics were also observed over a dose range of 50 mg to 400 mg.

Single Dose Versus Multiple Doses

When 50 mg SIMPONI was administered subcutaneous to patients with RA, PsA, or AS every 4 weeks, serum concentrations appeared to reach steady state by Week 12. With concomitant use of methotrexate (MTX), treatment with 50 mg SIMPONI subcutaneous every 4 weeks resulted in a mean steady-state trough serum concentration of approximately 0.4-0.6 mcg/mL in patients with active RA, approximately 0.5 mcg/mL in patients with active PsA, and approximately 0.8 mcg/mL in patients with active AS. Patients with RA, PsA, and AS treated with SIMPONI 50 mg and MTX had approximately 52%, 36% and 21% higher mean steady-state trough concentrations of golimumab, respectively compared with those treated with SIMPONI 50 mg without MTX. The presence of MTX also decreased anti-golimumab antibody incidence from 7% to 2% [*see Adverse Reactions (6.1)*]. For RA, SIMPONI should be used with MTX. In the PsA and AS trials, the presence or absence of concomitant MTX did not appear to influence clinical efficacy and safety parameters [*see Drug Interactions (7.1) and Clinical Studies (14.1)*].

When induction doses of 200 mg and 100 mg SIMPONI at week 0 and 2, respectively, followed by maintenance doses of 100 mg SIMPONI every 4 weeks were administered subcutaneously in patients with UC, serum golimumab concentrations reached steady-state by week 8 after the first maintenance dose. Treatment with 100 mg SIMPONI subcutaneous every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 1.8 ± 1.1 mcg/mL.

Effect of Weight on Pharmacokinetics in Adults

Higher apparent clearance of golimumab was associated with increasing weight. Treatment with the recommended maintenance dose regimen of SIMPONI 100 mg in adult patients with UC did not result in meaningful differences in clinical efficacy among different weight groups. Across the PsA and AS populations, no meaningful differences in clinical efficacy were observed among the subgroups by weight quartile. The RA trial in MTX-experienced and TNF-blocker-naïve patients (Trial RA-2) did show evidence of a reduction in clinical efficacy with increasing body weight, but this effect was observed for both tested doses of SIMPONI (50 mg and 100 mg). There is no need to adjust the dosage of SIMPONI in adult patients based on body weight.

Specific Populations

In adults, population PK analyses suggested no PK differences between male and female patients after body-weight adjustment in the RA, PsA and UC trials. In the AS trial, female patients showed 13% higher apparent clearance than male patients after body-weight adjustment. Subgroup analysis based on gender showed that both female and male patients achieved clinically significant response at the proposed clinical dose. Dosage adjustment based on gender is not needed.

Population PK analyses indicated that PK parameters of golimumab were not influenced by age in adult patients. Patients with age ≥ 65 years had apparent clearance of golimumab similar to patients with age < 65 years. No ethnicity-related PK differences were observed between Caucasians and Asians, and there were too few patients of other races to assess for PK differences.

No formal trial of the effect of renal or hepatic impairment on the PK of golimumab was conducted.

Pediatric Patients Weighing at Least 15 kg with Ulcerative Colitis

The pharmacokinetics of golimumab were studied in pediatric patients with UC aged 4 to 17 years. The pharmacokinetics of golimumab are predicted to be similar between adult patients and pediatric patients with UC. There are no expected clinically significant differences in golimumab systemic exposure between adult patients and pediatric patients weighing 15 kg and above who receive the recommended dosage [*see Dosage and Administration (2.3)*].

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of golimumab or of other golimumab products.

Results from the EIA Method

Using an enzyme immunoassay (EIA method), antibodies to golimumab were detected in 57 (4%) of SIMPONI-treated adult patients across the Phase 3 RA, PsA and AS trials through Week 24. Similar rates were observed in each of the 3 indications. Patients who received SIMPONI with concomitant MTX had a lower proportion of antibodies to golimumab than patients who received SIMPONI without MTX (approximately 2% vs. 7%, respectively).

With the EIA method, the presence of serum concentrations of golimumab can interfere with the detection of antibodies to golimumab leading to inconclusive results. In adult UC trials, 34 (3%), 341 (28%) and 823 (69%) of SIMPONI-treated patients were positive, negative and inconclusive for antibodies to golimumab, respectively. Treatment with concomitant immunomodulators (AZA, 6-MP or MTX) resulted in a lower proportion of patients with antibodies to golimumab than patients receiving SIMPONI without immunomodulators (2% vs. 4%, respectively).

Of the adult patients with a positive antibody response to golimumab in the Phase 2 and 3 trials, most were determined to have neutralizing antibodies to golimumab as measured by a cell-based functional assay.

Results from the Drug-Tolerant EIA Method

A drug-tolerant enzyme immunoassay (drug-tolerant EIA) method for detecting antibodies to golimumab was developed and validated, which eliminated the inconclusive category as reported above. This method is approximately 16-fold more sensitive than the original EIA method with less interference from golimumab in serum.

Based on the drug-tolerant EIA method, 246 (23%) of SIMPONI-treated patients across the Phase 3 RA, PsA and AS trials in adults, antibodies to golimumab were detected in 59 (16%), 106 (28%), and 81 (24%) patients, respectively. Treatment with concomitant MTX resulted in a lower proportion of patients with antibodies to golimumab than in patients receiving SIMPONI without MTX in RA patients (7% vs. 35%), in PsA patients (18% vs. 38%) and in AS patients (6% vs. 29%). A trend of decreasing drug concentrations with increasing antibody titers was observed. While an overall decrease in clinical efficacy for ADA positive patients compared with ADA negative patients was not observed in patients with RA (ACR 20: 75% vs. 75%), PsA (ACR 20: 72% vs. 66%) and AS (ASAS 20: 57% vs. 65%), higher titer antibodies may be associated with diminished efficacy.

In UC trials in adults, 254 (21%) of SIMPONI-treated patients were positive for antibodies to golimumab through week 54 while the remaining 941 (79%) patients were negative. Treatment with concomitant immunomodulators (AZA, 6-MP or MTX) in the UC trials resulted in a lower proportion of patients with antibodies to golimumab than in patients receiving SIMPONI without immunomodulators (12% vs. 26%). There is a trend of decreasing drug concentrations with increasing antibody titers. Although the development of antibodies to golimumab did not preclude clinical response, a trend toward decreased efficacy in ADA positive patients was observed compared to ADA negative patients in the UC trials (clinical response 38% vs. 53%).

In the pediatric UC trial, 22% (15/69) of SIMPONI-treated patients developed ADA to golimumab through the final safety visit using the drug-tolerant EIA method. Of the 15 subjects who tested positive for ADA, 20% (3/15) tested positive for neutralizing antibodies. The incidence of antibodies to golimumab was comparable between pediatric and adult patients with UC. Pediatric UC patients who developed antibodies to golimumab generally had lower trough steady-state serum concentrations of golimumab. While there is insufficient data to assess whether the observed ADA-associated pharmacokinetic changes reduce effectiveness, a trend toward decreased efficacy in ADA positive patients was observed compared to ADA negative patients in the pediatric UC trial.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of golimumab have not been conducted to evaluate its carcinogenic potential. Mutagenicity studies have not been conducted with golimumab. A fertility study conducted in mice using an

analogous anti-mouse TNF α antibody administered by the intravenous route at doses up to 40 mg/kg once per week showed no impairment of fertility.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The efficacy and safety of SIMPONI were evaluated in 3 multicenter, randomized, double-blind, controlled trials (Trials RA-1, RA-2, and RA-3) in 1542 patients $\geq$ 18 years of age with moderately to severely active RA, diagnosed according to the American College of Rheumatology (ACR) criteria, for at least 3 months prior to administration of trial agent. Patients were required to have at least 4 swollen and 4 tender joints. SIMPONI was administered subcutaneously at doses of 50 mg or 100 mg every 4 weeks. Double-blinded controlled efficacy data were collected and analyzed through Week 24. Patients were allowed to continue stable doses of concomitant low dose corticosteroids (equivalent to $\leq$ 10 mg of prednisone a day) and/or NSAIDs and patients may have received oral MTX during the trials.

Trial RA-1 evaluated 445 patients who were previously treated (at least 8 to 12 weeks prior to administration of trial agent) with one or more doses of a biologic TNF blocker without a serious adverse reaction. Patients may have discontinued the biologic TNF blocker for a variety of reasons. Patients were randomized to receive placebo (N=150), SIMPONI 50 mg (N=147), or SIMPONI 100 mg (N=148). Patients were allowed to continue stable doses of concomitant MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

Trial RA-2 evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with a biologic TNF blocker. Patients were randomized to receive background MTX (N=133), SIMPONI 50 mg + background MTX (N=89), SIMPONI 100 mg + background MTX (N=89), or SIMPONI 100 mg monotherapy (N=133). The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited.

Trial RA-3 evaluated 637 patients with active RA who were MTX naïve and had not previously been treated with a biologic TNF blocker. Patients were randomized to receive MTX (N=160), SIMPONI 50 mg + MTX (N=159), SIMPONI 100 mg + MTX (N=159), or SIMPONI 100 mg monotherapy (N=159). For patients receiving MTX, MTX was administered at a dose of 10 mg/week beginning at Week 0 and increased to 20 mg/week by Week 8. The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited.

The primary endpoint in Trial RA-1 and Trial RA-2 was the percentage of patients achieving an ACR 20 response at Week 14 and the primary endpoint in Trial RA-3 was the percentage of patients achieving an ACR 50 response at Week 24.

In Trials RA-1, RA-2, and RA-3, the median duration of RA disease was 9.4, 5.7, and 1.2 years and 99%, 75%, and 54% of the patients used at least one DMARD in the past, respectively. Approximately 77% and 57% of patients received concomitant NSAIDs and low dose corticosteroids, respectively, in the 3 pooled RA trials.

Clinical Response

In the 3 RA trials, a greater percentage of patients treated with the combination of SIMPONI and MTX achieved ACR responses at Week 14 (Trials RA-1 and RA-2) and Week 24 (Studies RA-1, RA-2, and RA-3) versus patients treated with the MTX alone. There was no clear evidence of improved ACR response with the higher

SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). In Trials RA-2 and RA-3, the SIMPONI monotherapy groups were not statistically different from the MTX monotherapy groups in ACR responses. Table 3 shows the proportion of patients with the ACR response for the SIMPONI 50 mg and control groups in Trials RA-1, RA-2, and RA-3. In the subset of patients who received SIMPONI in combination with MTX in Trial RA-1, the proportion of patients achieving ACR 20, 50 and 70 responses at Week 14 were 40%, 18%, and 12%, respectively, in the SIMPONI 50 mg + MTX group (N=101) compared with 17%, 6%, and 2%, respectively, in the placebo + MTX group (N=103). Table 4 shows the percent improvement in the components of the ACR response criteria for the SIMPONI 50 mg + MTX and MTX groups in Trial RA-2. The percentage of patients achieving ACR 20 responses by visit for Trial RA-2 is shown in Figure 1. ACR 20 responses were observed in 38% of patients in the SIMPONI 50 mg + MTX group at the first assessment (Week 4) after the initial SIMPONI administration.

Table 3: Trials RA-1, RA-2, and RA-3 Proportion of Patients with an ACR Response^a

	Trial RA-1 Active RA previously treated with one or more doses of TNF blockers		Trial RA-2 Active RA, despite MTX		Trial RA-3 Active RA, MTX Naïve	
	Placebo ± DMARDs ^b	SIMPONI 50 mg ± DMARDs ^b	Background MTX	SIMPONI 50 mg + Background MTX	MTX	SIMPONI 50 mg + MTX
N ^c	150	147	133	89	160	159
ACR 20						
Week 14	18%	35%	33%	55%	NA ^c	NA ^c
Week 24	16%	31%	28%	60%	49%	62%
ACR 50						
Week 14	7%	15%	10%	35%	NA ^c	NA ^c
Week 24	4%	16%	14%	37%	29%	40%
ACR 70						
Week 14	2%	10%	4%	13%	NA ^c	NA ^c
Week 24	2%	9%	5%	20%	16%	24% ^d

^a Approximately 78% and 58% of the patients received concomitant NSAIDs and low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day), respectively, during the 3 pooled RA trials.

^b DMARDs in Trial RA-1 included MTX, HCQ, and/or SSZ (about 68%, 8%, and 5% of patients received MTX, HCQ, and SSZ, respectively).

^c N reflects randomized patients.

^d Not significantly different from MTX monotherapy.

^e NA = Not applicable, as data was not collected at Week 14 in Trial RA-3.

Table 4: Trial RA-2 — Median Percent Improvement from Baseline in the Individual ACR Components at Week 14^a

	Background MTX	SIMPONI 50 mg +Background MTX
N ^b	133	89
Number of swollen joints (0-66)		
Baseline	12	13
Week 14	38%	62%
Number of tender joints (0-68)		
Baseline	21	26
Week 14	30%	60%
Patient's assessment of pain (0-10)		
Baseline	5.7	6.1
Week 14	18%	55%
Patient's global assessment of disease activity (0-10)		

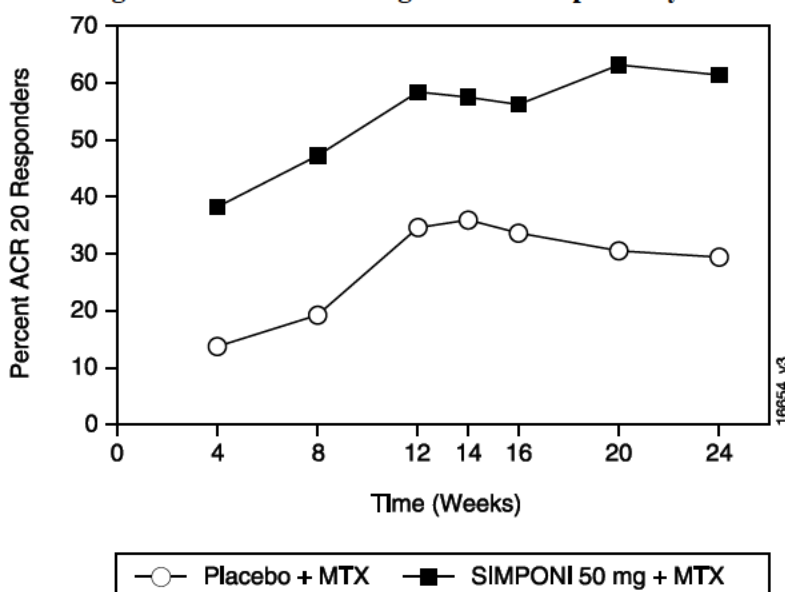
Baseline	5.3	6.0
Week 14	15%	45%
Physician's global assessment of disease activity (0-10)		
Baseline	5.7	6.1
Week 14	35%	55%
HAQ score (0-3)		
Baseline	1.25	1.38
Week 14	10%	29%
CRP (mg/dL)		
Baseline	0.8	1.0
Week 14	2%	44%

Note: Baseline values are medians.

^a In Trial RA-2, about 70% and 85% of patients received concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and/or NSAIDs during the trials, respectively.

^b N reflects randomized patients; actual number of patients evaluable for each endpoint may vary.

Figure 1: Trial RA-2 – Percentage of Patients Achieving ACR 20 Response by Visit: Randomized Patients*



* The same patients may not have responded at each timepoint.

Physical Function Response in Patients with RA

In Trials RA-1 and RA-2, the SIMPONI 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to Week 24: 0.23 vs. 0.03 in RA-1, 0.47 vs. 0.13 in RA-2, respectively. Also in Trials RA-1 and RA-2, the SIMPONI 50 mg groups compared to the control groups had a greater proportion of HAQ responders (change from baseline > 0.22) at Week 24: 43% vs. 27%, 65% vs. 35%, respectively.

14.2 Psoriatic Arthritis

The safety and efficacy of SIMPONI were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 405 adult patients with moderately to severely active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite NSAID or DMARD therapy (Trial PsA). Patients in this trial had a diagnosis of PsA for at least 6 months with a qualifying psoriatic skin lesion of at least 2 cm in diameter. Previous treatment with a biologic TNF blocker was not allowed. Patients were randomly assigned to placebo (N=113), SIMPONI 50 mg (N=146), or SIMPONI 100 mg (N=146) given subcutaneously every 4 weeks. Patients were allowed to receive

stable doses of concomitant MTX (≤ 25 mg/week), low dose oral corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and/or NSAIDs during the trial. The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited. The primary endpoint was the percentage of patients achieving ACR 20 response at Week 14. Placebo-controlled efficacy data were collected and analyzed through Week 24.

Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). The median duration of PsA disease was 5.1 years, 78% of patients received at least one DMARD in the past, and approximately 48% of patients received MTX, and 16% received low dose oral steroids.

Clinical Response in Patients with PsA

SIMPONI $\pm$ MTX, compared with placebo $\pm$ MTX, resulted in significant improvement in signs and symptoms as demonstrated by the proportion of patients with an ACR 20 response at Week 14 in Trial PsA (see Table 5). There was no clear evidence of improved ACR response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). ACR responses observed in the SIMPONI-treated groups were similar in patients receiving and not receiving concomitant MTX. Similar ACR 20 responses at Week 14 were observed in patients with different PsA subtypes. However, the number of patients with arthritis mutilans was too small to allow meaningful assessment. SIMPONI 50 mg treatment also resulted in significantly greater improvement compared with placebo for each ACR component in Trial PsA (Table 6). Treatment with SIMPONI resulted in improvement in enthesitis and skin manifestations in patients with PsA. However, the safety and efficacy of SIMPONI in the treatment of patients with plaque psoriasis has not been established.

The percentage of patients achieving ACR 20 responses by visit for Trial PsA is shown in Figure 2. ACR 20 responses were observed in 31% of patients in the SIMPONI 50 mg + MTX group at the first assessment (Week 4) after the initial SIMPONI administration.

Table 5: Trial PsA - Proportion of Patients with ACR Responses

	Placebo $\pm$ MTX ^a	SIMPONI 50 mg $\pm$ MTX ^a
N ^b	113	146
ACR 20		
Week 14	9%	51%
Week 24	12%	52%
ACR 50		
Week 14	2%	30%
Week 24	4%	32%
ACR 70		
Week 14	1%	12%
Week 24	1%	19%

^a In Trial PsA, about 48%, 16%, and 72% of the patients received stable doses of MTX (≤ 25 mg/week), low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and NSAIDs, respectively.

^b N reflects randomized patients.

Bold text indicates primary endpoint.

Table 6: Trial PsA - Percent Improvement in ACR Components at Week 14

	Placebo $\pm$ MTX ^a	SIMPONI 50 mg $\pm$ MTX ^a
N ^b	113	146

Table 6: Trial PsA - Percent Improvement in ACR Components at Week 14

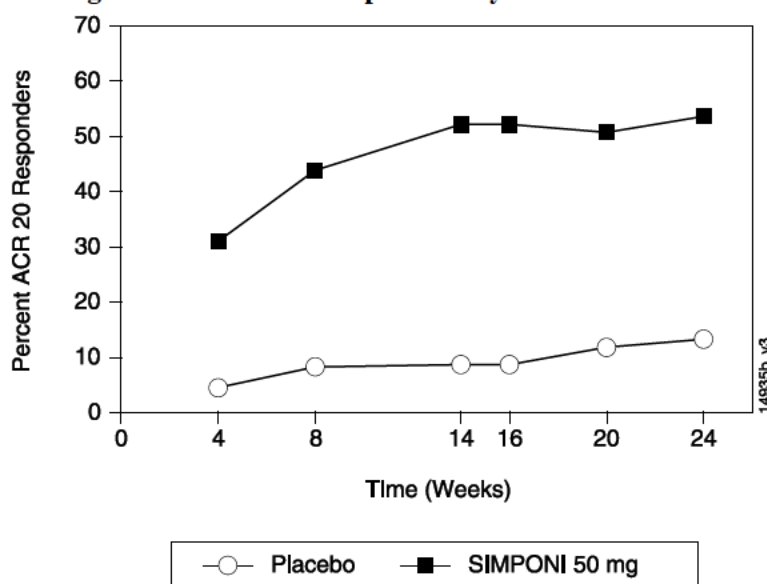
	Placebo ± MTX ^a	SIMPONI 50 mg ± MTX ^a
Number of swollen joints (0-66)		
Baseline	10.0	11.0
Week 14	8%	60%
Number of tender joints (0-68)		
Baseline	18.0	19.0
Week 14	0%	54%
Patient's assessment of pain (0-10)		
Baseline	5.4	5.8
Week 14	-1%	48%
Patient's global assessment of disease activity (0-10)		
Baseline	5.2	5.2
Week 14	2%	49%
Physician's global assessment of disease activity (0-10)		
Baseline	5.2	5.4
Week 14	7%	59%
HAQ score (0-10)		
Baseline	1.0	1.0
Week 14	0%	28%
CRP (mg/dL) (0-10)		
Baseline	0.6	0.6
Week 14	0%	40%

Note: Baseline are median values.

^a In Trial PsA, about 48%, 16%, and 78% of the patients received stable doses of MTX (≤ 25 mg/week), low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and NSAIDs, respectively.

^b N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint.

Figure 2: Trial PsA – Percentage of ACR 20 PsA Responders by Visit: Randomized Patients*



* The same patients may not have responded at each timepoint.

Physical Function Response in Patients with PsA

In Trial PsA, SIMPONI 50 mg demonstrated a greater improvement compared to placebo in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to Week 24 (0.33 and -0.01, respectively). In addition, the SIMPONI 50 mg group compared to the placebo group had a greater proportion of HAQ responders (≥ 0.3 change from baseline) at Week 24: 43% vs. 22%, respectively.

14.3 Ankylosing Spondylitis

The safety and efficacy of SIMPONI were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 356 adult patients with active ankylosing spondylitis according to modified New York criteria for at least 3 months (Trial AS). Patients had symptoms of active disease [defined as a Bath AS Disease Activity Index (BASDAI) ≥ 4 and VAS for total back pain of ≥ 4 , on scales of 0 to 10 cm] despite current or previous NSAID therapy. Patients were excluded if they were previously treated with a biologic TNF blocker or if they had complete ankylosis of the spine. Patients were randomly assigned to placebo (N=78), SIMPONI 50 mg (N=138), or SIMPONI 100 mg (N=140) administered subcutaneously every 4 weeks. Patients were allowed to continue stable doses of concomitant MTX, sulfasalazine (SSZ), hydroxychloroquine (HCQ), low dose corticosteroids (equivalent to < 10 mg of prednisone a day), and/or NSAIDs during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

The primary endpoint was the percentage of patients achieving an Assessment in Ankylosing Spondylitis (ASAS) 20 response at Week 14. Placebo-controlled efficacy data were collected and analyzed through Week 24.

In Trial AS, the median duration of AS disease was 5.6 years, median duration of inflammatory back pain was 12 years, 83% were HLA-B27 positive, 24% had prior joint surgery or procedure, and 55% received at least one DMARD in the past. During the trial, the use of concomitant DMARDs and/or NSAIDs was as follows: MTX (20%), SSZ (26%), HCQ (1%), low dose oral steroids (16%), and NSAIDs (90%).

Clinical Response in Patients with AS

In Trial AS, SIMPONI $\pm$ DMARDs treatment, compared with placebo $\pm$ DMARDs, resulted in a significant improvement in signs and symptoms as demonstrated by the proportion of patients with an ASAS 20 response at Week 14 (see Table 7). There was no clear evidence of improved ASAS response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). Table 8 shows the percent improvement in the components of the ASAS response criteria for the SIMPONI 50 mg $\pm$ DMARDs and placebo $\pm$ DMARDs groups in Trial AS.

The percentage of patients achieving ASAS 20 responses by visit for Trial AS is shown in Figure 3. ASAS 20 responses were observed in 48% of patients in the SIMPONI 50 mg + MTX group at the first assessment (Week 4) after the initial SIMPONI administration.

Table 7: Trial AS – Proportion of ASAS Responders at Weeks 14 and 24

	Placebo $\pm$ DMARDs^a	SIMPONI 50 mg $\pm$ DMARDs^a
N ^b	78	138
Responders, % of patients		
ASAS 20		
Week 14	22%	59%
Week 24	23%	56%
ASAS 40		
Week 14	15%	45%
Week 24	15%	44%

^a During the trial, the concomitant use of stable doses of DMARDs was as follows: MTX (21%), SSZ (25%), and HCQ (1%). About 16% and 89% of patients received stable doses of low dose oral steroids and NSAIDs during the trial, respectively.

^b N reflects randomized patients.
Bold text indicates primary endpoint.

Table 8: Trial AS — Median Percent Improvement in ASAS Components at Week 14

	Placebo ± DMARDs ^a	SIMPONI 50 mg ± DMARDs ^a
N ^b	78	138
ASAS components		
Patient global assessment (0-10)		
Baseline	7.2	7.0
Week 14	13%	47%
Total back pain (0-10)		
Baseline	7.6	7.5
Week 14	9%	50%
BASFI (0-10)^c		
Baseline	4.9	5.0
Week 14	-3%	37%
Inflammation (0-10)^d		
Baseline	7.1	7.1
Week 14	6%	59%

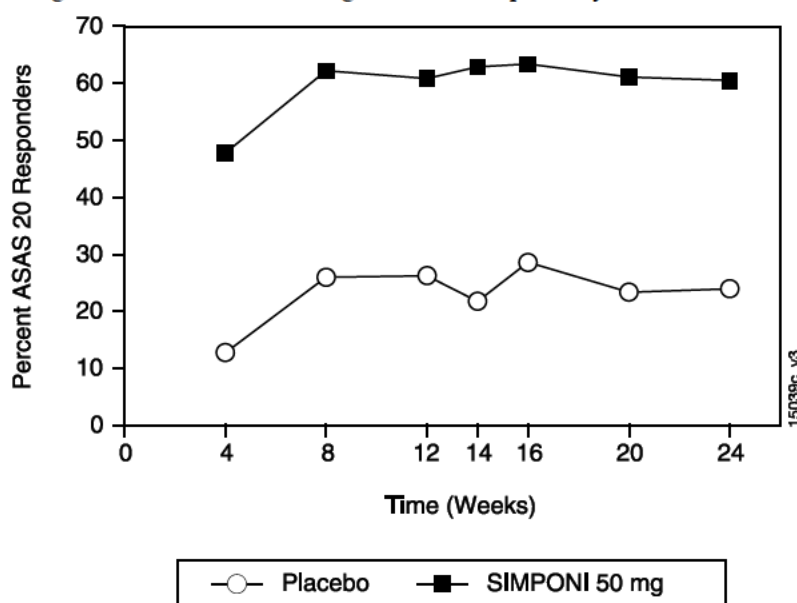
^a During the trial, the concomitant use of stable doses of DMARDs was as follows: MTX (21%), SSZ (25%), and HCQ (1%). About 16% and 89% of patients received stable doses of low dose oral steroids and NSAIDs during the trial, respectively.

^b N reflects randomized patients.

^c BASFI is Bath Ankylosing Spondylitis Functional Index.

^d Inflammation is the mean of 2 patient-reported stiffness self-assessments in the Bath AS Disease Activity Index (BASDAI).

Figure 3: Trial AS – Percentage of AS Patients Achieving ASAS 20 Response by Visit: Randomized Patients*



* The same patients may not have responded at each timepoint.

14.4 Adult Ulcerative Colitis

The efficacy and safety of SIMPONI was evaluated in 2 multicenter, randomized, double-blind, placebo-controlled clinical trials in adults with moderately to severely active ulcerative colitis (UC). Trial UC-1 (NCT00487539) was a 6-week induction trial. Trial UC-2 (NCT00488631) was a randomized-withdrawal maintenance trial that evaluated 456 patients who achieved clinical response with SIMPONI induction and tolerated SIMPONI treatment.

In Trial UC-1 moderately to severely active UC was, defined as a Mayo score of 6 to 12 [the Mayo score ranges from 0 to 12 and has 4 subscales that are each scored from 0 (normal) to 3 (most severe): stool frequency, rectal bleeding, findings on endoscopy, and physician global assessment]. At baseline, subjects also had an endoscopy subscore of 2 or 3 on a 3-point scale (an endoscopy score of 2 is defined by marked erythema, absent vascular pattern, friability, erosions; and a score of 3 is defined by spontaneous bleeding, ulceration). Patients were corticosteroid dependent (i.e., an inability to successfully taper corticosteroids without a return of the symptoms of UC) or had an inadequate response to or had failed to tolerate at least one of the following therapies: oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine.

Trial UC-1 was divided into 2 parts. In Part 1 (dose finding), patients were randomized to one of 4 treatment groups: 400 mg SIMPONI administered subcutaneously (SC) at Week 0 and 200 mg at Week 2 (400/200 mg), 200 mg SIMPONI SC at Week 0 and 100 mg at Week 2 (200/100 mg), 100 mg SIMPONI SC at Week 0 and 50 mg at Week 2 (100/50 mg), or placebo SC at Weeks 0 and 2. In Part 2 (dose confirming), efficacy was evaluated in 761 patients who were randomized to receive either 400 mg SIMPONI SC at Week 0 and 200 mg at Week 2, 200 mg SIMPONI SC at Week 0 and 100 mg at Week 2, or placebo SC at Weeks 0 and 2. SIMPONI 100/50 mg SC was not evaluated in Part 2; its safety and effectiveness has not been established in UC. Concomitant stable doses of oral aminosalicylates (5-ASA), oral corticosteroids (less than 40 mg/day), azathioprine (AZA), 6-mercaptopurine (6-MP), and/or methotrexate (MTX) were permitted. Patients who received previous TNF inhibitors were excluded. The primary endpoint in UC-1 was the percent of patients in clinical response at Week 6, defined as a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 (no blood seen) or 1 (streaks of blood with stool less than half the time).

Trial UC-2 evaluated 456 patients who achieved clinical response with SIMPONI induction and tolerated SIMPONI treatment. Patients were randomized to receive SIMPONI 50 mg, SIMPONI 100 mg or placebo administered subcutaneously every 4 weeks. Concomitant stable doses of oral aminosalicylates, azathioprine, 6-mercaptopurine, and/or methotrexate were permitted. Corticosteroids were to be tapered at the start of the maintenance trial. The primary endpoint in UC-2 was the percent of patients maintaining clinical response through Week 54.

Clinical Response, Clinical Remission and Improvement of Endoscopic Appearance of the Mucosa

In Trial UC-1, a greater proportion of patients achieved clinical response, clinical remission and had improvement of endoscopic appearance of the mucosa at Week 6 in the SIMPONI 200/100 mg group compared with the placebo group. The SIMPONI 400/200 mg group did not demonstrate additional clinical benefit over the SIMPONI 200/100 mg group. Clinical response was defined as a decrease from baseline in the Mayo score of $\geq 30\%$ and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1. Clinical remission was defined as a Mayo score ≤ 2 points, with no individual subscore > 1 . Improvement of endoscopic appearance of the mucosa was defined as a Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability).

In Trial UC-2, a greater proportion of patients maintained clinical response through Week 54 in the SIMPONI 100 mg group compared with the placebo group. In Trial UC-2, SIMPONI-treated patients in clinical response (which included the subset of patients in clinical remission) in Trial UC-1, were again assessed for clinical remission at Week 30 and Week 54. A greater proportion of patients had clinical remission at both Weeks 30

and 54 without demonstrating a loss of response at any time point through Week 54 in the SIMPONI 100 mg group compared with the placebo group.

These results are shown in Table 9 below.

Table 9: The Proportion of Patients with UC in Clinical Response, Clinical Remission and with Improvement of Endoscopic Appearance of the Mucosa in Trials UC-1 and UC-2

Trial UC-1 (6-Week Induction Trial)			
	Placebo N=251	SIMPONI 200/100 mg N=253	Treatment difference (95% CI)
Clinical response ^a at Week 6	30%	51%	21% (12%, 29%)*
Clinical remission ^a at Week 6	6%	18%	11% (6%, 17%)*
Improvement of endoscopic appearance of the mucosa at Week 6 ^a	29%	42%	14% (5%, 22%) [†]
Trial UC-2 (54-Week Maintenance Trial) ^b			
	Placebo N=154	SIMPONI 100 mg N=151	Treatment difference (95% CI)
Clinical response ^a through Week 54 ^c	31%	50%	19% (8%, 29%) [‡]
Clinical remission ^a at both Week 30 and Week 54 ^d	16%	28%	12% (3%, 21%) [§]

* p<0.0001; [†] p=0.0014; [‡] p<0.001; [§] p=0.004

^a Patients who had a prohibited change in concomitant UC medication, an ostomy or colectomy, discontinued trial agent due to lack of therapeutic effect, or a dose adjustment in Trial UC-2 were considered not to be in clinical response, clinical remission or have an improvement in endoscopic appearance of the mucosa from the time of the event onward.

^b Results in Trial UC-2 are based on patients who were in clinical response to SIMPONI at trial entry.

^c Patients were assessed for UC disease activity by partial Mayo score every 4 weeks (loss of response was confirmed by endoscopy). Therefore, a patient who maintained clinical response was in response at each evaluation through Week 54.

^d A patient had to be in remission at both Weeks 30 and 54 (without demonstrating a loss of response at any time point through Week 54) to achieve sustained remission.

14.5 Pediatric Ulcerative Colitis

The efficacy and safety of SIMPONI was evaluated in a multi-center, open-label pediatric study of 69 patients (NCT03596645). Efficacy was assessed in 66 patients weighing at least 15 kg with moderately to severely active ulcerative colitis defined as a Mayo score of 6 to 12 with an endoscopy subscore of ≥ 2 who had an inadequate response to corticosteroids, 6-mercaptopurine (6-MP), or azathioprine (AZA), or who were intolerant to or had medical contraindications for such therapies. Patients with prior exposure to TNF blockers were ineligible. Of the 66 subjects assessed for efficacy, the mean age was 13.4 years (range 4 to 17 years), the median weight was 51 kg, and 53% were female. Twenty-four percent identified as Hispanic or Latino; 71% identified as White, 18% as Asian, 3% as American Indian or Alaskan Native, 3% as Black, and 2% identified as part of multiple racial subgroups.

Patients weighing 15 to less than 45 kg received SIMPONI subcutaneously at 120 mg/m² at dosages of 120 mg/m² at Week 0, 60 mg/m² at Week 2 and 60 mg/m² every 4 weeks from Week 6 onward.

Patients weighing at least 45 kg received SIMPONI 200 mg at Week 0, 100 mg at Week 2 and 100 mg every 4 weeks from Week 6 onward.

The recommended body-weight tiered dosage for pediatric patients weighing 15 to less than 40 kg and 40 to less than 45 kg differs from the body surface area-based dosage administered in this study. There are no anticipated clinically relevant differences in efficacy between the recommended and studied pediatric dosages of SIMPONI [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*].

At weeks 6, and 54, efficacy was assessed by the Mayo score.

Efficacy Endpoints Week 6

The results of the primary endpoint of clinical remission at Week 6 and secondary endpoint of clinical response at Week 6, both assessed by Mayo score are shown in Table 10.

Table 10: Proportion of Pediatric Patients Weighing at Least 15 kg with UC in Clinical Remission and Clinical Response at Week 6

Endpoint	SIMPONI n (%) [90% CI] N=66
Clinical remission at Week 6 ^a	21 (32%) [22%, 41%]
Clinical response at Week 6 ^b	38 (58%) [48%, 68%]

^a Clinical remission is defined as a Mayo score ≤ 2 points, with no individual subscore > 1 .

^b Clinical response is defined as a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

Additional Secondary Endpoints

Of the 38 pediatric subjects with clinical response at Week 6, 13 subjects (34%) were in clinical remission and 15 subjects (39%) had endoscopic improvement, defined as an endoscopy subscore of 0 or 1 based on local endoscopy, at Week 54. Of the 21 subjects in clinical remission at Week 6, 12 subjects (57%) maintained clinical remission at Week 54.

16 HOW SUPPLIED/STORAGE AND HANDLING

SIMPONI® (golimumab) Injection is a preservative-free, sterile, clear to slightly opalescent, colorless to light yellow solution for subcutaneous use in a single-dose prefilled autoinjector (contains a prefilled glass syringe) or a single-dose prefilled glass syringe. The Type 1 glass syringe has a coated stopper. The fixed stainless-steel needle (5 bevel, 27G, ½ inch) is covered with a needle shield to prevent leakage of the solution through the needle and to protect the needle during handling prior to subcutaneous administration. The needle shield is made of a dry natural rubber containing latex.

50 mg/0.5 mL single-dose prefilled syringe	1 pack	NDC 57894-070-01
100 mg/mL single-dose prefilled syringe	1 pack	NDC 57894-071-01
50 mg/0.5 mL single-dose prefilled SmartJect® autoinjector	1 pack	NDC 57894-070-02
100 mg/mL single-dose prefilled SmartJect® autoinjector	1 pack	NDC 57894-071-02

Storage and Handling

Refrigerate SIMPONI between 36 °F to 46 °F (2 °C to 8 °C) in the original carton to protect from light until the time of use. Do not freeze. Do not shake. Do not use SIMPONI beyond the expiration date (EXP) on the carton or the expiration date on the prefilled syringe (observed through the viewing window) or the prefilled SmartJect® autoinjector.

If needed, SIMPONI may be stored at room temperature up to 77 °F (25 °C) for a maximum single period of 30 days in the original carton to protect from light. Once a syringe or autoinjector has been stored at room temperature, do not return the product to the refrigerator. If not used within 30 days at room temperature, discard SIMPONI.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use)

Patients should be advised of the potential benefits and risks of SIMPONI. Physicians should instruct their patients to read the Medication Guide before starting SIMPONI therapy and to read it each time the prescription is renewed.

Infections

Inform patients that SIMPONI may lower the ability of their immune system to fight infections. Advise patients not to start taking SIMPONI if they have an active infection. Instruct patients to contact their healthcare provider if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and hepatitis B reactivation [see *Warnings and Precautions* (5.1, 5.5)].

Malignancies

Inform patients that SIMPONI may increase their risk of lymphoma and other malignancies while receiving SIMPONI [see *Warnings and Precautions* (5.2)].

Hypersensitivity Reactions

Advise patients to stop taking SIMPONI and contact their healthcare provider immediately if they experience any symptoms of hypersensitivity reactions while taking SIMPONI [see *Warnings and Precautions* (5.12)].

Advise latex-sensitive patients that the needle cover on the prefilled syringe as well as the prefilled syringe in the prefilled SmartJect® autoinjector contains dry natural rubber (a derivative of latex) [see *How Supplied/Storage and Handling* (16)].

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, demyelinating disorders, autoimmune diseases, liver disease, or cytopenias [see *Warnings and Precautions* (5.3, 5.4, 5.5, 5.6, 5.10)].

Instructions for Safe Administration

The first injection should be performed under the supervision of a qualified healthcare professional. Only the prefilled syringe is recommended for pediatric self-injection.

SIMPONI Prefilled Syringe

- Adult and pediatric patients 12 years of age and older may self-inject with SIMPONI prefilled syringe.

SIMPONI SmartJect® Autoinjector

- Adult patients may self-inject with SIMPONI SmartJect® autoinjector.
- Use of the SmartJect® autoinjector for pediatric self-administration has not been evaluated.

If a patient or caregiver is to administer SIMPONI, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of SIMPONI.

Advise the patient to read the FDA-approved Instructions for Use and provide the following instructions to patients:

- Prior to use, remove the prefilled syringe or the prefilled SmartJect® autoinjector from the refrigerator and allow SIMPONI to sit at room temperature outside of the carton for at least 30 minutes and out of the reach of children.
- Do not warm SIMPONI in any other way. For example, do not warm SIMPONI in a microwave or in hot water.
- Do not remove the prefilled syringe needle cover or SmartJect® autoinjector cap while allowing SIMPONI to reach room temperature. Remove these immediately before injection.
- Do not pull the autoinjector away from the skin until you hear a first “click” sound and then a second “click” sound (the injection is finished and the needle is pulled back). It usually takes about 3 to 6 seconds but may take up to 15 seconds for you to hear the second “click” after the first “click”. If the autoinjector is pulled away from the skin before the injection is completed, a full dose of SIMPONI may not be administered.
- A puncture-resistant container for disposal of needles and syringes should be used. Patients or caregivers should be instructed in the technique of proper syringe and needle disposal, and be advised not to reuse these items.

Manufactured by:

Janssen Biotech, Inc.

Horsham, PA 19044, USA

U.S. License No. 1864

For patent information: www.janssenpatents.com

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MEDICATION GUIDE
SIMPONI® (SIM-po-nee)
(golimumab)

injection, for subcutaneous use

What is the most important information I should know about SIMPONI?

SIMPONI is a medicine that affects your immune system. SIMPONI can lower the ability of your immune system to fight infections. Some people have serious infections while taking SIMPONI, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that spread throughout their body. Some people have died from these serious infections.

- Your doctor should test you for TB and hepatitis B before starting SIMPONI.
- Your doctor should monitor you closely for signs and symptoms of TB during treatment with SIMPONI.

You should not start taking SIMPONI if you have any kind of infection unless your doctor says it is okay.

Before starting SIMPONI, tell your doctor if you:

- think you have an infection or have symptoms of an infection such as:
 - fever, sweat, or chills
 - muscle aches
 - cough
 - shortness of breath
 - blood in phlegm
 - weight loss
 - warm, red, or painful skin or sores on your body
 - diarrhea or stomach pain
 - burning when you urinate or urinate more often than normal
 - feel very tired
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live, have lived, or traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may happen or become more severe if you use SIMPONI. Ask your doctor if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B.
- use the medicine ORENCIA (abatacept), KINERET (anakinra), ACTEMRA (tocilizumab) or RITUXAN (rituximab).

After starting SIMPONI, call your doctor right away if you have any symptoms of an infection. SIMPONI can make you more likely to get infections or make worse any infection that you have.

Cancer

- For children and adults taking TNF-blocker medicines, including SIMPONI, the chances of getting cancer may increase.
- There have been cases of unusual cancers in children and teenage patients taking TNF-blocking agents.
- People with inflammatory diseases including rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis, especially those with very active disease, may be more likely to get lymphoma.
- Some people receiving medicines that are like SIMPONI, called TNF blockers, developed a rare type of cancer called hepatosplenic T cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn's disease or ulcerative colitis with a TNF blocker and another medicine called azathioprine or 6 mercaptopurine (6-MP).
- Some people treated with SIMPONI have developed certain kinds of skin cancer. If any changes in the appearance of your skin or growths on your skin occur during or after your treatment with SIMPONI, tell your doctor.
- You should see your doctor periodically for skin examinations, especially if you have a history of skin cancer.

What is SIMPONI?

SIMPONI is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker. SIMPONI is used to treat:

- adults with the medicine methotrexate to treat moderately to severely active rheumatoid arthritis (RA)
- adults with active psoriatic arthritis (PsA) alone or with methotrexate
- adults with active ankylosing spondylitis (AS)

- adults and children weighing at least 33 pounds (15 kg) with moderately to severely active ulcerative colitis (UC)
- You may continue to use other medicines that help treat your condition while taking SIMPONI, such as non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as recommended by your doctor.
- It is not known if SIMPONI is safe and effective in children under 18 years of age in RA, PsA, AS and or weighing less than 33 pounds (15 kg) in pediatric ulcerative colitis.

What should I tell my doctor before starting treatment with SIMPONI?

SIMPONI may not be right for you. See “**What is the most important information I should know about SIMPONI?**”

Before starting SIMPONI, tell your doctor about all your medical conditions, including if you:

- have an infection.
- have or have had lymphoma or any other type of cancer.
- have or had heart failure.
- have or have had a condition that affects your nervous system, such as multiple sclerosis or Guillain-Barré syndrome.
- have recently received or are scheduled to receive a vaccine. People taking SIMPONI should not receive live vaccines or treatment with a weakened bacteria (such as BCG for bladder cancer). People taking SIMPONI can receive non-live vaccines.
- have a baby and you were using SIMPONI during your pregnancy. Tell your baby’s doctor before your baby receives any vaccine. Your baby may have an increased chance of getting an infection for up to 6 months after birth.
- are allergic to rubber or latex. The needle cover on the prefilled syringe and SmartJect® autoinjector contains dry natural rubber.
- are pregnant or planning to become pregnant. It is not known if SIMPONI will harm your unborn baby.
- are breastfeeding or plan to breastfeed. You and your doctor should decide if you will take SIMPONI or breastfeed.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you:

- use ORENCIA (abatacept) or KINERET (anakinra). You should not take SIMPONI while you are also taking ORENCIA (abatacept) or KINERET (anakinra).
- use other TNF blocker medicines, including REMICADE (infliximab), HUMIRA (adalimumab), ENBREL (etanercept), or CIMZIA (certolizumab pegol).
- receive RITUXAN (rituximab) or ACTEMRA (tocilizumab).

Ask your doctor if you are not sure if your medicine is one listed above.

Keep a list of all your medicine with you to show your doctor and pharmacist each time you get a new medicine.

How should I use SIMPONI?

- SIMPONI is given as an injection under the skin (subcutaneous injection).
- SIMPONI comes in a prefilled syringe or SmartJect® autoinjector. Your doctor will prescribe the type that is best for you.
- If your doctor decides that you, your child, or a caregiver may be able to give your injections of SIMPONI at home, **you should receive training on the right way to prepare and inject SIMPONI. Do not try to inject SIMPONI yourself until you have been shown the right way to give the injections by your doctor or nurse.**
 - Adults and children 12 years of age and older may self-inject with SIMPONI prefilled syringe.
 - Only adults may self-inject with SIMPONI SmartJect autoinjector.
- Use SIMPONI exactly as prescribed by your doctor. Your doctor will tell you how much SIMPONI to inject and when to inject it depending on your medical condition.
- See the detailed **Instructions for Use** that comes with your SIMPONI for information about the right way to prepare and give your SIMPONI injections at home.

- Do not miss any doses of SIMPONI. If you miss a dose of SIMPONI, inject the missed dose as soon as possible. Then, take your next dose at your regular scheduled time. In case you are not sure when to inject SIMPONI, call your doctor or pharmacist.

What are the possible side effects of SIMPONI?

SIMPONI can cause serious side effects, including:

See “**What is the most important information I should know about SIMPONI?**”

Serious Infections.

- Some patients have an increased chance of getting serious infections while receiving SIMPONI. These serious infections include TB and infections caused by viruses, fungi, or bacteria that have spread throughout the body. Some patients die from these infections. **Do not** start using SIMPONI if you have an active infection. If you get an infection while receiving treatment with SIMPONI your doctor will treat your infection and may need to stop your SIMPONI treatment. Tell your doctor right away if you have any of the following signs of an infection while taking or after taking SIMPONI:
 - a fever
 - feel very tired
 - have a cough
 - have flu-like symptoms
 - warm, red, or painful skin
- Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with SIMPONI and during treatment with SIMPONI. Even if your TB test is negative your doctor should carefully monitor you for TB infections while you are taking SIMPONI. People who had a negative TB skin test before receiving SIMPONI have developed active TB. Tell your doctor if you have any of the following symptoms while taking or after taking SIMPONI:
 - cough that does not go away
 - low grade fever
 - weight loss
 - loss of body fat and muscle (wasting)

Hepatitis B infection in people who carry the virus in their blood.

- If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you use SIMPONI. Your doctor should do blood tests before you start treatment with SIMPONI and while you are using SIMPONI. Tell your doctor if you have any of the following symptoms of a possible hepatitis B infection:
 - feel very tired
 - dark urine
 - skin or eyes look yellow
 - little or no appetite
 - vomiting
 - muscle aches
 - clay-colored bowel movements
 - fevers
 - chills
 - stomach discomfort
 - skin rash

Heart failure, including new heart failure or worsening of heart failure that you already have, can happen in people who use TNF-blocker medicines including SIMPONI. If you develop new or worsening heart failure with SIMPONI, you may need to be treated in a hospital, and it may result in death.

- If you have heart failure before starting SIMPONI, your condition should be watched closely during treatment with SIMPONI.
- Call your doctor right away if you get new or worsening symptoms of heart failure during treatment with SIMPONI (such as shortness of breath or swelling of your lower legs or feet, or sudden weight gain).

Nervous System Problems. Rarely, people using TNF-blocker medicines, including SIMPONI, have nervous system problems such as multiple sclerosis or Guillain-Barré syndrome. Tell your doctor right away if you get any of these symptoms:

- vision changes
- weakness in your arms or legs
- numbness or tingling in any part of your body

Immune System Problems. Rarely, people using TNF-blocker medicines have developed symptoms that are like the symptoms of Lupus. Tell your doctor if you have any of these symptoms:

- a rash on your cheeks or other parts of the body
- sensitivity to the sun
- new joint or muscle pains
- becoming very tired
- chest pain or shortness of breath
- swelling of the feet, ankles, or legs

Liver Problems. Liver problems can happen in people who use TNF-blocker medicines, including SIMPONI. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms:

- feel very tired
- skin or eyes look yellow
- poor appetite or vomiting
- pain on the right side of your stomach (abdomen)

Blood Problems. Low blood counts have been seen with SIMPONI. Your body may not make enough blood cells that help fight infections or help stop bleeding. Symptoms include fever, bruising or bleeding easily, or looking pale. Your doctor will check your blood counts before and during treatment with SIMPONI.

Allergic Reactions. Allergic reactions can happen in people who use TNF-blocker medicines, including SIMPONI. Some reactions may be serious and can be life-threatening. Some of these reactions can happen after receiving your first dose of SIMPONI. Stop using SIMPONI and call your doctor right away if you have any of these symptoms of an allergic reaction:

- hives
- swollen face
- breathing trouble
- chest pain

The most common side effects of SIMPONI include:

- upper respiratory infection (runny nose, sore throat, and hoarseness or laryngitis)
- reaction at the site of injection (redness, swelling, itching, pain, bruising, or tingling)
- viral infections such as flu and oral cold sores

Psoriasis. Some people using SIMPONI had new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps that are filled with pus. Your doctor may decide to stop your treatment with SIMPONI.

These are not all of the possible side effects of SIMPONI. Tell your doctor about any side effect that bothers you or does not go away. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SIMPONI?

- Refrigerate SIMPONI between 36 °F to 46 °F (2 °C to 8 °C).
- If needed, you may store SIMPONI at room temperature up to 77 °F (25 °C) for one period of time up to 30 days.
 - Write the date of that you remove SIMPONI from the refrigerator on the carton.
 - If SIMPONI has reached room temperature, **do not** put it back in the refrigerator.
 - Throw away SIMPONI if it has been kept at room temperature for 30 days and has not been used.
- **Do not** freeze SIMPONI.
- Keep SIMPONI in the original carton to protect it from light when not being used.
- **Do not** shake SIMPONI.
- Do not use SIMPONI after the expiration date on the carton or on the prefilled syringe, prefilled pen or SmartJect® autoinjector.

Keep SIMPONI and all medicines out of the reach of children.

General information about the safe and effective use of SIMPONI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SIMPONI for a condition for which it was not prescribed. Do not give SIMPONI to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about SIMPONI. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about SIMPONI that is written for health professionals. For more information go to www.simpONI.com or call 1-800-JANSSEN (1-800-526-7736).

What are the ingredients in SIMPONI?

Active ingredient: golimumab.

Inactive ingredients: L-histidine, and L-histidine monohydrochloride monohydrate, polysorbate 80, sorbitol, and water for injection. SIMPONI does not contain preservatives.

Manufactured by: Janssen Biotech, Inc. Horsham, PA 19044, USA. U.S. License No. 1864.

For patent information: www.janssenpatents.com

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: Oct 2025

INSTRUCTIONS FOR USE
SIMPONI® (SIM-po-nee)
(golimumab)
injection, for subcutaneous use

This Instructions for Use contains information on how to inject SIMPONI using the SmartJect Autoinjector.

Please read this Instructions for Use before using SIMPONI SmartJect and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

Important information

If your doctor decides that you or a caregiver may be able to give your SIMPONI injections at home, you should receive training on the right way to prepare and inject SIMPONI using SmartJect.

Do not try to inject SIMPONI yourself until you have been shown the right way to give the injections by your doctor or nurse.

Do not pinch the skin while injecting. Pinching the skin can cause failure of the device and injury, including needlestick injury.

Do not inject into the arm to avoid failure of the device or injury.



Store SIMPONI in the refrigerator at **36°F to 46°F** (2°C to 8°C).

Do not freeze SmartJect.

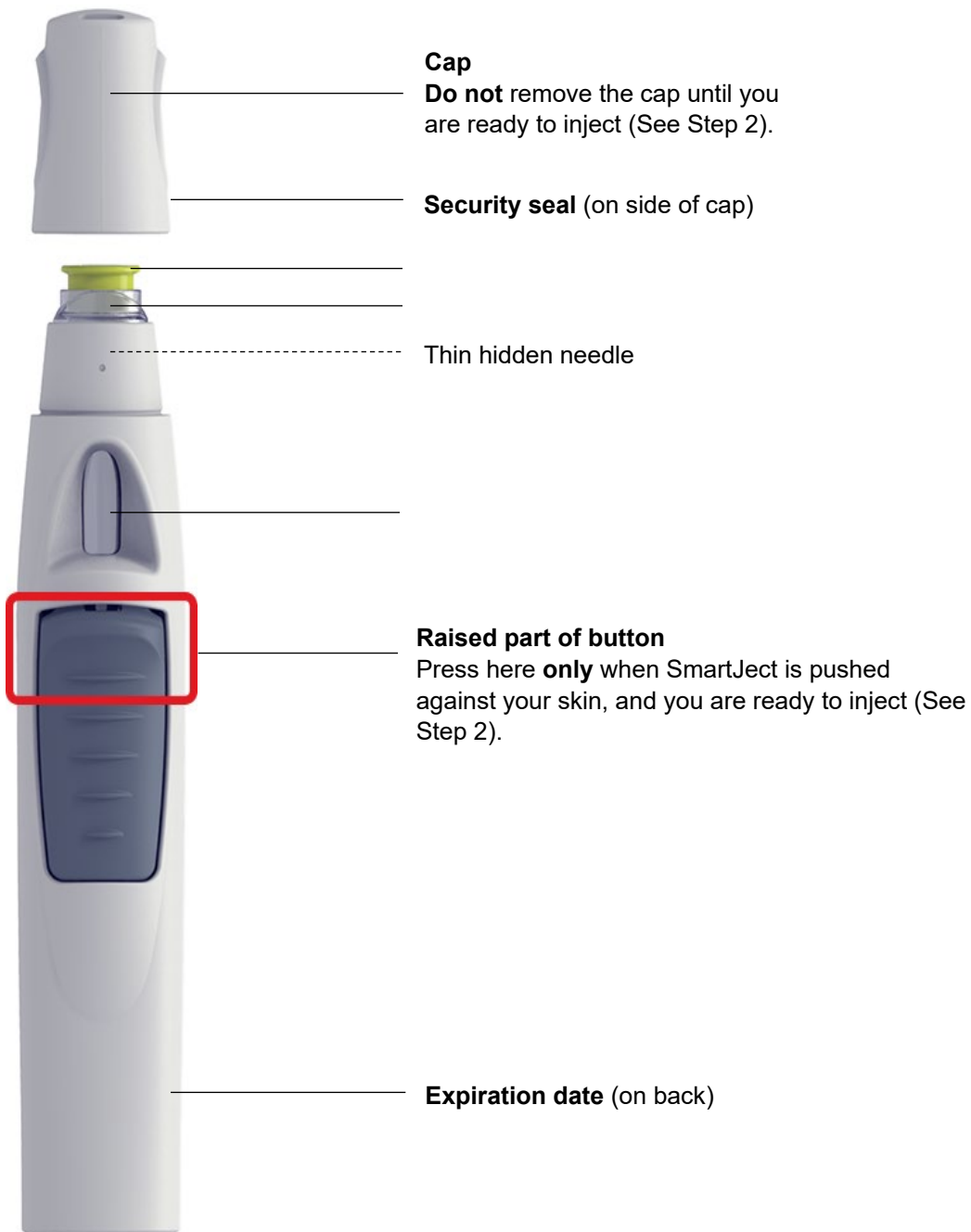
Do not shake SmartJect.

If needed, store SIMPONI at room temperature, up to 77°F (25°C) for one period of time up to 30 days. Do not return it to the refrigerator. Throw away (dispose of) if not used within 30 days at room temperature.

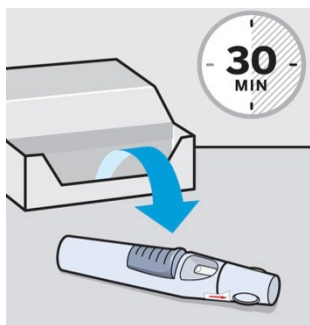
Keep SIMPONI in the original carton to protect from light before use.

Keep SIMPONI and all medicines out of the reach of children.

Your SmartJect at-a-glance



1. Preparing to inject SIMPONI using SmartJect



Take out SmartJect

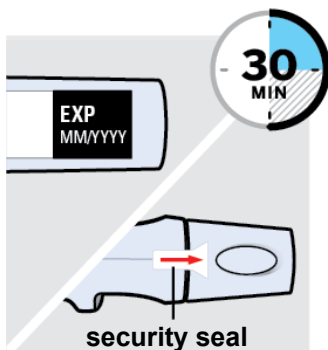
Take SmartJect out of the refrigerator and remove it from the carton.

Place on a flat surface out of reach of children.

SmartJect should sit at room temperature for **at least 30 minutes** to ensure proper injection.

Do not warm any other way.

Do not remove the cap yet.



Inspect SmartJect

Check the expiration date ('EXP') on the back of SmartJect.

Do not use SIMPONI SmartJect if the expiration date has passed. Call your doctor or pharmacist for a refill.

Check the security seal on the cap.

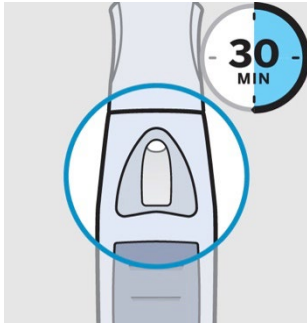
Do not inject if the seal is broken.

Gather supplies

While SmartJect sits at room temperature for 30 minutes, gather your supplies:

- **1 Alcohol swab**
- **1 Cotton ball or gauze pad**

- **1 Sharps** container (See Step 3)

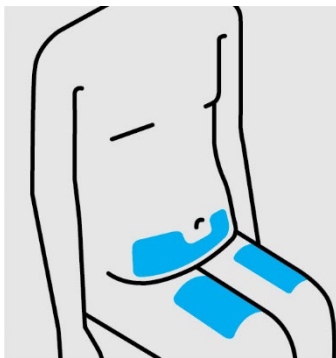


Check liquid in the SmartJect

After 30 minutes, check the liquid in the viewing window. It should be clear to slightly yellow and may contain tiny white or clear particles.

It is also normal to see a small air bubble.

Do not inject if the liquid is cloudy or discolored, or has large particles.



Do not inject into the arm to avoid failure of the device or injury.

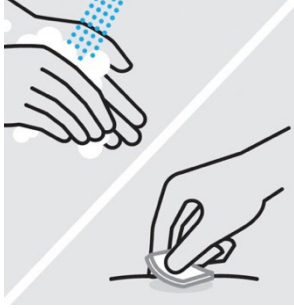
Choose injection site

Select from the following areas for your injection:

- Front of thighs
- Lower abdomen (**do not** use the 2-inch area around your navel (belly-button))
- **Do not** inject into the arms

Choose a different site within your preferred area for each injection.

Do not inject into skin that is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.

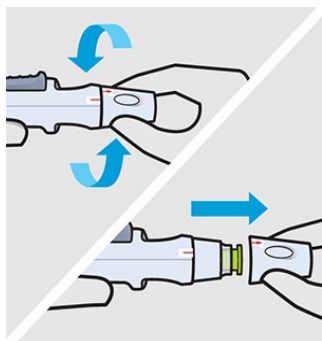
**Wash hands and clean injection site**

Wash your hands well with soap and warm water.

Wipe your chosen injection site with an alcohol swab and allow it to dry.

Do not touch, fan or blow on the injection site after you have cleaned it.

2. Injecting SIMPONI using SmartJect



Remove cap

Twist the cap to break the security seal, then pull it straight off. Dispose of the cap right away.

It is important to **inject within 5 minutes** of removing the cap.

Do not put the cap back on, this may damage the hidden needle.

Do not inject if SmartJect is dropped **without** the cap on.

Do not pinch the skin while injecting. Pinching the skin can cause failure of the device and injury, including needlestick injury.



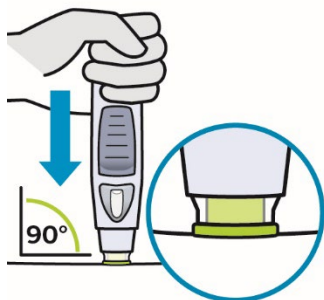
Position

Hold SmartJect comfortably with one hand **above the blue button** and position it straight onto your skin, as shown.

Make sure the green safety sleeve is stable and as flat as possible against your skin. If the device is not stable during the injection, you risk bending the needle.

Do not pinch your skin while positioning SmartJect onto your skin.

Do not pinch the skin to avoid injury, including needlestick injury.



Push down

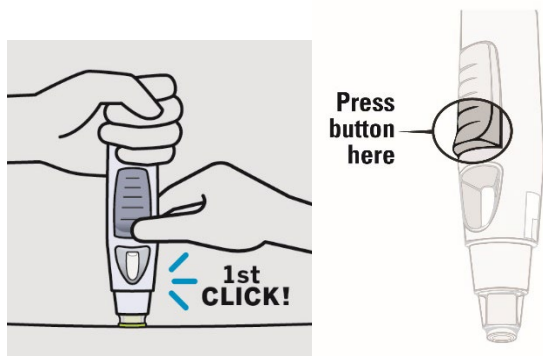
Push the open end of SmartJect against your skin at a 90-degree angle. Apply enough pressure to slide the green safety sleeve up and to keep it inside the clear cover. Only the wider part of the green safety sleeve stays outside of the clear cover.

Do not touch or press the blue button while pushing SmartJect against your skin.

⚠ The green safety sleeve helps prevent accidental injections.

Pushing the blue button before the safety sleeve is pressed down can lead to device failure.

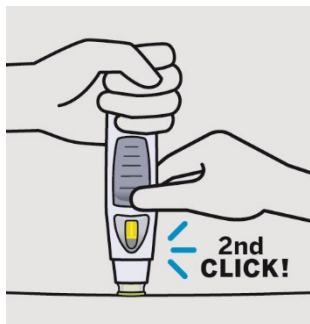
Inject without pinching the skin.



Press button and wait

Keep holding SmartJect against your skin. Use your **other hand** to press the **raised part of the blue button** to start your injection. **Do not** press the button until SmartJect is pressed against your skin and the safety sleeve slides into the clear cover.

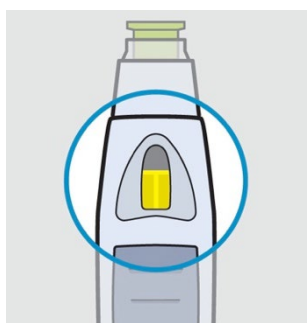
You will hear a **loud 1st 'click'** as you press the button. This is normal, the medication is just beginning to be delivered. You may or may not feel a needle prick.



Listen for 2nd 'click'

Keep holding SmartJect against your skin until you hear the **2nd 'click'** (or for 15 seconds). It usually takes about 3-6 seconds, but may take up to 15 seconds for you to hear the second 'click' sound.

The 2nd 'click' means the injection is complete and you can lift SmartJect from your skin.



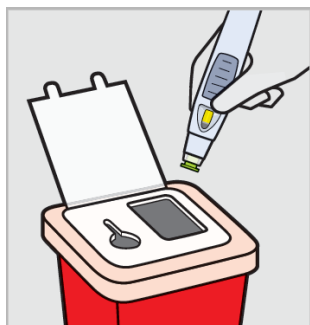
Check the viewing window

After lifting SmartJect from your skin, look for the yellow indicator in the viewing window to confirm SmartJect worked properly. The yellow indicator will fill about half of the viewing window.

If you do not see the yellow indicator, call 800-JANSSEN (800-526-7736).

Do not administer a second dose without speaking to your doctor.

3. Disposing of SIMPONI SmartJect



Dispose of your SmartJect

Put your used SmartJect in an FDA-cleared sharps disposal container right away after use.

Do not recycle your used sharps disposal container.

For more information, see “Helpful tips”.



Check injection site

There may be a small amount of blood or liquid at the injection site.

Hold pressure over your skin with a cotton ball or gauze pad until any bleeding stops.

Do not rub the injection site.

If needed, cover injection site with a bandage. Your injection is now complete!



Need help?

Call your doctor or pharmacist to talk about any questions you may have. For additional assistance or to share your feedback call 800-JANSSEN (800-526-7736).

Helpful tips

If you are having difficulty injecting:

- ✓ Make sure the cap is removed.
- ✓ Make sure SmartJect is pushed against your skin, so the green safety sleeve slides into the clear cover.
- ✓ Make sure you are pressing the **raised part of button**.
- ✓ If the button is hard to depress, do not press the button harder. Let go of the button, then lift SmartJect and start again. Ensure no pressure is on the button until the green safety sleeve is fully depressed against the skin, then press the button.
- ✓ Try a different injection site.

Additional Disposal Information

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic
- can be closed with a tight -fitting, puncture-resistant lid, without sharps being able to come out
- upright and stable during use
- leak-resistant
- properly labeled to warn of hazardous waste inside the container

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
US License No. 1864

Revised: September 2025

Instructions for Use
SIMPONI®
(SIM-po-nee)
(golimumab)
Prefilled Syringe



SINGLE-DOSE

Important

SIMPONI comes as a single-dose prefilled syringe containing one 50 mg or one 100 mg dose. Each SIMPONI prefilled syringe can only be used one time. Throw away (dispose of) the used prefilled syringe (See Step 3) after one dose, even if there is medicine left in it. Do not reuse your SIMPONI prefilled syringe.

The SIMPONI prefilled syringe should be administered by a healthcare provider, adult, child 12 years of age and older, or caregiver.

If your healthcare provider decides that you, your child or a caregiver may be able to give your injections of SIMPONI at home, you should receive training on the right way to prepare and inject SIMPONI using the prefilled syringe before attempting to inject.

Do not try to inject yourself until you have been shown the right way to give the injections by your healthcare provider.

Read this Instructions for Use before using your SIMPONI prefilled syringe and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

The SIMPONI prefilled syringe is intended for injection under the skin, not into the muscle or vein. After injection, the needle will retract into the body of the device and lock into place.



Storage information

Store SIMPONI in the refrigerator between **36 °F to 46 °F** (2 °C to 8 °C).

If needed, store SIMPONI at room temperature, up to 77 °F (25 °C) for one period of time up to 30 days. Do not return it to the refrigerator. Throw away (dispose of) if not used within 30 days at room temperature.

Do not freeze SIMPONI prefilled syringe.

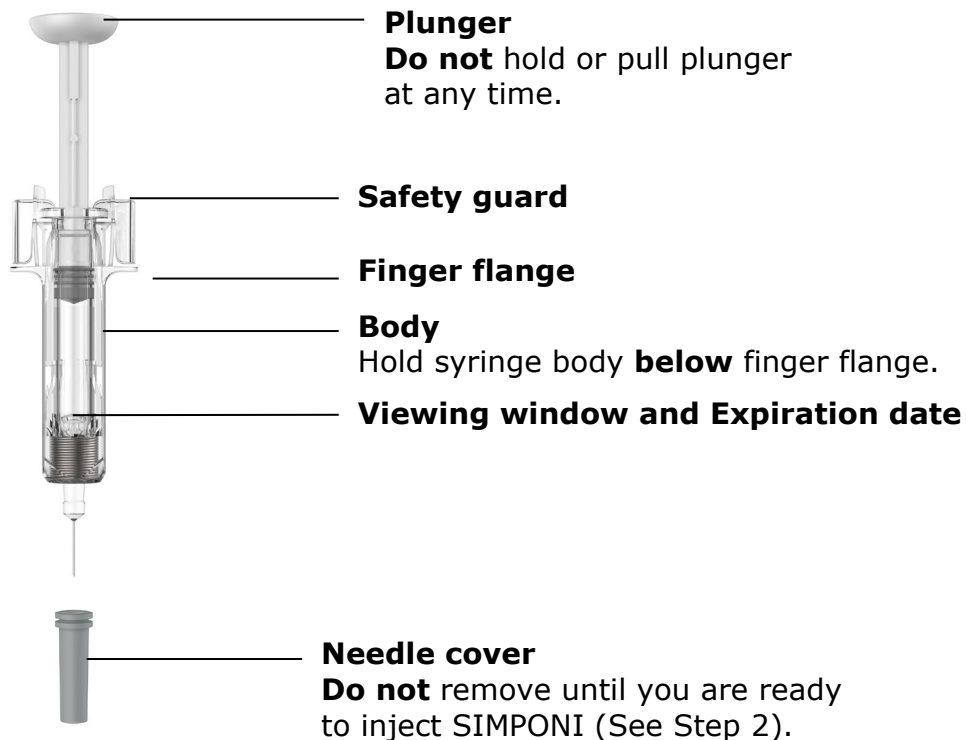
Do not shake SIMPONI prefilled syringe.

Keep SIMPONI prefilled syringe in the original carton to protect from light before use.

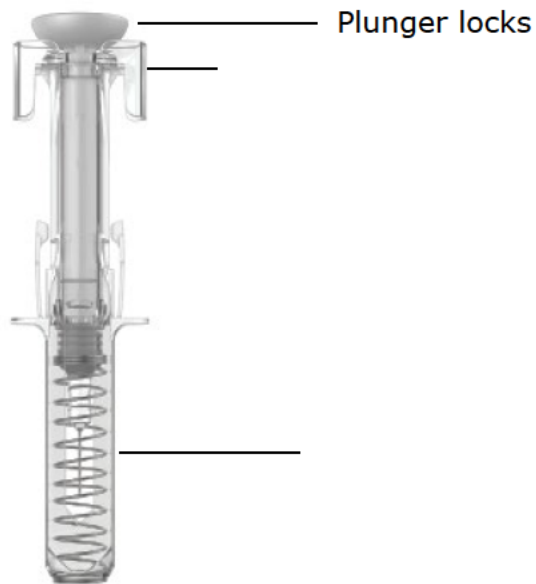
Keep SIMPONI prefilled syringe and all medicines out of the reach of children.

Prefilled syringe parts

Before use



After use



You will need these supplies:

- **1 SIMPONI prefilled syringe**

**Not provided in the SIMPONI
prefilled syringe carton:**

- **1 Alcohol swab**
- **1 Cotton ball or gauze pad**
- **1 Adhesive bandage**
- **1 Sharps container** (See Step 3)

1. Prepare for your injection



Inspect carton

Remove your SIMPONI prefilled syringe carton from the refrigerator.

Remove the prefilled syringe from the carton and let it sit on a flat surface at room temperature for **at least 30 minutes** before use.

Do not warm the prefilled syringe any other way.

Check the expiration date ('EXP') on the back panel of the carton and on the prefilled syringe (through the viewing window).

Do not use your prefilled syringe if the expiration date has passed.

Do not inject SIMPONI if the perforations on the carton are broken. Call your healthcare provider or pharmacist for a refill.



Choose injection site

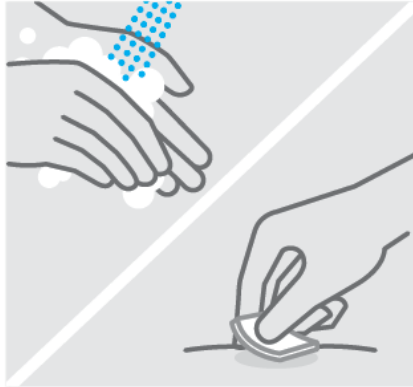
Select from the following areas for your injection:

- **Front of thighs** (recommended)
- Lower stomach area (lower abdomen), except for a 2-inch area right around your navel (belly-button)
- Back of upper arms (only if someone else is giving you the injection)

Choose a different site within your preferred area for each injection.

Do not inject into skin that is tender, bruised, red, hard, thick or scaly.

Do not inject into areas with scars or stretch marks.

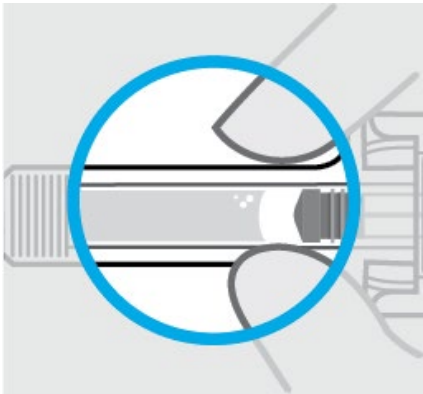


Clean injection site

Wash your hands well with soap and warm water.

Wipe your chosen injection site with an alcohol swab and allow it to dry.

Do not touch, fan, or blow on the injection site after you have cleaned it.

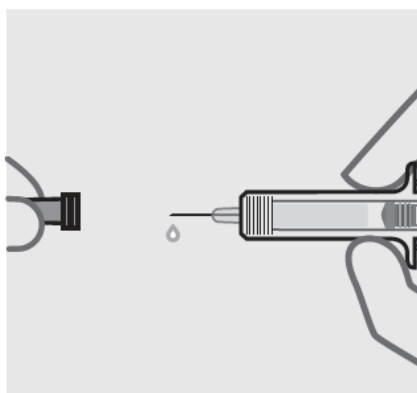


Inspect liquid

Check the SIMPONI prefilled syringe liquid in the viewing window. It should be clear and colorless to light yellow and may contain tiny white or clear particles. You may also see one or more air bubbles. This is normal.

Do not inject if the liquid is cloudy or discolored, or has large particles. Call your healthcare provider or pharmacist for a refill.

2. Inject SIMPONI using prefilled syringe



Remove needle cover

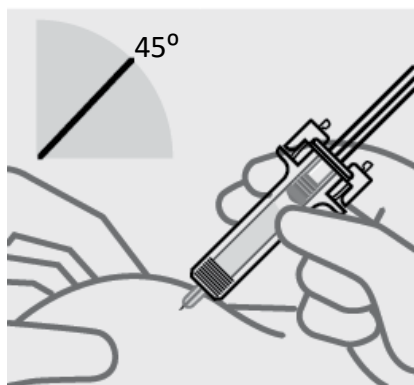
Hold your prefilled syringe by the body and pull needle cover straight off. It is normal to see a drop of liquid.

Inject SIMPONI within 5 minutes of removing the needle cover.

Do not put needle cover back on, as this may damage the needle or cause a needle stick injury.

Do not touch needle or let it touch any surface.

Do not use a SIMPONI prefilled syringe if it is dropped. Call your healthcare provider or pharmacist for a refill.



Position fingers and insert needle

Place your thumb, index and middle fingers **directly under the finger flange**, as shown.

Do not touch plunger or area above finger flange as this may cause the needle safety device to activate.

Use your other hand to pinch skin at the injection site. Position syringe at about a 45 degree angle to the skin.

It is important to pinch enough skin to **inject under the skin** and not into the

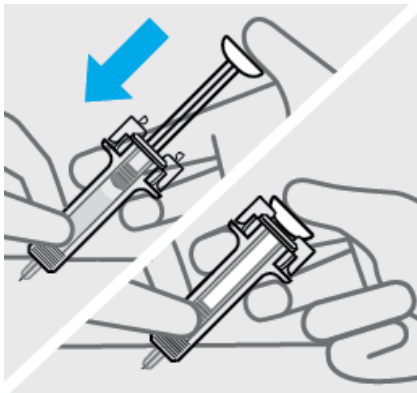
muscle.

Insert needle with a quick, dart-like motion.



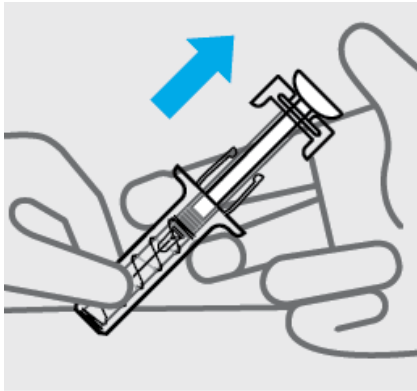
Release pinch and reposition hand

Use your free hand to grasp the body of the prefilled syringe.



Press plunger

Place thumb from the opposite hand on the plunger and press the plunger **all the way down until it stops.**



Release pressure from plunger

The safety guard will cover the needle and lock into place, removing the needle from your skin.

3. After your injection



Dispose of your prefilled syringe

Put your used SIMPONI prefilled syringe in an approved sharps disposal container right away after use.

Do not throw away (dispose of) your used SIMPONI prefilled syringe in your household trash.

Do not recycle your used sharps disposal container.

For more information, see "How should I dispose of the used prefilled syringe?"



Check injection site

There may be a small amount of blood or liquid at the injection site. Hold pressure over your skin with a cotton ball or gauze pad until any bleeding stops.

Do not rub the injection site.

If needed, cover injection site with a bandage.



Need help?

Call your healthcare provider to talk about any questions you may have. For additional assistance or to share your feedback call 1-800-JANSSEN (1-800-526-7736).

How should I dispose of the used prefilled syringe?

If you do not have an approved sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
- upright and stable during use
- leak-resistant
- properly labeled to warn of hazardous waste inside the container

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away (dispose of) used needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: October 2025

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125289Orig1s157

MULTI-DISCIPLINE REVIEW

Summary Review

Statistical Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy supplement																	
Application Number(s)	BLA 125289/s-157																	
Priority or Standard	Standard																	
Submit Date(s)	12/12/2024																	
Received Date(s)	12/12/2024																	
PDUFA Goal Date	12/12/2025																	
Division/Office	Division of Gastroenterology																	
Review Completion Date	09/25/2025																	
Established/Proper Name	Golimumab																	
(Proposed) Trade Name	Simponi																	
Pharmacologic Class	Tumor necrosis factor (TNF) blocker																	
Code name	L04AB06																	
Applicant	Janssen Biotech, Inc.																	
Dosage form	Subcutaneous Injection (SC)																	
Applicant proposed Dosing Regimen	<table border="1"> <tr> <th>Weight Range</th><th>Induction Dose Regimen (Week 0 and Week 2)</th><th>Maintenance Dose Regimen (Week 6 and Q4W Thereafter)</th></tr> <tr> <td>≥40 kg</td><td>200→100 mg</td><td>100 mg Q4W</td></tr> <tr> <td>≥15 kg to <40 kg</td><td>100→50 mg</td><td>50 mg Q4W</td></tr> </table>	Weight Range	Induction Dose Regimen (Week 0 and Week 2)	Maintenance Dose Regimen (Week 6 and Q4W Thereafter)	≥40 kg	200→100 mg	100 mg Q4W	≥15 kg to <40 kg	100→50 mg	50 mg Q4W	(b) (4)							
Weight Range	Induction Dose Regimen (Week 0 and Week 2)	Maintenance Dose Regimen (Week 6 and Q4W Thereafter)																
≥40 kg	200→100 mg	100 mg Q4W																
≥15 kg to <40 kg	100→50 mg	50 mg Q4W																
Applicant Proposed Indication(s)/Population(s)	(b) (4)																	
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	64766004 Ulcerative colitis (disorder)																	
Recommendation on Regulatory Action	Approval																	
Recommended Indication(s)/Population(s)	Treatment of adults and pediatric patients weighing 15 kg or greater with moderately to severely active UC																	
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	64766004 Ulcerative colitis (disorder)																	
Recommended Subcutaneous Dosage for Adults and Pediatric Patients Weighing at least 15 kg with Moderately to Severely Active Ulcerative Colitis	<table border="1"> <tr> <th rowspan="2">Weight for Patients With UC</th><th colspan="3">Recommended Dosage of SIMPONI</th></tr> <tr> <th>Week 0</th><th>Week 2</th><th>Week 6 and Every 4 Weeks Thereafter</th></tr> <tr> <td>Adults and pediatric patients 40 kg and greater</td><td>200 mg</td><td>100 mg</td><td>100 mg</td></tr> <tr> <td>Pediatric patients at least 15 kg to less than 40 kg</td><td>100 mg</td><td>50 mg</td><td>50 mg</td></tr> </table>	Weight for Patients With UC	Recommended Dosage of SIMPONI			Week 0	Week 2	Week 6 and Every 4 Weeks Thereafter	Adults and pediatric patients 40 kg and greater	200 mg	100 mg	100 mg	Pediatric patients at least 15 kg to less than 40 kg	100 mg	50 mg	50 mg		
Weight for Patients With UC	Recommended Dosage of SIMPONI																	
	Week 0	Week 2	Week 6 and Every 4 Weeks Thereafter															
Adults and pediatric patients 40 kg and greater	200 mg	100 mg	100 mg															
Pediatric patients at least 15 kg to less than 40 kg	100 mg	50 mg	50 mg															

Abbreviations: BLA, biologics license application; IgG, immunoglobulin G; mAb, monoclonal antibody; NDA, new drug application; PDUFA, Prescription Drug User Fee Act; Q4W, every 4 weeks; TNF-α, tumor necrosis factor-alpha

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Abbreviations: CDRH, Center of Devices and Radiological Health; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DPMH, Division of Pediatric and Maternal Health; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology

Glossary

ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARC	Anticipated Event Review Committee
AS	ankylosing spondylitis
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
5-ASA	5-aminosalicylic acid
BLA	biologics license application
BSA	body surface area
CDER	Center for Drug Evaluation and Research
CDS	clinical data scientist
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent clearance
C _{max}	maximum concentration
C _{trough}	trough concentration
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CS	corticosteroid
CSR	clinical study report
DBL	database lock
DMEPA	Division of Medication Error Prevention and Analysis
eCRF	electronic case report form
E-R	exposure-response
FDA	Food and Drug Administration
HF	human factor
IBD	inflammatory bowel disease
IgG	immunoglobulin G
IgM	immunoglobulin M
IND	investigational new drug
IR	information request
IV	intravenous(ly)
KLH	keyhole limpet hemocyanin
NDA	new drug application
NOAEL	no-observed-adverse-effect level
OCP	Office of Clinical Pharmacology
OPQ	Office of Pharmaceutical Quality
OPQAI	Office of Pharmaceutical Quality Assessment III

PFP prefilled pen
 PFS prefilled syringe

(b) (4)

PGA physician's global assessment
 PK pharmacokinetics
 PMC postmarketing commitment
 popPK population pharmacokinetics
 PsA psoriatic arthritis
 PT preferred term
 PUCAI Pediatric Ulcerative Colitis Activity Index
 Q4W every 4 weeks
 RA rheumatoid arthritis
 SAE serious adverse event
 SAP statistical analysis plan
 sBLA supplemental biologics license application
 SC subcutaneous(ly)
 SOC system organ class
 TEAE treatment-emergent adverse event
 TNF tumor necrosis factor
 TNF- α tumor necrosis factor-alpha
 UC ulcerative colitis
 ULN upper limit of normal
 URTI upper respiratory tract infection
 U.S. United States (adj.)
 USPI United States prescribing information
 V/F apparent volume of distribution

1 Executive Summary

1.1. Product Introduction

Simponi (golimumab) injection is a human monoclonal antibody with an immunoglobulin G (IgG) one heavy chain isotype) and a kappa light chain isotype. Golimumab binds with high affinity to both soluble and transmembrane forms of tumor necrosis factor-alpha (TNF- α) and inhibits TNF- α bioactivity. Golimumab is given by subcutaneous (SC) injection. Other members of this therapeutic class include infliximab, etanercept, adalimumab, and certolizumab pegol.

Golimumab was first approved in the United States on April 24, 2009, for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). The indications were subsequently expanded to include moderately to active psoriatic arthritis (PsA) and ankylosing spondylitis (AS), nonradiographic axial spondyloarthritis in adult patients. On May 15, 2013, golimumab was approved adult patients with moderately to severely active ulcerative colitis (UC) who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for:

- Inducing and maintaining clinical response
- Improving endoscopic appearance of the mucosa during induction
- Inducing clinical remission
- Achieving and sustaining clinical remission in induction responders

The approved dosage for adults with UC is a 200 mg SC injection at Week 0 followed by a 100 mg SC injection at Week 2 as induction treatment (noted as 200 mg $\rightarrow$ 100 mg), followed by maintenance therapy of 100 mg SC every 4 weeks (Q4W). The Simponi SC formulation is not currently approved for use in pediatric patients in the United States.

While the current submission pertains to Simponi (golimumab) injection, another form of golimumab, Simponi Aria, is administered intravenous (IV) and is approved for the treatment of adult patients with RA, PsA, and AS (similar to Simponi SC injection), and also patients with active polyarticular juvenile idiopathic arthritis and juvenile PsA in children ≥ 2 years of age and older.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Expansion of the indication for golimumab to include pediatric patients weighing at least 15 kg with moderately to severely active UC is supported by data from adequate and well controlled studies in adults and children, and relies upon partial extrapolation of efficacy, given the established similarity in disease progression and anticipated response to treatment between adult and pediatric patients with UC.

The pediatric UC development program consisted of Study UCO1001 (a phase 1b, single-arm, open-label study of 35 pediatric UC patients to establish pharmacokinetics and dosing), and Study UCO3003 (a phase 3, single-arm, open-label trial in 69 pediatric patients aged 2 to 17 years). Efficacy was evaluated in Study UCO3003 based upon clinical remission using the full Mayo score.¹ The study met its primary efficacy endpoint, demonstrating clinical remission at Week 6 in 31.8% of patients (90% confidence interval [CI]: 22.4%-41.2%), which exceeded the prespecified success criterion when compared to a historical adult placebo rate of 11.2% derived from a meta-analysis of seven phase 3 adult UC studies using a random-effects model with sample-size weighting.

The clinical remission rate of 31.8% at Week 6 is numerically higher than the remission rate of 17.8% in the adult golimumab UC induction study C0524T17. The clinical response rate of 57.6% at Week 6 is numerically comparable to the adult golimumab UC induction study C0524T17 which showed response rates of 51.0%. Long-term efficacy was demonstrated with 57.1% of Week 6 remitters maintaining clinical remission at Week 54, meeting the post hoc success criterion for maintenance of remission.

Some secondary endpoints including endoscopic healing² at Week 54 and clinical remission at Week 54 among Week 6 responders did not meet their respective success criteria. However, it is reassuring that Bayesian analyses demonstrated that minimal borrowing of adult data (one to three subjects) would be sufficient to achieve success for the Week 54 endpoints, indicating that the pediatric study provides adequate evidence of long-term efficacy.

The efficacy results are further supported by population pharmacokinetic modeling and simulation that confirmed the proposed weight-tiered dosing regimen (200 mg→100 mg for patients ≥40 kg; 100 mg→50 mg for patients 15-<40 kg) achieves golimumab exposures comparable to those observed in Study UCO3003 and the adult UC program.

The totality of evidence, including the consistency of results with adult experience, the established mechanism of action of TNF- α inhibition in UC, and the similar pathophysiology between pediatric and adult UC, provides substantial evidence that golimumab is effective for the treatment of moderately to severely active ulcerative colitis in pediatric patients weighing 15 kg and above.

¹ This endpoint was selected to facilitate extrapolation to the adult studies. The Applicant also provided additional analyses using the currently recommended definition of Remission per the modified Mayo score (excluding physician global assessment) and results were consistent.

² The Applicant's endpoint of "endoscopic healing" is generally consistent with the Division's description of "endoscopic improvement;" herein, defined as a Mayo endoscopy subscore of 0 or 1 on local endoscopy.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ulcerative colitis (UC) in pediatric patients represents a serious, chronic inflammatory condition with significant unmet medical need. The disease course in children may be more aggressive as compared to adults, with children more likely to present with pancolitis and severe manifestations.^{3,4} The prevalence of pediatric patients with UC has increased over time in the United States, and highlighting the severity and progression of disease in this population, 16-20% of pediatric as compared to 7-15% of adults patients require colectomy within 10 years of diagnosis.^{5,6,7,8} Currently, only two therapies are approved for moderately to severely active pediatric UC: (i) infliximab, which is administered intravenously (IV), for patients ≥ 6 years of age, and (ii) adalimumab, which is administered subcutaneously, for patients ≥ 5 years of age. Of note, infliximab has associated IV infusion treatment burden and potential infusion reactions, while the adalimumab treatment regimen requires frequent, every other week administration.

The primary evidence of efficacy of golimumab for the treatment of pediatric UC comes from the pediatric golimumab Study UCO3003. This study is a single-arm, open-label phase 3 trial which enrolled subjects 4 to 17 years of age. Efficacy was assessed in 66 subjects who met the criteria for moderately to severely active disease at enrollment. The primary endpoint of this study was successfully met, which demonstrated clinical remission at Week 6 in 32% of subjects (90% CI: 22%-41%). This result exceeded the

³ Siow VS, et al. Management of acute severe ulcerative colitis in children. *Semin Pediatr Surg.* 2017;26(6):367-72.

⁴ Afzali A, Katz S. Inflammatory Bowel Disease in the Baby-to-Baby Boomer: Pediatric and Elderly Onset of IBD. *Curr Treat Options Gastroenterol.* 2018;16(3):289-305.

⁵ Virta LJ, et al. Inflammatory Bowel Disease Incidence is on the Continuous Rise Among All Paediatric Patients Except for the Very Young: A Nationwide Registry-based Study on 28-Year Follow-up. *J Crohns Colitis.* 2017 Feb;11(2):150-156.

⁶ Hope E, et al. The Impact of Biologic Therapies on Rate of Colectomy in Paediatric-onset Ulcerative Colitis - A Population-Based Cohort Study. *J Pediatr Surg.* 2024 Feb;59(2):230-234.

⁷ Fumery M, et al. Review article: the natural history of paediatric-onset ulcerative colitis in population-based studies. *Aliment Pharmacol Ther.* 2016 Feb;43(3):346-55.

⁸ Feuerstein JD, et al. AGA Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology.* 2020 Apr;158(5):1450-1461.

prespecified success criterion when compared to a historical adult placebo rate of 11%, as derived from a meta-analysis of 7 phase 3 adult UC studies using a random-effects model with sample-size weighting. Additionally, the clinical response and remission rates at Week 6 (58% and 32%, respectively) in Study UCO3003, were numerically comparable or higher to the response and remission rates observed in the adult golimumab UC induction trial CO524T17 (51% and 18%, respectively). For support of the long-term efficacy, 57% (12/21) of Week 6 remitters maintained clinical remission at Week 54, meeting the post hoc success criterion for maintenance of remission. While some secondary endpoints, including clinical remission at Week 54 among patients in clinical response at Week 6 [34% (13/38)] and endoscopic healing at Week 54 [39% (15/38)], did not meet the post hoc success criteria when comparing with adult historical placebo control, Bayesian analyses demonstrated that minimal borrowing of adult data (1 to 3 subjects) would be sufficient to achieve success for these Week 54 endpoints, indicating that the pediatric study provides adequate evidence of long-term efficacy. Overall, the pediatric UC study efficacy results were numerically comparable to the efficacy of the adult UC golimumab trials.

Additionally, population pharmacokinetic modeling and simulation that confirmed the proposed weight-tiered dosing regimen (200 mg→100 mg for patients ≥40 kg; and 100 mg→50 mg for patients 15-<40 kg) achieves golimumab exposures comparable to those observed in Study UCO3003 and the adult UC program further supports the efficacy results.

The safety database included 69 subjects (46 patient-years of exposure up to Week 54), which demonstrated a safety profile consistent with the known risks of tumor necrosis factor-alpha (TNF-α) inhibitors and adult golimumab experience with no pediatric-specific safety signals identified. Most patients (97%) experienced at least one treatment-emergent adverse event (TEAE), with the majority being mild to moderate in severity. The most common TEAEs included worsening UC (62%), viral infections (including COVID-19 infection during the pandemic [39%]), and upper respiratory tract infections (20%). TEAEs of headache (17%) and pyrexia (10%), occurred in ≥10% of the pediatric study population and warrant inclusion into Simponi labeling as adverse drug reactions (ADRs) that were not previously labeled based on adult trial data. Serious adverse events (SAEs) occurred in 41% of subjects, primarily consisting of worsening UC (26%), with 3 cases of opportunistic infections reported (including 1 case of *Candida* bacteremia), which are consistent with the immunosuppressive effects of TNF inhibitors. Importantly, no deaths, tuberculosis, or malignancies were reported during the study period, and the safety profile was generally similar across demographic subgroups, though interpretation is limited by small sample sizes.

While the study design presents some limitations including the single-arm design without a concurrent control group, limited safety data in youngest patients (4 years of age was the lowest age and 16 kg was the smallest weight for enrolled subjects), small overall safety database, some secondary endpoints not meeting prespecified success criteria, and limited representation of diverse racial and ethnic populations, the totality of evidence supports a favorable benefit-risk profile. The application originally

proposed

(b) (4)

. Moreover, since no clinical data were available to inform the safety and efficacy of golimumab treatment of patients with UC weighing less than 15 kg, the recommended indication includes the treatment of patients ≥ 15 kg with the currently available 50 mg and 100 mg device presentations (i.e., prefilled syringes and autoinjectors).

The demonstrated efficacy with clinically meaningful response rates and acceptable safety profile consistent with the TNF- α inhibitor class provide meaningful clinical benefit for this serious condition with limited treatment options. While the single-arm study design and limited safety database present some uncertainty, the consistency with adult experience, established mechanism of action, and urgent medical need in this population support approval. The proposed weight-based dosing regimen appears appropriate based on population pharmacokinetic modeling, and routine pharmacovigilance will continue to monitor safety of golimumab therapy in the postmarket setting.

In general, golimumab represents a valuable addition to the limited therapeutic armamentarium for pediatric UC, offering families and clinicians another effective treatment option for patients weighing 15 kg or greater with moderately to severely active disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Ulcerative colitis is a chronic, relapsing inflammatory disease with significant impact on pediatric patients. - Disease pathophysiology is similar between pediatric and adult populations; however, children present with more extensive disease (pancolitis) and severe manifestations compared to adults. - Pediatric UC prevalence increased over time in the United States. 16-20% of pediatric patients with UC require colectomy within 10 years, as compared to 7-15% in adults.^{5,6,7,8} - Potential uncertainties include the limited long-term natural history data in pediatric populations and variability in disease presentation across different age groups within the pediatric population.	- Pediatric UC represents a serious condition with significant unmet medical need. The more aggressive disease course in children compared to adults supports the need for effective treatment options. - Similar pathophysiology between pediatric and adult UC supports extrapolation approaches for drug development.
Current Treatment Options	- Only two biologic therapies are currently approved for the treatment of pediatric patients with moderately to severely active UC: (i) infliximab (intravenous [IV], for patients ≥6 years of age) and (ii) adalimumab (subcutaneous [SC], for patients ≥5 years of age). - Infliximab requires IV infusion with associated burden of frequent visits to infusion center/hospital, and the risk of infusion reactions, as opposed to SC injection administration with golimumab treatment which can be administered at home. - Adalimumab requires every-other-week dosing, as opposed to every 4 weeks for long-term maintenance treatment with golimumab. - Standard therapies include corticosteroids, aminosalicylates, and immunomodulators with limited long-term efficacy.	- Limited treatment options exist for pediatric UC, particularly convenient subcutaneous options. - Golimumab would provide an additional SC biologic with less frequent dosing than approved alternatives, offering potential advantages in treatment burden and compliance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	- Study UCO3003 met its primary endpoint with 32% clinical remission at Week 6 versus 11% historical placebo rate (90% CI: 22%-41%), clinical response rate of 58% at Week 6 and maintenance of remission in 57% of Week 6 remitters at Week 54. - Both the clinical response and remission rates at Week 6 (58% and 32%, respectively) in Study UCO3003, were numerically comparable or higher to the response and remission rates observed in the adult golimumab UC induction trial CO524T17 (51% and 18%, respectively). - For support of the long-term efficacy, 57% of Week 6 remitters maintained clinical remission at Week 54, meeting the post hoc success criterion for maintenance of remission. - While some secondary endpoints including clinical remission and endoscopic healing at Week 54 did not meet success criteria, Bayesian analyses demonstrated that minimal borrowing of adult data (one to three subjects) would be sufficient to achieve success for these Week 54 endpoints. - Overall, the pediatric UC study efficacy results were numerically comparable to the efficacy of the adult UC golimumab trials. - Population pharmacokinetic modeling supports appropriate dosing to achieve target exposures. - Uncertainties include that the trial was a single-arm study design without concurrent control; Limited data in youngest patients (ages 2-5, n=2); Some secondary endpoints did not meet prespecified success criteria; Generalizability to diverse racial/ethnic populations (94% enrolled outside United States).	- Golimumab demonstrates clinically meaningful efficacy in pediatric UC based on established endpoints. - The magnitude of benefit is consistent with adult experience and clinically relevant for this serious condition.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	- Safety database consists of 69 patients with 46 patient-years exposure at Week 54. 97% experienced ≥ 1 TEAE, mostly mild to moderate in severity. - The majority of TEAEs were mild to moderate in severity, including worsening UC (62%), viral infections (including COVID-19, as the study was conducted during the pandemic [39%]), upper respiratory tract infections (20%). - TEAEs of headache (17%) and pyrexia (10%), occurred in $\geq 10\%$ of the pediatric study population and warrant inclusion into Simponi labeling as adverse drug reactions (ADRs) that were not previously included based on adult trial data. - Three opportunistic infections occurred including one Candida bacteremia. No deaths, tuberculosis, or malignancies occurred. The Safety profile was consistent with adult experience and tumor necrosis factor-alpha (TNF-α) inhibitor class. - Uncertainties include the limited safety data in youngest subjects, with no observed data in patients < 4 years of age or < 16 kg in weight; Long-term safety beyond 54 weeks is limited; Potential for rare serious events not captured in small database. (b) (4)	- Safety profile is acceptable and consistent with known TNF-α inhibitor risks. No pediatric-specific safety signals identified. Risks are manageable with appropriate monitoring and patient selection. - Established risk management through labeling is appropriate. Continued routine pharmacovigilance is sufficient for postmarketing safety surveillance and no postmarketing requirements (PMRs)/postmarketing commitments (PMCs) are needed. (b) (4) - Current presentations (50 mg, 100 mg prefilled syringes/autoinjectors) are adequate for patients ≥ 15 kg.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that were submitted as part of the application include:		Section of review where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as	Section of review where discussed, if applicable
✓	☒	Patient-reported outcome (PRO)	Mayo, PUCAI, IMPACT III questionnaire
	☒	Observer reported outcome (ObsRO)	Mayo, PUCAI (for younger children)
	☒	Clinician reported outcome (ClinRO)	Mayo endoscopic subscore and PGA components
	☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.		

2 Therapeutic Context

2.1. Analysis of Condition

Ulcerative colitis is a chronic, relapsing inflammatory disease primarily affecting the rectum and large intestine. As one of the two main forms of inflammatory bowel disease (IBD), UC is characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. Patients typically experience symptoms such as bloody diarrhea, rectal bleeding, weight loss, abdominal pain, and fever, with the disease course marked by periods of exacerbation and remission. UC can also manifest extraintestinally, affecting joints, skin, eyes, and the biliary system (e.g., arthritis, dermatological conditions, uveitis, and primary sclerosing cholangitis).^{9,10} Severe complications may include intestinal perforation, toxic megacolon, and massive hemorrhage, with an increased risk of colorectal and biliary (bile duct and gallbladder) cancers. Up to 30% of patients with UC may eventually require proctocolectomy.¹¹

The incidence of UC varies globally, ranging from 1.2 to 20.3 cases per 100,000 persons annually.¹¹ Notably, pediatric IBD cases are on the rise worldwide, particularly in the United States. A recent observational retrospective cross-sectional study involving two U.S. claims databases reported a 152% increase in UC prevalence among pediatric patients 2 to 17 years of age from 2007 to 2016 (the pooled prevalence in 2016 per 100,000 was 21.6 for UC [95% CI: 20.3 to 22.8]), primarily driven by the 10-to-17-year-old age group.^{5,12}

While UC shares many similarities between adult and pediatric populations in terms of demographics, clinical features, and pathophysiology, some distinctions exist.^{13,14,15} Children are more likely to present with pancolitis, whereas adults typically experience limited or left-sided colitis. Disease onset can occur at any age, but it is rare in infants and relatively infrequent in early childhood. Additionally, UC often manifests more severely in pediatric

⁹ Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet*. 2012;380(9853):1606-19.

¹⁰ Turner D, Griffiths AM. Acute severe ulcerative colitis in children: a systematic review. *Inflamm Bowel Dis*. 2011;17(1):440-9.

¹¹ Gajendran M, Loganathan P, Jimenez G, Catinella AP, Ng N, Umapathy C, et al. A comprehensive review and update on ulcerative colitis. *Dis Mon*. 2019;65(12)

¹² Ye Y, Manne S, Treem WR, Bennett D. Prevalence of Inflammatory Bowel Disease in Pediatric and Adult Populations: Recent Estimates From Large National Databases in the United States, 2007-2016. *Inflamm Bowel Dis*. 2020 Mar 4;26(4):619-625.

¹³ Kelsen J, Baldassano RN. Inflammatory bowel disease: the difference between children and adults. *Inflamm Bowel Dis*. 2008;14 Suppl 2:S9-11.

¹⁴ Sauer CG, Kugathasan S. Pediatric inflammatory bowel disease: highlighting pediatric differences in IBD. *Gastroenterol Clin North Am*. 2009;38(4):611-28.

¹⁵ Stefanska AM, et al. Extrapolation in the development of paediatric medicines: examples from approvals for biological treatments for paediatric chronic immune-mediated inflammatory diseases. *Arch Dis Child*. 2017;102(10):952-7.

patients.^{3,4} Despite these differences, treatment approaches remain largely analogous for both groups, employing similar pharmacological therapies such as corticosteroids (CSs), aminosaliclates, immunosuppressants, and TNF inhibitors (i.e., infliximab and adalimumab).^{12,16}

Outcomes, including the likelihood of colectomy, are generally comparable between adults and children with UC. The cumulative probability of requiring colectomy is approximately 6% after one year and 29% after 20 years.¹³ However, the 10-year colectomy rate shows a slight variation, ranging from 7% to 15% in adults and 16% to 20% in pediatric patients.^{5,6,7,8} These statistics underscore the long-term impact of UC on both adult and pediatric populations, highlighting the need for effective management strategies across all age groups.

2.2. Analysis of Current Treatment Options

The goals of UC treatment include reducing disease-related signs and symptoms, inducing and maintaining remission, achieving improvement and/or resolution of mucosal ulcerations, reducing long-term CS use and the risk of colorectal carcinoma, and improving the quality of life.

The treatment of mild-to-moderate UC includes oral aminosaliclates, topical 5-aminosalicylic acid (5-ASA) (such as mesalamine suppository and enemas) or topical steroids given rectally.¹⁷ Oral corticosteroids, such as budesonide or oral prednisone, may be required in patients who are refractory to topical therapies, or who are systemically ill and require rapid treatment. Mesalamines and budesonide are approved treatments for mild-to-moderate UC disease. As off-label treatments, immunomodulators such as azathioprine and 6-mercaptopurine are typically used for patients refractory to or dependent on oral CSs, and for those experiencing disease relapse on aminosaliclates.

Moderately to severely active UC requires more aggressive treatment than more mildly active disease. For adults with UC, numerous treatments across a variety of mechanisms of action are approved (including infliximab, adalimumab, vedolizumab, ustekinumab, risankizumab, mirikizumab, guselkumab, tofacitinib, upadacitinib, and ozanimod) in the United States for moderately to severely active UC. Treatment of pediatric patients with UC generally follows the same treatment paradigms that are used to treat adult patients with UC. Currently, there are two approved biologics for children with UC: infliximab, which is administered by IV infusion, and Humira, which is administered by SC injection. Infliximab is approved from age 6 years of age and adalimumab is approved from 5 years of age.

¹⁶ Turner D, et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care-An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; 67:257.

¹⁷ Singh S, et al. AGA Living Clinical Practice Guideline on Pharmacological Management of Moderate-to-Severe Ulcerative Colitis. *Gastroenterology*. 2024;167(7):1307-43.

Infliximab received U.S. approval in 2011 for the treatment of pediatric UC based on extrapolation of data from adult studies and the results of an open-label study in 60 pediatric patients. Infliximab is administered intravenously, has a risk of infusion reactions, and is time-consuming to administer, since it requires traveling to a hospital or infusion center, thus imposing a burden on pediatric patients and their families. Adalimumab was approved in 2021 for the treatment of pediatric UC and is administered SC. Approval for adalimumab was based on extrapolation from adult studies and a randomized, double-blind study of two adalimumab doses in 93 pediatric subjects.

The Applicant proposes that golimumab could offer another option for effective treatment of pediatric UC and provides an alternative for those patients who could not tolerate infliximab or adalimumab. Also, golimumab is administered Q4W by SC injection which could offer a benefit to patients due to less frequent SC injections than adalimumab and would be an alternative SC option compared to infliximab which is given IV.

APPEARS THIS WAY ON ORIGINAL

Table 1. Currently Approved FDA Treatments for Moderately to Severely Active Pediatric UC¹⁸

Product(s) Name/ Drug Class	Relevant Indication	Dosing/ Administration	Efficacy Information Pediatric Trial	Important Safety and Tolerability Issues
Infliximab (Remicade) BLA 103772 Tumor necrosis factor- α blockers	Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use	Intravenous (IV) 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	Of the 60 patients treated, 44 were in clinical response at Week 8. Of 32 patients taking concomitant immunomodulators at baseline, 23 achieved clinical response at Week 8, compared to 21 of 28 of those not taking concomitant immunomodulators at baseline. At Week 8, 24 of 60 patients were in clinical remission as measured by the Mayo score and 17 of 51 patients were in remission as measured by the PUCAI score. At Week 54, 8 of 21 patients in every 8-week maintenance group and 4 of 22 patients in the every 12-week maintenance treatment group achieved remission as measured by the PUCAI score. During maintenance phase, 23 of 45 randomized patients (9 in every 8-week group and 14 in the every 12-week treatment group) required an increase in their dose and/or increase in frequency of infliximab administration due to loss of response. Nine of the 23 patients who required a change in dose had achieved remission at Week 54. Seven of those patients received the 10 mg/kg every 8-week dosing	<u>Boxed Warning</u> Serious infections (including tuberculosis, bacterial sepsis, invasive fungal infections [such as histoplasmosis], and opportunistic infections), malignancies (including lymphoma, hepatosplenic T-cell lymphoma [HSTCL], melanoma), hepatitis B virus reactivation, hepatotoxicity, hypersensitivity (serious infusion reactions including anaphylaxis or serum sickness-like reactions), cytopenias, demyelinating disease, heart failure, lupus-like syndrome. Most common adverse reactions: infections (e.g., upper respiratory, sinusitis, pharyngitis), infusion-related reactions, headache, and abdominal pain.

¹⁸ Numerous biosimilars to Infliximab and Adalimumab are also approved.

Product(s) Name/ Drug Class	Relevant Indication	Dosing/ Administration	Efficacy Information Pediatric Trial	Important Safety and Tolerability Issues
Adalimumab (Humira) BLA 125057 (TNF- α blockers)	Inducing and sustaining clinical remission in adult patients with moderately to severely active UC who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of adalimumab has not been established in patients who have lost response to or were intolerant to TNF blocker.	Subcutaneous (SC) Pediatric weight of 20 kg (44 lbs) to less than 40 kg (88 lbs): - Day 1: 80 mg - Day 8: 40 mg - Day 15: 40 mg - Starting on Day 29: 40 mg every other week or 20 mg every week Pediatric weight of 40 kg (88 lbs) and greater: - Day 1: 160 mg (single dose or split over two consecutive days) - Day 8: 80 mg - Day 15: 80 mg - Starting on Day 29: 80 mg every other week or 40 mg every week	Efficacy was assessed at Week 8 by partial Mayo score (PMS), and 60% (28/47) patients who received the recommended adalimumab dosage achieved remission by PMS, as compared with 43% (13/30) in the group that received the lower studied dose. At Week 52, clinical remission was assessed by full Mayo score (including endoscopy) in the population of patients who achieved Week 8 PMS response; 45.2% (14/31) patients who received the recommended weekly dosage achieved remission, as compared to 29% (9/31) who received the lower studied dose, and 33% (4/12) among those who received placebo. A dose response was also noted for the secondary endpoints of endoscopic improvement and clinical remission among Week 8 PMS remitters.	<u>Boxed Warning</u> Serious infections including tuberculosis [TB], bacterial sepsis, invasive fungal infections, and opportunistic infections, malignancies (including lymphoma, HSTCL, leukemia, NMSC), anaphylaxis or serious allergic reactions, hepatitis B virus reactivation, demyelinating disease, cytopenias/ pancytopenia, heart failure, lupus-like syndrome. Most common adverse reactions: infections (upper respiratory, sinusitis), injection site reactions, headache, and rash.

Source: Reviewer's Table based on information in the approved USPI for infliximab and adalimumab

Abbreviations: NMSC, nonmelanoma skin cancer; PUCAI, Pediatric Ulcerative Colitis Activity Index; TNF- α , tumor necrosis factor-alpha; UC, ulcerative colitis

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Simponi (golimumab) injection is currently approved in the United States for the treatment of adult patients with moderately to severely active RA in combination with methotrexate; active PsA alone or in combination with methotrexate; active ankylosing spondylitis; and moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosaliclates, oral corticosteroids, azathioprine, or 6-mercaptopurine. On March 16, 2012, the Applicant received orphan drug designation (#12-3651) for Simponi (golimumab) for the treatment of pediatric UC thereby exempting the Applicant to the requirements to conduct studies in this population as described in the Pediatric Research Equity Act.

Upon submission of the adult UC supplements on July 16, 2012, the Applicant provided a pediatric development plan to conduct studies in the pediatric population. On May 15, 2013, the following postmarketing commitments (PMCs) were issued in the approval letter of the UC indication:

- PMC #4 (2909-4): Conduct a study to evaluate the pharmacokinetics of Simponi (golimumab) in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis. Pharmacokinetic measurements should be conducted for exposure-response analysis and compared to adult patients with ulcerative colitis treated with Simponi (golimumab). Also, collect serum samples for immunogenicity testing and conduct analyses of the impact of immunogenicity on the pharmacokinetics of Simponi (golimumab).
- PMC #5 (2909-5): Conduct a study to evaluate the effectiveness and safety of Simponi (golimumab) in pediatric patients 5 to <18 years of age with moderately to severely active UC. The study should be designed to establish that the dose regimen(s) of Simponi (golimumab) identified in PMC #4 is (are) effective and safe for induction treatment, as well as for continued treatment after induction. Pharmacokinetic measurements should be conducted for exposure-response (E-R) analysis. Collect serum samples for immunogenicity testing and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy, and safety.

As of October 4, 2017, PMC #4 (2909-4) has been deemed fulfilled. The purpose of this submission is to expand the ulcerative colitis indication to include pediatric (b) (4) and to provide study reports in fulfillment of PMC #5 (2909-5).

A summary of key regulatory history is provided in [Table 2](#).

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2. Summary of Regulatory History

Date and Application	Summary
November 23, 2015 IND 100181	Type C meeting minutes issued by FDA providing guidance on the Sponsor's revised pediatric clinical drug development plan which includes a second PK study (CNTO148UCO1002) in lieu of a phase 3 trial and development program in support of a new pediatric presentation
August 1, 2016 IND 100181	Type C written responses issued in discussion of the Sponsor's proposal for a 2-arm trial design instead of a 3-arm design as recommended by FDA in previous meeting minutes. FDA reiterated recommendation to utilize an active comparator arm to establish assay sensitivity.
June 12, 2017 IND 100181	FDA meeting minutes issued for type C meeting request to reach agreement on the final study design for CNTO148UCO3001 (formerly CNTO148UCO1002)
October 4, 2017 BLA 125289	FDA Fulfillment of PMC issued for PMC #4 (2909-4) following receipt of CSR of supporting study CNTO148UCO1001
May 22, 2018 IND 100181	Submission of protocol CNTO148UCO3003
August 24, 2018 IND 100181	FDA issued advice letter which highlighted the importance of evaluating efficacy at Week 54, even if primary efficacy assessment was conducted at Week 6 and provided additional comments on aspects of safety and efficacy data collection plans.
September 28, 2018 IND 100181	Teleconference held to discuss previously communicated comments on phase 3 study design. FDA reiterated importance of evaluating efficacy at Week 54.
August 13, 2019 IND 100181	FDA reviewed the statistical analysis plan and amendments to the phase 3 study protocol; comments were provided regarding the approach to evaluating efficacy at Week 54.
October 14, 2020 IND 100181	FDA issued written responses to type C meeting request. Agreement reached to discontinue enrollment into the infliximab arm, advice provided regarding recommended efficacy analyses for study CNTO148UCO3003
December 21, 2021 BLA 125289	FDA acknowledgment of revised PMC milestones letter issued targeting study completion by January 2025 and final report submission by June 2025
October 5, 2022 IND 100181	FDA written response to type C meeting request. Agreement reached to reduce sample size to at least 60 golimumab treated subjects based upon enrollment challenges for study CNTO148UCO3003
June 17, 2024 IND 100181	Final meeting minutes issued for a Type B pre-sBLA meeting to discuss the content, format, and strategy of the incoming sBLA

Source: Regulatory Program Manager (RPM) created based on sBLA 125289 /157

Abbreviations: BLA, biologics license application; CSR, clinical study report; IND, investigational new drug; PK, pharmacokinetic; PMC, postmarketing commitment; sBLA, supplemental BLA

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Clinical site inspections were not requested for this application. There were no sites that appeared to be driving efficacy or safety, and the majority of sites enrolled a small number of subjects, such that results from a single site were unlikely to affect the overall conclusions. The one site that enrolled a disproportionately high number (in this case n=10) of patients in this small study had a recent, previously conducted inspection on file, and so no further inspection was indicated.

4.2. Product Quality

The Applicant

proposes to use the currently approved Simponi 50 mg/0.5 mL and 100 mg/mL PFS and SmartJect autoinjectors to support the pediatric UC indication. As no changes were made to Module 3 CMC information for the approved drug product presentations, no product quality assessment was required for the approved drug product presentations. For further details of OPQ review, refer to the OPQAIII review in the CDER Informatics Platform (Panorama) for additional details.

4.3. Clinical Microbiology

The total endotoxin contribution of Simponi 50 mg/0.5 mL and 100 mg/mL drug product solution given the product's endotoxin release specification and recommended dose based on pediatric patient weight, is below the USP <85>bacterial endotoxins threshold limit of 5 EU/kg/hr.

4.4. Devices and Companion Diagnostic Issues

(b) (4)

Regarding the approved presentations, DMEPA 1 noted that the Applicant submitted the same HF validation study results for the Tremfya 100 mg/mL PFS and Simponi PFS that included pediatric participants under BLA 761061 (Tremfya) on November 16, 2016, and under BLA 125289 (Simponi) on March 2, 2017, respectively. DMEPA 1 reviewed the HF validation study results report under BLA 761061 at that time and found it acceptable.¹⁹ DMEPA 1 noted that the HF validation study report submitted under BLA 761061 is also applicable to the Simponi 100 mg/mL PFS. As such, DMEPA 1 determined that the Applicant did not need to submit additional HF data for Simponi 50 mg/0.5 mL and 100 mg/mL single-dose prefilled syringes for pediatric UC self-administration. Regarding the use of the Simponi 50 mg/0.5 mL and 100 mg/mL single-dose prefilled SmartJect autoinjectors for the treatment of pediatric UC, DMEPA 1 noted that there are no HF validation study results data to support pediatric self-administration. As such, DMEPA 1 recommends the Division of Gastroenterology include language in the prescribing information restricting self-injection for the pediatric user group to use of the prefilled syringe.

(b) (4)

DMEPA 1 has no additional HF comments and recommendations. Refer to the DMEPA 1 review dated August 26, 2025, in DARRTS for additional details.

¹⁹ Mena-Grillasca, CM. Human Factors, Label, Labeling, and Packaging Review for Tremfya (BLA 761061). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 12. OSE RCM No.: 2016-2621 and 2016-2649.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical pharmacology and toxicology studies were submitted under this supplement. The relevant information was previously reviewed in the original BLA and is summarized below.

Golimumab is a fully human monoclonal antibody that neutralizes the biological activity of human TNF- α . Golimumab binds with high affinity ($K_D=18\text{pM}$) and specificity to both soluble and transmembrane bioactive forms of TNF- α . In vitro pharmacology studies showed that golimumab was up to 72-fold less potent at binding and neutralizing the effects of cynomolgus TNF- α than human TNF- α . This potency difference is a nonissue as the doses and dose regimens selected for the toxicology studies based on toxicokinetic data produced sustained high serum golimumab concentrations that were in excess of the concentrations required to neutralize all TNF- α in monkey serum.

The pivotal nonclinical studies in monkeys for golimumab included two 6-month chronic toxicology studies (SC and IV), an embryofetal development study (SC), and a pre- and postnatal development study (SC). Safety pharmacology endpoints were incorporated into the IV and SC repeated dose toxicology studies in cynomolgus monkeys as well as part of the SC prenatal and postnatal reproductive study which also included neonatal assessments. Studies of local tolerance/injection site effects in monkeys were also conducted. Supportive studies included chronic repeat dose toxicity studies and reproductive toxicology studies (fertility and early implantation, embryofetal development, and a pre- and postnatal development) in mice using an analogous anti-mouse TNF- α monoclonal antibody (cV1q).

Treatment related effects observed in the chronic IV monkey study were decreased IgG and IgM antibody responses to a keyhole limpet hemocyanin (KLH) challenge as fewer animals in the golimumab dose groups mounted measurable antibody responses to KLH than in the control group. IgG antibody production was more affected than IgM antibody production with the most notable decline present in the high dose group. In the SC study, treatment-related clinical symptoms and histological observations included reversible dosing site inflammation and edema. Humoral responses were not affected by treatment based on KLH analysis (unlike the 6-month IV study in monkeys). Reversible increases in B-lymphocytes were observed in the SC study. In both SC and IV chronic studies, no adverse effects were observed and the no-observed-adverse-effect level (NOAEL) for these studies was the highest dose tested at 50 mg/kg. Mean gender-combined toxicokinetic values at steady state were 2627 $\mu\text{g/mL}$ (maximum concentration [C_{max}]) and 11635 $\mu\text{g}\cdot\text{day/mL}$ (area under the concentration-time curve [AUC]) for 50 mg/kg IV group with terminal half-life of 18 days. The mean gender combined toxicokinetic values at steady state were 2459 $\mu\text{g/mL}$ (C_{max}) and 5657 $\mu\text{g}\cdot\text{day/mL}$ (terminal AUC) for the 50 mg/kg SC group with half-life of 14 days.

In the pre- and postnatal study in which pregnant female cynomolgus monkeys were dosed 0, 25, or 50 mg/kg golimumab SC twice weekly from day 50 of gestation to day 33 after delivery, neonates had significant exposure to golimumab as the mean fetal/maternal ratio 30 days after delivery was 0.16 and 0.18 for the 25 and 50 mg/kg dose groups, respectively. Fifteen days after birth, mean serum golimumab concentrations in these neonates were 218.57 µg/mL and 536.53 µg/mL in the 25 and 50 mg/kg dose groups, respectively. There were no remarkable findings in this study including on antibody production, B and T lymphocytes, hematopoietic stem cells, and associated organs. The NOAEL for the pre- and postnatal study was the high dose of 50 mg/kg resulting in maternal C_{max} of 1482 µg/mL and highest neonate blood levels of 537 µg/mL. Maternal milk levels were 3.6 µg/mL at 50 mg/kg. Up to 50% of maternal blood levels were measured in neonate blood.

The carcinogenic potential of golimumab cannot be evaluated in standard 2-year bioassays in rodents because golimumab does not neutralize rodent TNF- α . Preneoplastic/neoplastic lesions were assessed as part of chronic studies in monkeys and mice with no indications of treatment-related preneoplastic/neoplastic lesions. Based on labeling of similar TNF- α blocking drugs, a carcinogenic risk may be expected.

There are no proposed changes to the nonclinical sections of the labeling under this supplement. From the nonclinical perspective, no approvability issues have been identified.

6 Clinical Pharmacology

6.1. Executive Summary

The development program for golimumab in pediatric UC consists of a completed phase 1b open-label study to assess the safety and pharmacokinetics of SC administered golimumab in subjects aged 2 to 17 years (UCO1001) and a completed phase 3 randomized, open-label study to assess the efficacy, safety, and pharmacokinetics of golimumab treatment in subjects aged 2 to 17 years (UCO3003).

In the clinical development program for pediatric UC, the Applicant studied body surface area (BSA)-based (mg/m^2) dosing regimens in their phase 1b open-label study (UCO1001) and phase 3 study (UCO3003) ([Table 3](#)). In the phase 3 study UCO3003, the Applicant used BSA-based dosing for pediatric subjects with body weight <45 kg ($120 \text{ mg}/\text{m}^2 \rightarrow 60 \text{ mg}/\text{m}^2$) while using the approved adult dose for higher body weight subjects. However, the proposed pediatric dosing regimen in the current submission is different from the dosing regimens used in phase 3 study UCO3003. In this submission the Applicant has proposed body weight-tiered pediatric doses with (b) (4) 15 to <40 kg, and 40 kg or above) ([Table 3](#)). Based on population PK (popPK) modeling and simulation, the proposed dosing regimen is intended to result in pharmacokinetic (PK) exposures comparable to those observed in the adult UC program and Study UCO3003.

The review team had the following concerns with the proposed dosing regimens:

1.



2. We noted that the C_{max} in the 15 to <20 kg group with the proposed dosing regimen is higher compared to the C_{max} in adults receiving the currently approved 200 mg→100 mg dosing regimen; however, the C_{max} in the 15 to <20 kg group would be within the range of adult C_{max} observed in the clinical study evaluating the 400 mg→200 mg dose regimen (Study C0524T17).
3. We also noted the potential for lower golimumab exposures with the proposed dosing regimen in pediatric subjects weighing 30 kg to <40 kg compared to the dosage administered in Study UCO3003; however, results from the phase 1b open-label study (UCO1001) which evaluated lower doses with resulting lower exposure did not identify a difference in efficacy with a comparable reduction in exposure.

Table 3. Golimumab Dosing Regimens

Table 3: Camidanib Dosing Regimens					Applicant's Proposed Dosage for Patients (b) (4)			Adult Dosage
Week #	Phase 1b (Study UCO1001)		Phase 3 (Study UCO3003)		(b) (4)	15 to (b) (4)		
	<45 kg	≥45 kg	<45 kg	≥45 kg		<40 kg	≥40 kg	
Week 0 (first dose)	90 mg/m ²	200 mg	120 mg/m ²	200 mg	(b) (4)	100 mg	200 mg	200 mg
Week 2 and Q4W thereafter	45 mg/m ²	100 mg	60 mg/m ²	100 mg		50 mg	100 mg	100 mg

Source: Summary of Clinical Pharmacology and currently approved USPI

Abbreviations: Q4W, every 4 weeks

Overall, the clinical pharmacology assessment adequately supports the golimumab dosage described in [Table 4](#) for the proposed indication.

Table 4. FDA's Recommended SC Golimumab Dosage in Pediatric Patients With Moderately to Severely Active Ulcerative Colitis

Body Weight Tier	Induction Dose Regimen		Maintenance Dose Regimen
	Week 0	Week 2	Week 6 and Onward
≥40 kg	200 mg	100 mg	100 mg Q4W
≥15 kg to <40 kg	100 mg	50 mg	50 mg Q4W

Source: FDA Review

Abbreviations: Q4W, every 4 weeks; SC, subcutaneous

6.1.1. Recommendation

The Division of Pharmacometrics and the Division of Inflammation and Immune Pharmacology have reviewed the clinical pharmacology information in the current application and determined that this supplemental BLA is acceptable to support the approval of Simponi (golimumab) for the treatment of moderately to severely active UC in pediatric patients with body weight 15 kg and above.

The clinical pharmacology assessment supports the following golimumab dosage in pediatric patients with UC:

- Pediatric patients with UC weighing 40 kg and above: 200 mg SC at Week 0, followed by 100 mg SC at Week 2, and then 100 mg SC Q4W (hereafter referred to as “200 mg → 100 mg”)
- Pediatric patients with UC weighing 15 to <40 kg: 100 mg SC at Week 0, followed by 50 mg SC at Week 2, and then 50 mg SC Q4W (hereafter referred to as “100 mg → 50 mg”)

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Clinical Pharmacokinetics

Pharmacokinetics of golimumab was studied in pediatric subjects with moderately to severely active UC in the phase 1b study (UCO1001) and the phase 3 study (UCO3003).

The Applicant used a validated streptavidin-coated plate-based “sandwich” electrochemiluminescent immunoassay (ECLIA) on the MSD platform (Meso Scale Discovery) to determine serum golimumab concentrations in UCO1001 and UCO3003. This assay was used in the clinical studies in prior submissions of golimumab in adult RA, adult PsA, adult UC, and pediatric pJIA. Method validation and in-study bioanalysis were found to be acceptable.

UCO1001 was a phase 1b, multicenter, open-label study to assess the pharmacokinetics and safety of golimumab treatment in pediatric subjects, aged 6 through 17 years of age with moderately to severely active UC. Subjects ≥ 45 kg received induction doses of golimumab of 200 mg SC at Week 0 and 100 mg SC at Week 2 followed by maintenance doses of 100 mg SC Q4W at Week 6 through Week 54. Subjects weighing <45 kg in UCO1001 received 90 mg/m² (up to a maximum of 200 mg) SC at Week 0 and 45 mg/m² (up to a maximum of 100 mg) SC at Week 2 followed by maintenance doses of 45 mg/m² (maximum of 100 mg) SC Q4W at Week 6 through Week 54. [Table 5](#) compares serum golimumab concentrations through Week 6 across the two baseline dose regimen subgroups (<45 kg: 90 mg/m² → 45 mg/m² and ≥ 45 kg: 200 mg → 100 mg). The median and mean serum golimumab concentrations over time in patients weighing <45 kg were generally lower compared with those in patients weighing ≥ 45 kg in UCO1001.

Table 5. Summary of Serum Golimumab Concentrations at Week 4 and Week 6 by Golimumab SC Dose Regimen, Study UCO1001

	Golimumab SC Dose Regimen	
	90 mg/m ² → 45 mg/m ²	200 mg → 100 mg
	<45 kg	≥45 kg
Week 4		
N	12	19
Mean (SD)	4.48 (3.313)	7.79 (2.791)
Median	3.30	8.60
IQ range	(2.04; 5.93)	(6.53; 9.72)
Range	(1.6; 12.4)	(1.7; 11.4)
Week 6		
N	12	19
Mean (SD)	1.53 (1.551)	3.21 (1.400)
Median	1.06	3.44
IQ range	(0.52; 1.48)	(2.44; 3.97)
Range	(0.2; 5.3)	(0.6; 5.0)

Source: Table 3 in Module 2.7.2 Summary of Clinical Pharmacology

Serum golimumab concentrations are reported in units of µg/mL.

Abbreviations: IQ, interquartile; N, number of subjects; SC, subcutaneous; SD, standard deviation

UCO3003 was a phase 3, multicenter, randomized, open-label golimumab study in pediatric subjects aged 2 to <18 years with moderately to severely active UC. The following dose regimens were evaluated:

- <45 kg: 120 mg/m² at Week 0, 60 mg/m² at Week 2, 60 mg/m² at Week 6 and Q4W thereafter. Doses are capped at 200 mg and 100 mg for the 120 mg/m² and 60 mg/m² doses, respectively.
- ≥45 kg: 200 mg at Week 0, 100 mg at Week 2, 100 mg at Week 6 and Q4W thereafter.

After considering the PK data from study UCO1001, the Applicant selected higher BSA adjusted doses of 120 mg/m² → 60 mg/m² for study UCO3003 patients weighing <45 kg to more closely match the exposure in the reference adult UC population.

[Table 6](#) compares serum golimumab concentrations at Week 2 and Week 6 in the two dose regimen subgroups in Study UCO3003 (<45 kg: 120 mg/m² → 60 mg/m² and ≥45 kg: 200 mg → 100 mg) and the reference adult UC study (C0524T17). Serum golimumab concentrations observed in the overall pediatric UC population at Week 2 and Week 6 were generally comparable to those observed in the reference adult UC population. Also, median and mean serum golimumab concentrations at Week 2 and Week 6 were generally comparable between subjects with body weight <45 kg and those at ≥45 kg.

Table 6. Summary of Observed Golimumab Concentrations in Pediatric Patients and Adults With UC

Pediatric Patients in Study UCO3003						Adult Patients in Study C0524T17
<45 kg: 120 → 60 mg/m ²						
Week #	Parameter	<30 kg	30 to <45 kg	Combined	≥45 kg: 200 → 100 mg	200 → 100 mg
Week 2 serum golimumab concentration (µg/mL)	N	8	8	16	51	322
	Mean (SD)	10.07 (3.06)	7.32 (2.99)	8.69 (3.25)	6.70 (3.09)	6.40 (2.90)
	Median	9.51	7.74	8.80	6.08	6.27
	Range	(5.9, 15.7)	(3.1, 12.5)	(3.1, 15.7)	(2.1, 15.6)	(0.2, 19.4)
	IQR	(8.33, 11.67)	(4.84, 8.88)	(6.65, 10.15)	(4.36, 8.53)	(4.21, 8.09)
Week 6 serum golimumab concentration (µg/mL)	N	8	7	15	46	292
	Mean (SD)	1.34 (1.03)	2.39 (1.43)	1.83 (1.31)	2.17 (1.83)	2.11 (1.48)
	Median	1.04	2.62	1.18	1.57	1.78
	Range	(0.4, 3.3)	(0.6, 4.6)	(0.4, 4.6)	(0.0, 8.0)	(0.0, 8.9)
	IQR	(0.58, 1.87)	(0.68, 3.27)	(0.63, 2.94)	(1.04, 2.78)	(1.06, 2.75)

Source: Table 31 and 32 from CSR for UCO3003

Note: Concentrations below the lowest quantifiable concentration (i.e., 0.03905 µg/mL) are treated as zero in calculating the summary statistics.

Abbreviations: IQR, interquartile range; PK, pharmacokinetic; SD, standard deviation; WT, body weight

6.2.2. Immunogenicity Assessment

The Applicant used a validated enzyme immunoassay method to detect antibodies to golimumab in human serum samples. Serum samples from subjects identified as containing antibodies to golimumab were further characterized for the ability of those antibodies to neutralize the bioactivity of golimumab using a validated noncell-based bioassay. Refer to the product quality review for details of the assays used for immunogenicity assessment.

Incidence

Of the 69 subjects treated with golimumab in Study UCO3003, 15 (21.7%) were positive for antibodies to golimumab through the final safety visit. Of these 15 subjects, 3 (20%) tested positive for neutralizing antibodies. Antidrug antibody (ADA) incidence in the pediatric study was comparable to adults (21.3%, 254/1195).

Impact of Immunogenicity on Pharmacokinetics, Efficacy and Safety

Median serum golimumab concentrations were lower in subjects who developed antibodies to golimumab compared to those who tested negative for antibodies to golimumab during induction and maintenance. This is similar to the trends observed in clinical studies in adult UC subjects.

In Study UCO3003, there was an apparent trend towards lower clinical efficacy outcomes among pediatric UC subjects who were positive for antibodies to golimumab during induction and during maintenance at Week 54 ([Table 7](#)). Regarding safety/adverse events, among the 56 subjects who were negative for antibodies to golimumab through Week 54, 2 (3.6%)

experienced injection-site reactions. In comparison, of the 13 subjects who were positive for antibodies to golimumab, 2 (15.4%) experienced injection-site reactions. However, these findings should be interpreted with caution due to the limited number of subjects who developed antibodies to golimumab.

Table 7. Summary of Immunogenicity Effects on Efficacy Endpoints at Week 54, Study UCO3003

Analysis set: Immunogenicity Analysis Set During the Long-Term Phase	Golimumab	
	Positive ^f 9	Negative ^g 41
Clinical remission as assessed by the Mayo score at Week 54 ^{a,h,i}	2 (22.2%)	15 (36.6%)
Clinical response as assessed by the Mayo score at Week 54 ^{b,h,i}	4 (44.4%)	22 (53.7%)
Clinical remission as assessed by the PUCAI score at Week 54 ^{c,h,i}	2 (22.2%)	17 (41.5%)
Endoscopic healing at Week 54 ^{d,h,i}	2 (22.2%)	17 (41.5%)
Symptomatic remission at Week 54 ^{e,h,i}	2 (22.2%)	21 (51.2%)

Source: Table TEFIR01b, from CSR for UCO3003

*19 participants were excluded from this analysis set because the subjects did not receive golimumab after Week 6 (n=14) or they didn't have appropriate samples for detection of antibodies at Week 54

Abbreviations: PUCAI, Pediatric Ulcerative Colitis Activity Index

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The dosage described in [Table 4](#) in Section [6.1](#) is not expected to yield any clinically significant differences in PK exposure compared to the dosage administered to pediatric patients in Study UCO3003. Refer to the next subsection in Section [6.3.1](#) for the detailed assessment of exposure following the proposed dosage.

The exposure-response analysis of efficacy at Week 6 in pediatric patients also generally supports the efficacy of golimumab for the proposed indication. Refer to Section [15.3.1.3](#) for the detailed exposure-response assessment.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The PK modeling and simulation adequately support the weight-tiered dosage described in [Table 4](#) in Section [6.1](#) for the treatment of moderately to severely active UC in pediatric patients weighing 15 kg and above. Refer to Section [15.3.1.2](#) for the assessment of the popPK model utilized to simulate exposure and assess the proposed golimumab dosage.

The Applicant's proposed dosage regimen differed from the studied pediatric dosage regimens, which utilized body surface area-based dosing in pediatric patients weighing <45 kg. [Table 8](#) summarizes the studied pediatric dosage regimens along with the Applicant's originally proposed pediatric dosage and the approved adult dosage.

(b) (4)

any golimumab dosage approved in this review cycle must be able to be administered using the currently available presentations (i.e., 50 mg or 100 mg in a single dose prefilled syringe or single dose prefilled autoinjector).

(b) (4)

Table 8. Comparison of Studied Pediatric Dosages, Proposed Pediatric Dosage, and Approved Adult Dosage of Golimumab SC in Patients With Ulcerative Colitis

Week #	Phase 1b Study UCO1001*		Phase 3 Study UCO3003**		Applicant's Proposed Dosage for Pediatric Patients (b) (4)		Approved Adult Dosage
	<45 kg	≥45 kg	<45 kg	≥45 kg	(b) (4)	(b) (4)	
Week 0 (first dose)	90 mg/m ²	200 mg	120 mg/m ²	200 mg	(b) (4)	15 to <40 kg 100 mg ≥40 kg 200 mg	200 mg
Week 2	45 mg/m ²	100 mg	60 mg/m ²	100 mg	(b) (4)	50 mg 100 mg	100 mg
Week 6 then Q4W thereafter	45 mg/m ²	100 mg	60 mg/m ²	100 mg	(b) (4)	50 mg 100 mg	100 mg

Source: FDA Reviewer

* Study UCO1001 minimum body weight =19.7 kg; minimum age =6 years.

** Study UCO3003 minimum body weight =16.4 kg; minimum age =4 years.

Abbreviations: Q4W, every 4 weeks; SC, subcutaneous

The PK exposure following SC golimumab was simulated in 160,000 virtual pediatric subjects using the final popPK model (refer to Section [15.3.1.2](#) for the detailed assessment of the popPK model). Age was evenly distributed from 2 to <18 years in the virtual pediatric population, and weight and BSA were sampled from the 2017 to 2018 National Health and Nutrition Examination Survey dataset according to age. Albumin concentration in the virtual pediatric population was fixed to 4.2 g/dL, which was the median baseline albumin in adult and pediatric patients with UC. The FDA reviewer simulated various dosage regimens, including 200 mg → 100 mg, 150 mg → 100 mg, 150 mg → 50 mg, 100 mg → 50 mg, and the studied dosage regimen (i.e., 120 mg/m² → 60 mg/m² in pediatric patients weighing <45 kg and 200 mg → 100 mg in pediatric patients weighing 45 kg and above). The median PK exposure in Study UCO3003 (see [Table 9](#)) was used as reference to assess the acceptability of the proposed pediatric dosage and other simulated dosages across the proposed (b) (4) body weight range.

Table 9. Summary of Individual Predicted Golimumab Exposure, Study UCO3003

Exposure Metric	Statistic	Week 0 to 2 (N=69)	Week 0 to 6 (N=69)	Week 50 to 54 (N=39)
C _{max} (µg/mL)	Geo mean (CV%)	15 (28.9%)	15.1 (28.1%)	9 (31.5%)
	Geo mean 95% CI	14-16.1	14.1-16.1	8.2-9.9
	Median	15.5	15.6	9.1
	Min - max	6.7-27.2	6.7-27.2	3.8-16.7
AUC (µg·day/mL)	Geo mean (CV%)	114.1 (28.8%)	327.4 (32.2%)	128.7 (37.8%)
	Geo mean 95% CI	106.7-122.1	303.6-353	114.4-144.9
	Median	122.3	352.4	131.9
	Min - max	51.2-203.5	139.2-657	45.5-285.4
C _{trough} (µg/mL)	Geo mean (CV%)	9.3 (31.3%)	2.1 (106.2%)	1.4 (67.5%)
	Geo mean 95% CI	8.7-10	1.7-2.6	1.2-1.7
	Median	10	2	1.4
	Min - max	3.9-17.3	0.3-10.7	0.3-6.1

Source: Reviewer's analysis

Abbreviations: AUC, area under the concentration-versus-time curve; CI, confidence interval; C_{max}, maximum concentration; C_{trough}, trough concentration; CV, coefficient of variation

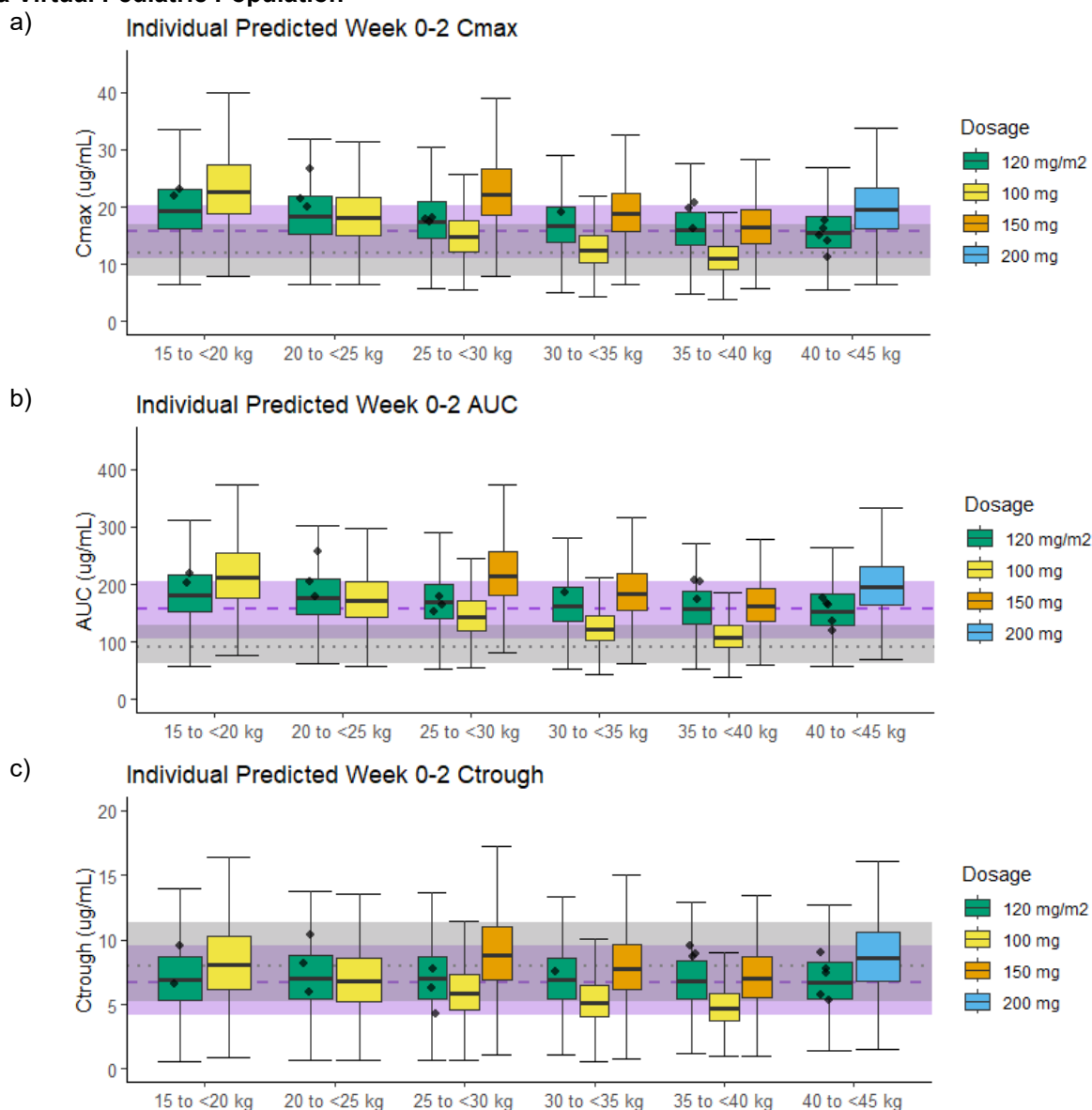
[Figure 1](#), [Figure 2](#), and [Figure 3](#) display the final PK exposure-matching comparison in virtual pediatric patients versus reference during Week 0 to 2, Week 0 to 6, and Week 50 to 54, respectively.

Clinical efficacy and safety data from Study UCO3003 support the 200 mg → 100 mg dosage in pediatric patients weighing 45 kg and above (refer to Clinical assessment in Section [8.1.1](#)). Although patients weighing 40 to <45 kg received a dosage of 120 mg/m² → 60 mg/m² in Study UCO3003, the proposed 200 mg → 100 mg dosage does not result in any clinically meaningful exposure differences compared to 120 mg/m² → 60 mg/m² in pediatric subjects weighing 40 to <45 kg. Therefore, the clinical pharmacology assessment supports 200 mg → 100 mg in pediatric patients weighing 40 kg and above.

The proposed 100 mg → 50 mg dosage is acceptable in pediatric patients weighing 15 to <40 kg from a clinical pharmacology perspective. The FDA's assessment of dosage in pediatric patients weighing <40 kg is summarized according to relevant weight subgroups below.

- In pediatric subjects weighing 15 to <20 kg, Week 0 to 2 and Week 0 to 6 AUC and C_{max} are higher following 100 mg → 50 mg compared to reference exposure. However, Week 0 to 2 and Week 0-6 exposures are not predicted to exceed those following the 400 mg → 200 mg dosage in adult patients which are summarized in [Table 10](#). FDA assessment previously determined that there were no clear safety differences between the 400 mg → 200 mg and 200 mg → 100 mg induction treatment cohorts in Study T17 adult patients with UC (source: *15 May 2013 FDA Clinical Review of sBLA 125289 supplements 77, 78, and 79 [Reference ID: 3308680]*). Therefore, PK and clinical safety data from adult patients with UC support the 100 mg → 50 mg dosage in pediatric patients weighing 15 to <20 kg.
- In pediatric patients weighing 20 to <30 kg, 100 mg → 50 mg does not result in any clinically meaningful exposure differences compared to the studied dosage (i.e., 120 mg/m² → 60 mg/m²) based on simulation in virtual pediatric subjects.

- In pediatric patients weighing 30 to <40 kg, [Figure 1](#), [Figure 2](#), and [Figure 3](#) suggest that 150 mg→ 50 mg (a dosing regimen explored by the FDA reviewer) would more closely match the reference induction exposure (b) (4). The 100 mg → 50 mg dosage is expected to result in 20 to 30% lower median induction and maintenance exposures in pediatric subjects (b) (4) compared to reference. However, a 20 to 30% median decrease in exposure is not expected to impact efficacy. Specifically, there is no expected efficacy difference between 150 mg→ 50 mg and 100 mg→ 50 mg in (b) (4) pediatric patients based on the E-R efficacy assessment in Section [15.3.1.3](#). This is further supported by the similarities in the observed efficacy results at Week 6 in subjects weighing <45 kg between the completed Study UCO1001 and Study UCO3003 (see summary results in [Table 11](#)). Furthermore, a dose of 150 mg would require a minimum of two injections to administer a full dose while each dose of the 100 mg→ 50 mg regimen can be administered with a single injection, as golimumab is marketed in presentations capable of administering 50 mg and 100 mg subcutaneously (source: golimumab USPI). A dosage of 150 mg→ 50 mg may unnecessarily increase the complexity of administration without offering any additional clinical benefit compared to 100 mg→ 50 mg. (b) (4)

Figure 1. Predicted Week 0 to 2 Exposure Following Various SC Golimumab Dosage Regimens in a Virtual Pediatric Population

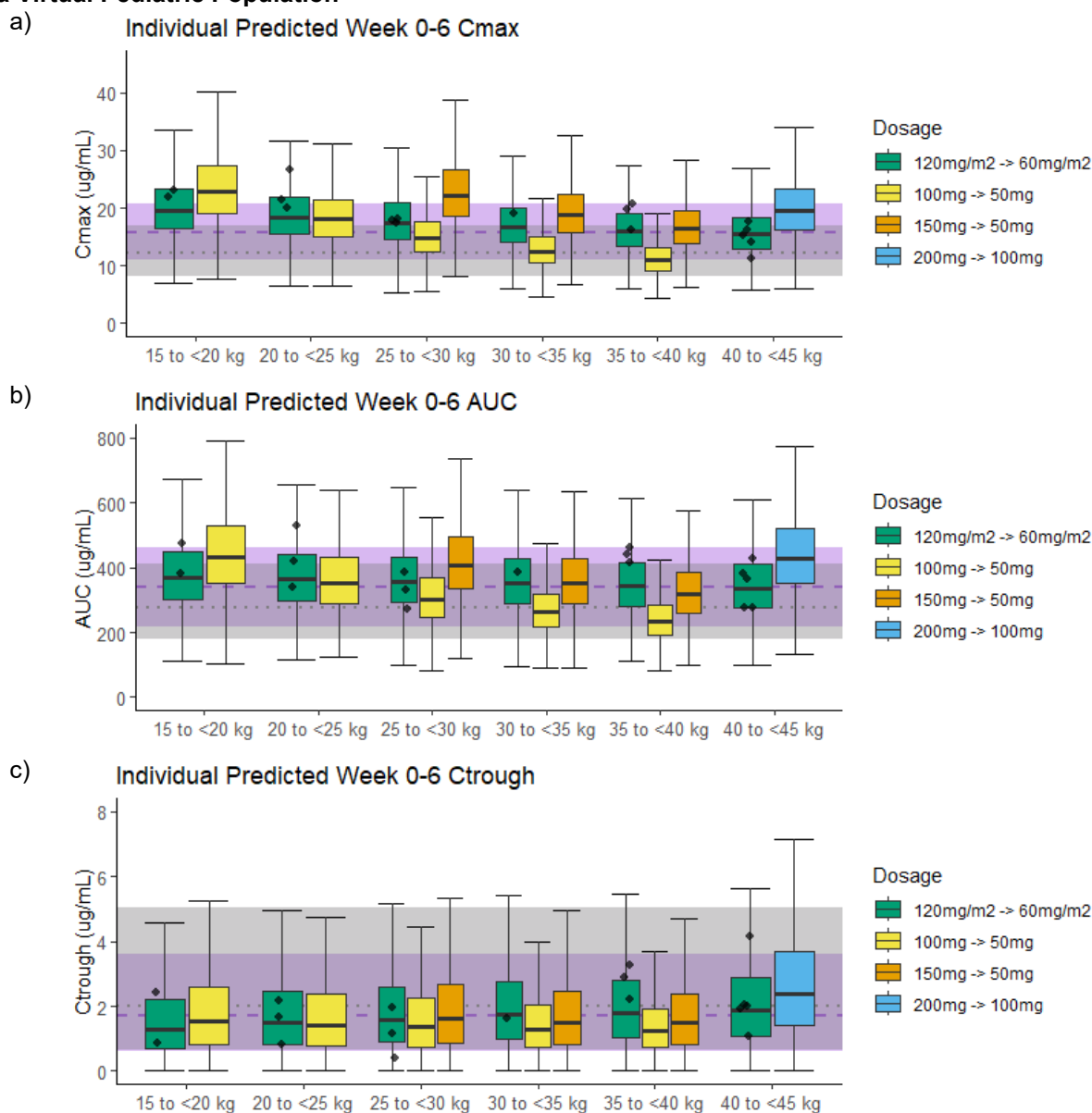
Source: Reviewer's analysis

Black points = individual predicted exposure in Study UCO3003 pediatric patients within each weight bin.

Purple dashed line and shaded area = median (10th to 90th percentile) individual predicted exposure in Study UCO3003 pediatric patients following scheduled dosage (i.e., 200→100 mg in patients weighing 45 kg and above and 120→60 mg/m² in patients weighing less than 45 kg).

Gray dotted line and shaded area = median (10th to 90th percentile) individual predicted exposure in Study T17+T18 adult patients following 200→100 mg.

Abbreviations: AUC, area under the concentration-versus-time curve; C_{max}, maximum concentration; C_{trough}, trough concentration; SC, subcutaneous

Figure 2. Predicted Week 0 to 6 Exposure Following Various SC Golimumab Dosage Regimens in a Virtual Pediatric Population

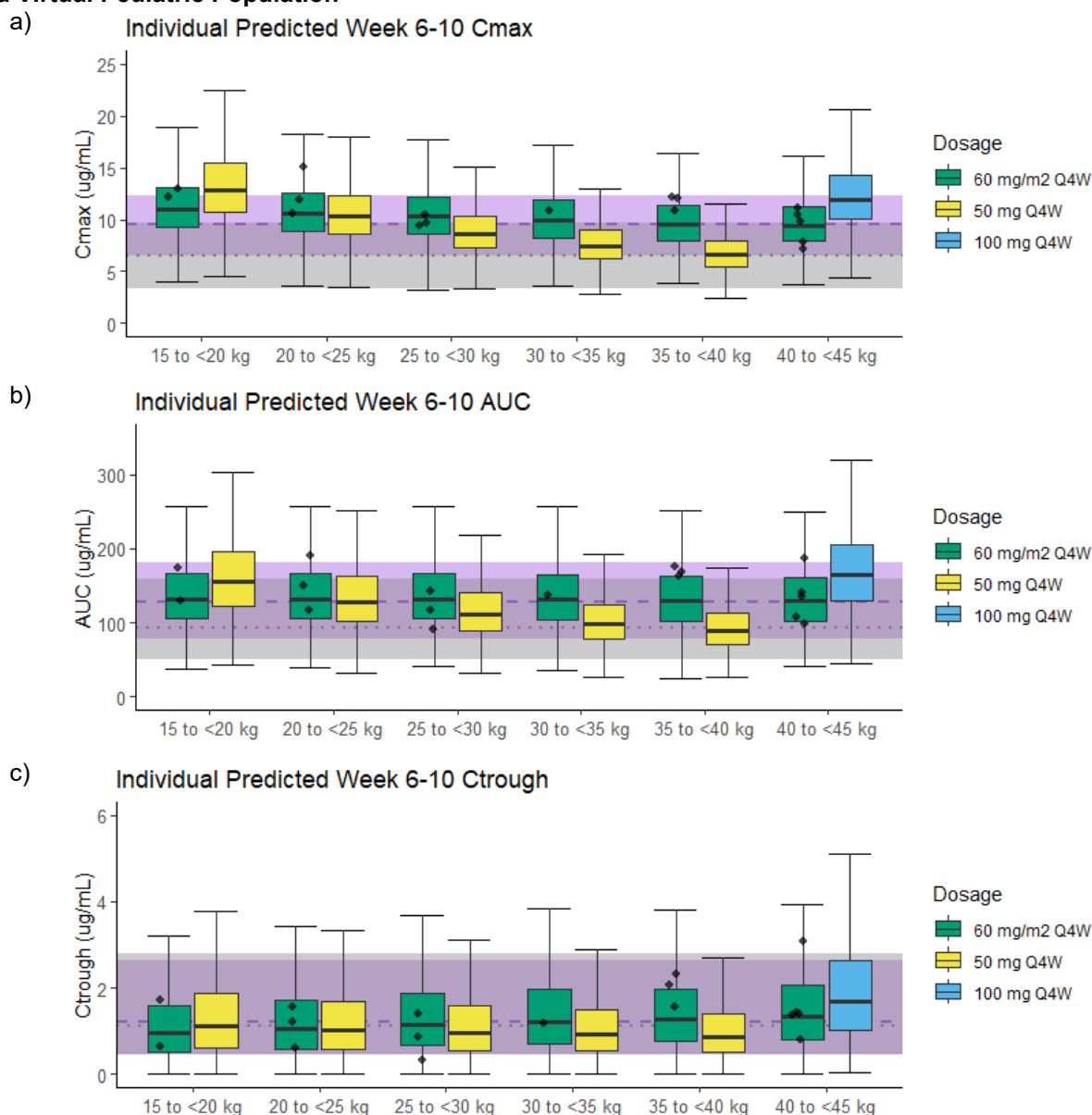
Source: Reviewer's analysis

Black points = individual predicted exposure in Study UCO3003 pediatric patients within each weight bin.

Purple dashed line and shaded area = median (10th to 90th percentile) individual predicted exposure in Study UCO3003 pediatric patients following scheduled dosage (i.e., 200→100 mg in patients weighing 45 kg and above and 120→60 mg/m² in patients weighing less than 45 kg).

Gray dotted line and shaded area = median (10th to 90th percentile) individual predicted exposure in Study T17+T18 adult patients following 200→100 mg.

Abbreviations: AUC, area under the concentration-versus-time curve; C_{max}, maximum concentration; C_{trough}, trough concentration; SC, subcutaneous

Figure 3. Predicted Week 6 to 10 Exposure Following Various SC Golimumab Dosage Regimens in a Virtual Pediatric Population

Source: Reviewer's analysis

Black points = individual predicted exposure in Study UCO3003 pediatric patients within each weight bin.

Purple dashed line and shaded area = median (10th to 90th percentile) individual predicted exposure in Study UCO3003 pediatric patients following scheduled dosage (i.e., 200→100 mg in patients weighing 45 kg and above and 120→60 mg/m² in patients weighing less than 45 kg).

Gray dotted line and shaded area = median (10th to 90th percentile) individual predicted exposure in Study T17+T18 adult patients following 200→100 mg.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; C_{trough}, trough concentration; Q4W, every 4 weeks; SC, subcutaneous

Table 10. Summary of Golimumab Exposure Following Induction Treatment Dosage in Pediatric Patients Weighing 15 to <20 kg

		100 mg→50 mg in Virtual Pediatric Subjects Weighing 15 to <20 kg (n=21,090)	Study UCO3003 Pediatric Patients (n=69)	Study T17 Adult Patients Who Received 400 mg→200 mg (n=327)
Exposure Metric	Statistic			
Week 0-2				
C _{max} (µg/mL)	Geo mean (CV%)	22.8 (27.6%)	15 (28.9%)	23 (28.9%)
	Median	22.8	15.5	22.3
	5 th to 95 th percentile	14.5-35.5	9.2-22.5	15-38
	Min - max	7.8-63.5	6.7-27.2	11.9-65.3
AUC (µg·day/mL)	Geo mean (CV%)	212.5 (27.2%)	114.1 (28.8%)	177.9 (29.6%)
	Median	212.6	122.3	174.7
	5 th to 95 th percentile	137.0-330.4	69.8-170.3	113.5-298.1
	Min - max	76.0-600.6	51.2-203.5	87.1-521.6
Week 0-6				
C _{max} (µg/mL)	Geo mean (CV%)	22.9 (27.8%)	15.1 (28.1%)	23.2 (29.2%)
	Median	22.9	15.6	22.4
	5 th to 95 th percentile	14.6-36.0	9.2-22.7	15.1-38.7
	Min - max	7.7-68.2	6.8-27.2	12-65.3
AUC (µg·day/mL)	Geo mean (CV%)	430.7 (30.9%)	327.4 (32.2%)	538.8 (36.3%)
	Median	433.3	352.4	528.3
	5 th to 95 th percentile	260.8-700.7	192.8-493.1	303.3-929.1
	Min - max	104.4-1526.0	139.2-657	192.5-1823.2

Source: Reviewer's analysis

Abbreviations: AUC, area under the concentration-versus-time curve; C_{max}, maximum concentration; CV, coefficient of variation**Table 11. Summary of Efficacy at Week 6 by Study and Dosage, Pediatric Studies UCO1001 and UCO3003**

Metric	Phase 1 Pediatric Study UCO1001			Phase 3 Pediatric Study UCO3003		
	90 → 45 mg/m ²	200 → 100 mg	OVERALL	120 → 60 mg/m ²	200 → 100 mg	OVERALL
Weight category	20 to <45 kg	≥45 kg	-	16 to <45 kg	≥45 kg	-
n	15	20	35	17	52	69
Clinical remission at Week 6 based on Mayo score	46.7%	40%	42.9%	41.2%	28.8%	31.9%
Clinical remission assessed by PUCAI score at Week 6	33.3%	35%	34.3%	35.3%	32.7%	33.3%
Clinical response as assessed by Mayo score at Week 6	66.7%	55%	60%	52.9%	57.7%	56.5%
Endoscopic healing at Week 6	60%	50%	54.3%	47.1%	38.5%	40.6%

Sources: Study UCO1001 CSR report-body-1 Table TEFEP02; Study UCO3003 CSR Tables TEFCREM01b, TEFCREM05b, TEFCRES01b, and TEFENDO01b

Abbreviations: PUCAI, Pediatric Ulcerative Colitis Activity Index

Overall, the Office of Clinical Pharmacology determined that the following dosage is appropriate for the proposed pediatric indication.

- Pediatric patients weighing 40 kg and above: 200 mg → 100 mg
- Pediatric patients weighing 15 to <40 kg: 100 mg → 50 mg

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Dosing for pediatric patients is based on body weight tiers (see above for additional details). No dose adjustment is required for patients with hepatic or renal impairment, for drug-drug interactions, or according to age, sex, and race.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

There are no drug interaction considerations that pertain specifically to pediatric patients with UC and no new drug interaction findings are reported in the current submission. The language in the currently approved labeling remains unchanged regarding drug interaction.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 12. Clinical Trials Submitted in Support of Efficacy and Safety Determinations for Simponi

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
CNT0148UCO3003 (Study UCO3003)	Pediatric subjects aged 2 to 17 years with moderately to severely active ulcerative colitis	Control type: Historical control Randomization: Standard randomization Randomization Ratio: 3:1 Blinding: Open-label Biomarkers: No biomarkers Innovative design features: None	Drug (established name): Simponi (Golimumab) Dose: (1) Subjects with body weight ≥ 45 kg received fixed induction doses of 200 mg SC at Week 0 and 100 mg at Week 2. (2) Subjects with body weight < 45 kg received BSA-adjusted induction doses of 120 mg/m ² SC (up to a maximum of 200 mg) at Week 0 and 60 mg/m ² SC (up to a maximum of 100 mg) at Week 2. Number treated: 84 Golimumab: 69 Infliximab ¹ : 15 Duration: 54 weeks Week 0 to Week 6 (induction) Week 6 to Week 54 (maintenance) After Week 54 (study extension)	Primary: Clinical remission at Week 6 as assessed by the Mayo score. Secondary (assessed at Week 54): • Symptomatic remission • Clinical remission by Mayo score • Clinical remission by PUCAI score • Endoscopic healing • Clinical remission at Week 54, as assessed by the Mayo score, for subjects who were in clinical remission at Week 6 • Corticosteroid-free clinical remission at Week 54 Secondary endpoints (assessed at Week 6): • Clinical remission by the PUCAI score. • Clinical response by the Mayo score • Endoscopic healing	Planned: 125 Actual: 84	Centers: 27 Countries: 9

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
CNT0148UCO1001 (Study UCO1001)	Pediatric subjects aged 2 to 17 years with moderately to severely active ulcerative colitis	Control Type: No treatment concurrent (single-arm) No randomization (single-arm) Randomization Ratio: N/A Blinding: Open-label Biomarkers: Biomarker as an enrichment strategy (predictive) Innovative design features: None	Drug (established name): Simponi (Golimumab) Dose: 1) Subjects with body weight ≥ 45 kg received fixed induction doses of 200 mg SC at Week 0 and 100 mg at Week 2. (2) Subjects with body weight < 45 kg received BSA-adjusted induction doses of 90 mg/m ² SC (up to a maximum of 200 mg) at Week 0 and 45 mg/m ² SC (up to a maximum of 100 mg) at Week 2. Number treated: 35 Duration: 126 weeks Week 0 to Week 14 (PK phase) Week 14 to Week 126 (study extension)	Primary: The primary focus of the study is to assess the PK of golimumab over time. Therefore, there is no primary efficacy endpoint, and no formal hypothesis testing was performed.	Planned: 30 Actual: 35	Centers: 24 Countries: 7

Source: BLA 125289 Study CNT0148UCO3003 and CNT0148UCO1001 Clinical Study Reports and adsl.xpt

¹ Subjects ≥ 30 kg received body weight-based golimumab SC, or infliximab IV, in a 3:1 ratio, at Weeks 0 and 2 (before Amendment 4) or golimumab SC only (after Amendment 4).

Subjects < 30 kg were not randomized and received weight-based golimumab. Upon implementation of Amendment 4, all newly enrolled subjects received golimumab. Infliximab arm was discontinued after consultation with Health Authorities and these data were not included in the clinical safety analyses.

In study CNT0148UCO3003, prior to Protocol Amendment 4, subjects ≥ 30 kg were randomized in a 3:1 ratio across intervention groups, golimumab SC and infliximab IV, respectively; subjects who weighed < 30 kg were not randomized and only allocated to the golimumab arm.

Abbreviations: BSA, body surface area; IV, intravenous; N/A, not applicable; No., number; (b) (4), pre-filled syringe with (b) (4); (b) (4); PK, pharmacokinetic; PUCAI, Pediatric Ulcerative Colitis Activity Index Score; SC, subcutaneous

7.2. Review Strategy

The application contains efficacy and safety data from two, open-label, treat-through studies - the phase 3 Study CNT0148UCO3003 (Study UCO3003) and the phase 1b Study UCO1001.

Study UCO3003 (which is the primary focus of this review) is a phase 3, randomized, multicenter, open-label study of golimumab to assess the efficacy, safety, and pharmacokinetics of golimumab in pediatric subjects aged 2 to 17 years with moderately to severely active UC, defined as a baseline Mayo score of 6 through 12, inclusive, with an endoscopy subscore of ≥ 2 . Additionally, all study subjects must have demonstrated an inadequate response to, failed to tolerate, or had a medical contraindication to conventional therapies (i.e., IV or oral corticosteroids or the immunomodulators methotrexate, azathioprine, or 6-mercaptopurine). Subjects with prior exposure to biologic anti-TNF- α agents were ineligible. The completed 54-week study consisted of a 6-week short-term period and a 48-week long-term period followed by a study extension (for eligible golimumab-treated subjects). Clinical nonresponders at Week 6 could continue to receive Golimumab up to Week 14, and those who showed partial Mayo score (pMS) response at Week 14 could continue in the maintenance phase of the study. The study extension is ongoing, and a 120-day study update was provided.

Study UCO1001 (which provided PK, short-term efficacy, and limited supportive safety data) was a phase 1b, multicenter, open-label study to assess the pharmacokinetics and safety of SC golimumab treatment in pediatric subjects aged 2 through 17 years with moderately to severely active UC. There were two parts to the study: the PK evaluation (through Week 14) and the study extension period. At Week 6, subjects in clinical response were eligible to receive open-label maintenance therapy with golimumab and to enter the study extension at Week 14. Subjects not in clinical response at Week 6 were withdrawn from further study intervention administration. Dosing differed slightly between Study UCO1001 and UCO3003 (see [Table 12](#)).

7.2.1. Efficacy Review Strategy

This review focuses on the efficacy data from the phase 3 Study UCO3003. The phase 3 study enrolled 69 subjects in the golimumab treatment arm. This study also initially included an infliximab arm per an FDA request to establish assay sensitivity which has since discontinued further enrollment as agreed by FDA on October 14, 2020 (and implemented in Protocol Amendment 4) for a number of reasons (including interpretable golimumab data without the infliximab data, limited ability to interpret the infliximab data, and updated feasibility assessments).

To establish the efficacy of golimumab in pediatric ulcerative colitis, the application relies on partial extrapolation of efficacy from the adequate and well controlled trials that supported approval in adults, and evaluation of the results from the pediatric trial utilizing the totality of available information to aid in interpreting the results from the single-arm, open-label trial. This included evaluation of the following:

1. Comparison with the results in adult patients with UC:
 - a) Review the results of the Applicant's meta-analysis of adult UC studies to derive an external adult placebo rate.²⁰
 - b) Evaluation of similarity between pediatric results and comparable adult results in the similar golimumab treatment exposures.
2. A Bayesian approach borrowing information from adult UC studies.
3. Evaluation of exposure-response relationships for efficacy (discussed in Section [15.3.1.3](#))

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used To Support Efficacy

8.1.1. Study UCO3003

Trial Design

Study UCO3003 is a phase 3, multicenter, single-arm, open-label study in pediatric subjects aged 2 to <18 years with moderately to severely active UC, defined as a baseline Mayo score of 6 through 12, inclusive, with an endoscopy subscore of ≥ 2 as assessed by the local endoscopist. The study consists of a 6-week short-term phase (Week 0 to Week 6), hereafter called the induction phase, and a 48-week long-term phase (Week 6 through Week 54), hereafter called the maintenance phase, and a study extension ([Figure 4](#)). In the induction phase, subjects received a golimumab SC induction dose at Week 0 and a second induction dose at Week 2, followed by assessment at Week 6. Upon completion of the induction phase, subjects entered the maintenance phase and received SC golimumab every 4 weeks through Week 50, followed by assessment at Week 54.

Initially, approximately 125 subjects were planned to be included in Study UCO3003. Of these, at least 5 subjects <30 kg were to receive golimumab, and the remaining 120 subjects were to be randomized 3:1 to golimumab (90 subjects) or infliximab (30 subjects). Per the amended study design (Study UCO3003 Protocol Amendment 4), with removal of the infliximab arm, 100 subjects were to be included (at least 90 subjects would receive golimumab, and at least 10 subjects would have received infliximab). The study design was further amended (Study UCO3003 Protocol Amendment 5) with approximately 70 subjects enrolled (the sample size was reduced from 90 to 60 golimumab-treated participants). The current protocol (Study UCO3003

²⁰ The remission rate on golimumab in pediatric subjects of Study UCO3003 is being compared with a historical placebo remission rate derived from a meta-analysis of 2 adult Phase 2/3 UC studies of golimumab (C0524T16 and C0524T17) and 5 adult Phase 3 studies of other biologic products (infliximab [C0168T37 and C0168T46], adalimumab [ULTRA 1 and ULTRA 2], and vedolizumab [GEMINI 1]) approved in this indication utilizing similar populations and endpoints.

Protocol Amendment 6) states that, of the 60 golimumab subjects, at least 15 would have a body weight <45 kg and at least 5 would have a body weight <30 kg.

Early Treatment Period (Weeks 0 to 6)

The dosing regimen for golimumab was:

- Subjects with body weight ≥ 45 kg received fixed induction doses of 200 mg at Week 0 and 100 mg at Week 2.
- Subjects with body weight <45 kg received body-surface area-adjusted induction doses of 120 mg/m² (up to a maximum of 200 mg) at Week 0 and 60 mg/m² (up to a maximum of 100 mg) at Week 2.

At Week 6, golimumab and infliximab subjects underwent sigmoidoscopy (or colonoscopy at the investigator's discretion) and were evaluated for efficacy, pharmacokinetics, and safety.

Long-Term Treatment Period (Week 6 Through Week 54 and the Final Study Visit)

At Week 6, subjects in clinical response to golimumab (as evaluated by the Mayo score using the local read for the endoscopy subscore, defined as a decrease from baseline score of $\geq 30\%$ and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1) continued to receive SC golimumab 100 mg or 60 mg/m² Q4W through Week 50. Subjects not in clinical response at Week 6, were eligible to receive two additional doses of golimumab (i.e., at Week 6 and Week 10, at the discretion of the investigator). Of these subjects, those who were partial Mayo responders at Week 14 (defined as a decrease from the Week 0 partial Mayo score of ≥ 3 points) continued to receive SC golimumab 100 mg or 60 mg/m² Q4W through Week 50. Subjects who were not in partial Mayo response at Week 14 were withdrawn from further study intervention administrations and completed a final safety follow-up period of 16 weeks (more than 5.5 half-lives for SC golimumab) following the last administration of study intervention.

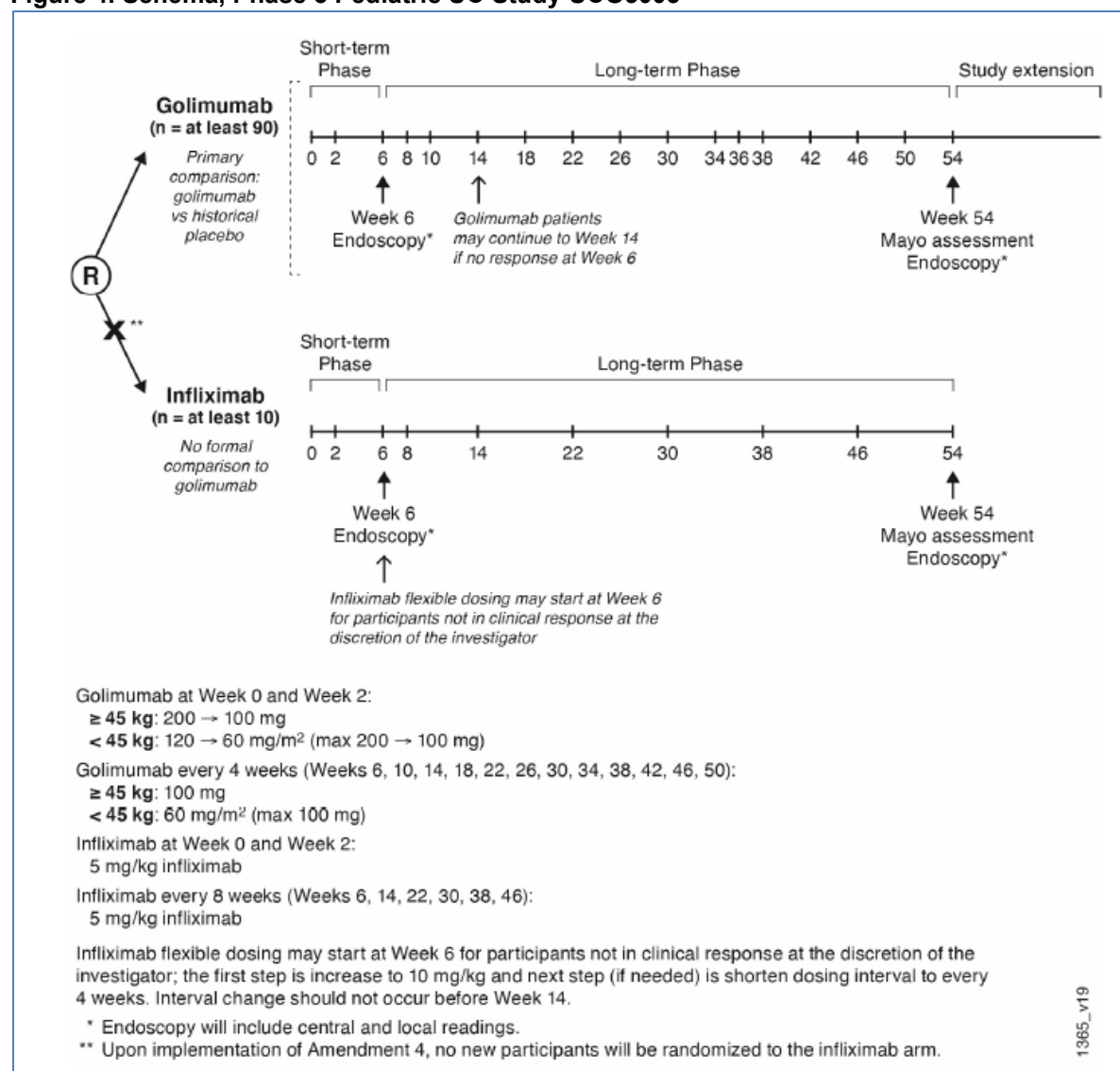
Assessments during the long-term period for both groups include efficacy, pharmacokinetics, and safety. At Week 54, all subjects remaining in the study undergo a sigmoidoscopy (or colonoscopy at the investigator's discretion) to permit a full Mayo score efficacy determination.

Study Extension (Week 54 to End of Study)

After the Week 54 evaluations, at the discretion of the investigator, if subjects receiving golimumab were benefitting from SC golimumab, the subjects could continue to receive SC golimumab Q4W starting at Week 54 under this protocol's study extension until marketing authorization is obtained for golimumab for the treatment of pediatric subjects with UC, the subject turns 18 and has access to commercially available golimumab, or until a decision is made not to pursue an indication in this pediatric UC population, whichever occurs first. Subjects who continue golimumab treatment as part of the study extension will be intermittently evaluated per the protocol for efficacy, pharmacokinetics, and safety.

Beginning with the Week 54 evaluations, subjects in those regions where the adult maintenance posology is weight-based (e.g., 50 mg for those weighing ≤80 kg and 100 mg for those weighing >80 kg) may make a one-time reduction in their golimumab dose to 50 mg Q4W. Subjects may return to the golimumab 100 mg Q4W dosing at the discretion of the investigator, but then no additional changes in dosing can be made for the duration of the study extension.

Figure 4. Schema, Phase 3 Pediatric UC Study UCO3003



Source: Applicant's submission (dated December 12, 2024), Study UCO3003 Protocol, pg. 17/209

Study Endpoints

Primary Efficacy Endpoint

- **Clinical remission at Week 6** as measured by Mayo score, defined as a Mayo score ≤ 2 points, with no individual subscore > 1 , based on the Mayo endoscopy subscore assigned by the local endoscopist.

Secondary Efficacy Endpoints

- **Clinical response at Week 6** as assessed by Mayo score, defined as a decrease from baseline score of $\geq 30\%$ and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.
- **“Endoscopic healing”²¹ at Week 6**, defined as an endoscopy subscore of the Mayo score of 0 or 1 based on local endoscopy.
- **Clinical remission at Week 54**, defined as a Mayo score ≤ 2 points, with no individual subscore > 1 , for participants who are in clinical response at Week 6
- **“Endoscopic healing”²¹ at Week 54**, defined as an endoscopy subscore of the Mayo score of 0 or 1, for participants who are in clinical response at Week 6
- **Clinical remission at Week 54**, defined as a Mayo score ≤ 2 points, with no individual subscore > 1 , for participants who are in clinical remission at Week 6

Each of the above secondary endpoints is associated with a prespecified or post hoc success criterion established by meta-analysis on historical adult placebo subjects (i.e., a historical control). In addition to these endpoints, in the statistical analysis plan (SAP), the Applicant also included the following secondary endpoints (without a corresponding historical control):

- Symptomatic remission at Week 54, defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0
- Clinical remission at Week 54, as assessed by the Pediatric Ulcerative Colitis Activity Index (PUCAI) score, defined as a PUCAI score < 10
- Clinical remission at Week 6, as assessed by the PUCAI score, defined as a PUCAI score < 10
- Participants who were not receiving corticosteroids for at least 12 Weeks prior to Week 54 and in clinical remission at Week 54, as assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist)

²¹ Applicant’s definition of “endoscopic healing” is typically referred to as “endoscopic improvement” in by the Division when included in labeling.

Statistical Analysis Plan

Data Handling Rules

Treatment Failure Rules

The Applicant's SAP states that for all efficacy endpoints through Week 54, treatment failure rules are applied. For dichotomous endpoints, subjects who met any treatment failure criteria were considered as not achieving the respective endpoints. Subjects who had any of the following events were considered as a treatment failure:

- Had a colectomy (partial or full) or ostomy
- Discontinued study intervention due to lack of efficacy or an adverse event (AE) of worsening of UC
- Use of a rescue medication after a clinical flare (Week 6 onwards)
- Had a prohibited change in UC medication

The treatment failure rules are reasonable.

Missing Data Rules

The SAP states that for all analyses, subjects with insufficient data for binary endpoints were considered to not have achieved their respective endpoint.

Note that treatment failure rules override missing data rules. This means that a subject having an event of treatment failure was considered as not achieving the respective endpoints regardless of whether the data were observed or missing. The missing data rules are considered reasonable.

Primary Endpoint Analysis

Mayo Scoring System

The primary endpoint was clinical remission at Week 6, which is derived from Mayo score using local endoscopies. The Mayo score consists of the following four subscores:

- Stool frequency
- Rectal bleeding
- Findings of endoscopy
- Physician's global assessment (PGA)

Each subscore is rated on a scale from 0 to 3, indicating normal to severe disease activity.

The Mayo score is calculated as the sum of the four subscores of stool frequency, rectal bleeding, physician's global assessment, and the findings of endoscopy. Thus, the Mayo score may take on values in the range of 0 to 12. The partial Mayo score, which is the Mayo score

excluding the findings on endoscopy, is calculated as the sum of the stool frequency, rectal bleeding, and physician's global assessment subscores, and may take on values from 0 to 9. The modified Mayo score, which is the Mayo score without the PGA subscore, is calculated as the sum of the stool frequency, rectal bleeding, and endoscopy subscores, and may take on values from 0 to 9. Although the Division's currently recommended approach to evaluating efficacy in UC programs is to utilize the modified Mayo score, this program used the full Mayo score (aligned with the Simponi adult UC program) as extrapolation of efficacy was employed, to allow a more direct comparison between adult and pediatric study results.

The SAP states that because one of the main objectives of the Simponi pediatric UC development program is to compare to the adult Simponi UC results, it is important to maintain consistency with the data handling rules used for the key endpoints at Week 6 in the adult study (C0524T17). Therefore, the Mayo scores at Week 6 were calculated if at least one of the four subscores is available at Week 6. Likewise, the partial Mayo scores were calculated if at least one of the three subscores is available from the visit at which the partial Mayo score is measured. If the Mayo score/partial Mayo score cannot be calculated, it will be considered missing (insufficient data) for that visit. In case of partially missing data (i.e., one to 3 of the subscore is missing, but not all four subscores), the last value for the missing subscore (including endoscopy) was carried forward in order to calculate the full Mayo score or partial Mayo score at Week 6. For a missing endoscopy subscore, this would mean that the baseline value for the endoscopy (i.e., a score of 2 or 3) was carried forward to Week 6. Even though the baseline value of the endoscopy was carried forward, the subject will not meet the criteria for clinical remission (i.e., Mayo score ≤ 2 with no subscore >1) and will also not have achieved endoscopic healing. However, the subject could still potentially achieve clinical response.

The baseline Mayo score is defined as the Mayo score calculated just prior to the first administration of study agent at Week 0 (using the screening endoscopy).

Stool Frequency and Rectal Bleeding Subscores

According to the SAP, the electronic case report forms (eCRFs) captured 7 days of rectal bleeding data and the number of stools per day prior to each visit in which the Mayo score or partial Mayo score was collected. Sites were instructed to check the boxes next to the 3 days which were used to calculate stool frequency and rectal bleeding subscores. The absolute number of stools is the average of the daily number of stools over the 3 days, and the rectal bleeding subscore is calculated using the average rectal bleeding number for the 3 days. At the screening visit, each subject indicates the number of stools they passed in a 24-hour period when in remission or before their UC diagnosis, thereby serving as their own control to establish the degree of abnormality of stool frequency. The stool frequency subscore was calculated by subtracting the number of stools when in remission or prior to UC from the absolute number of stools. The daily bleeding score represents the most severe bleeding of the day.

The SAP states that sites are directed to use the most recent 3 consecutive days within the week prior to the visit. If three consecutive days are not available, the sites are instructed to choose two consecutive days and the closest nonconsecutive day. If two consecutive days are not available, the three nonconsecutive days closest to the visit should be chosen. If 3 days (within the week prior to the indicated visit) that meet the criteria defined above are not available, then the absolute stool number, stool frequency subscore, and rectal bleeding subscore cannot be calculated and will be missing in the eCRF.

The SAP also states that the most recent 3 consecutive days should exclude (1) the day medications were taken for constipation, diarrhea, or irregularity; (2) the day of a procedure or preparation for procedure (e.g., enema, other laxatives, or clear liquid diet) that would affect stool frequency and/or blood content of the stool; (3) the 48 hours after the use of antimotility agents (i.e., diphenoxylate hydrochloride with atropine sulfate or loperamide); and (4) the 48 hours immediately following a colonoscopy.

The data provided by the Applicant did not specify the reason(s) a day was excluded from the subscore calculation, and this information was not directly collected in the eCRF. The review team performed a data check using the QS and SUPPQS SDTM datasets and ADSL ADaM dataset and found that 25 subjects among the 69 subjects at Week 6 and 5 subjects among the 41 subjects at Week 54 did not use the most recent 3 consecutive days of diary data from the 7-day collection period for the calculation of the stool frequency and rectal bleeding subscores. The review team requested the Applicant to provide the specific reasons for each of these subjects why certain day(s) were excluded from the most recent 3 consecutive days in the subscore calculation (e.g., day of colonoscopy) in the FDA letter of Filling Review Issues Identified (i.e., the Day 74 letter) dated February 24, 2025. The Applicant provided their response on March 3, 2025, and summarized the reasons why certain days were excluded from the Week 6 subscore calculation for the 25 subjects and from Week 54 calculation for the 5 subjects. The majority reasons are that sites skipped diary days of preparation for endoscopy and the day of endoscopy. A few sites skipped 2 days prior to endoscopy, which the Applicant explained it corresponds to the 24 to 48-hour period prior to a procedure when clear liquid diets are typically used. A couple of sites skipped more days prior to endoscopy and the Applicant explained that the site followed the instruction to prioritize 3 consecutive days of diary data, and to skip preparatory days and procedure days, and 48 hours post procedures. For Week 6 subscore calculation, there were two subjects that the sites chose the first 3 consecutive diary days in the 7-day window instead of the 3 consecutive days closest to the visit. The Applicant states that recalculation using the 3 consecutive days closest to the visit does not change the Week 6 clinical remission status for the two subjects. For Week 54 subscore calculation, one subject had a similar situation (the site inadvertently chose the first 3 consecutive diary days instead of the 3 consecutive days closest to the visit). The Applicant states that recalculation using the 3 consecutive days closest to the visit does not change the Week 54 clinical remission status of that subject. The review team verified the Applicant's report including the recalculations of the three subjects.

Endoscopy Subscore

The endoscopic subscore was assessed by the investigator (i.e., local endoscopist) during the endoscopy procedure and by a central reader reviewing a video of the endoscopy. The central readers were blinded to local endoscopist scores, treatment assignment and study visit. The central reader performed a friability assessment for each endoscopy (sigmoidoscopy or colonoscopy). If friability is presented, the central reader will also provide a confidence level (High or Low) when evaluating friability. The analysis of endpoints related to the endoscopy subscore, including the Mayo score, will be based on the locally read endoscopy subscore. The local endoscopy reader was used to maintain consistency in methodology for endoscopic data used in the comparison with the historical placebo control for the primary efficacy endpoint and other efficacy endpoints with the adult Simponi data.

Physician's Global Assessment Subscore

The physician's global assessment acknowledges the three other Mayo subscores, the subject's recall of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the subject's performance status.

Analysis Set

The Applicant's planned analysis set for the Week 6 endpoints (including the primary endpoint) uses all enrolled subjects who received at least one dose of golimumab during induction phase (N=69). However, three subjects from the planned analysis set were identified to have not met disease severity inclusion criteria of moderately to severely active UC upon Study UCO3003 enrollment and, therefore, are excluded from all efficacy analyses presented in this review unless otherwise stated (N=66). The analysis set for most Week 54 endpoints (except for the endpoint of clinical remission at Week 54 by Mayo score in subjects who had achieved clinical remission at Week 6) includes subjects who were in clinical response at Week 6 to golimumab as assessed by the Mayo score (local reader) and who received at least one dose of golimumab during the maintenance phase (N=38).

Analysis Methods

The primary analysis for the primary endpoint was based on the proportion of golimumab pediatric subjects in clinical remission at Week 6 based on the Mayo score and its associated 90% CI. The CI were constructed using the asymptotic formula based on the normal approximation to the binomial distribution. The remission rate of golimumab in pediatric subjects was compared with a historical placebo remission rate derived from a meta-analysis of two (2) phase 2/3 adult UC studies of golimumab (C0524T16 and C0524T17), and five (5) phase 3 adult UC studies, which include infliximab (C0168T37 and C0168T46), adalimumab (ULTRA 1 and ULTRA 2), and vedolizumab (GEMINI 1). The criterion for the primary analysis was met if the lower limit of the two-sided 90% CI for the proportion of golimumab subjects in clinical remission at Week 6 is greater than the upper limit of the 95% CI for the proportion of placebo subjects in clinical remission at Week 6 derived from the meta-analysis.

Retained Adult Studies in Meta-Analysis (Systematic Review)

For the purpose of the meta-analyses for the placebo rate to be descriptively compared with the primary endpoint, clinical remission at Week 6, studies were chosen that met the following criteria:

1. Studies that had a similar adult subject population
2. Studies that had similar trial design
3. Studies with similar definition for the primary efficacy endpoint
4. Studies with route of administration IV or SC
5. Phase 3, global clinical studies
6. Studies with endpoint ~6 weeks after study start
7. Studies that used local endoscopic assessment

Based on the study selection criteria, seven phase 3 adult studies were identified, as noted above (see Analysis Methods). Data from these studies were included in the meta-analysis ([Table 13](#)) to estimate the historical placebo rate.

Table 13. Characteristics of Past UC Studies in Adult Participants With Moderately to Severely Active UC, Timing of Clinical Remission Endpoint ~6 Weeks After Study Start

Study	Population	Route of Administration /Dosing Strategy for Induction	Timing of Clinical Remission Endpoint	Clinical Remission Definition	Placebo Point Estimate	Point Estimate for Active Labeled Drug Dosage
SIMPONI PURSUIT IV (C0524T16)	Naïve to TNF	IV Week 0	Week 6	Mayo score ≤2 with no individual subscore >1	11.0% (n=73)	16.0% for 2 mg/kg (n=75)
SIMPONI PURSUIT SC (C0524T17)	Naïve to TNF	SC Weeks 0, 2	Week 6	Mayo score ≤2 with no individual subscore >1	6.4% (n=251) Randomized participants in Part 2 of C0524T17 after the dose selection; 7.2% in all randomized (n=320); used in the meta-analysis	17.8% (n=253) Randomized participants in Part 2 of C0524T17 after the dose selection; assumed clinical remission rate for the pediatric study 17.9% in all randomized (n=324)
REMICADE ACT 1 (C0168T37)	Naïve to TNF	IV Weeks 0, 2, 6	Week 8	Mayo score ≤2 with no individual subscore >1	14.9% (n=121)	38.8% (n=121)

Study	Population	Route of Administration /Dosing Strategy for Induction	Timing of Clinical Remission Endpoint	Clinical Remission Definition	Placebo Point Estimate	Point Estimate for Active Labeled Drug Dosage
REMICADE ACT 2 (C0168T46)	Naïve to TNF	IV Weeks 0, 2, 6	Week 8	Mayo score ≤ 2 with no individual subscore >1	5.7% (n=123)	33.9% (n=121)
Adalimumab – ULTRA 1	Naïve to TNF	SC 160 mg at Week 0, 80 mg at Week 2, then 40 mg every other week starting at Week 4	Week 8	Mayo score ≤ 2 with no individual subscore >1	9.2% (n=130)	18.5% (n=130)
Adalimumab – ULTRA 2	Naïve to TNF	SC 160 mg at Week 0, 80 mg at Week 2, then 40 mg every other week starting at Week 4	Week 8	Mayo score ≤ 2 with no individual subscore >1	11.0% (n=145)	21.3% (n=150)
Vedolizumab (GEMINI 1)	Naïve to TNF	IV Weeks 0, 2	Week 6	Mayo score ≤ 2 with no individual subscore >1	6.6% (n=76)	23.1% (n=130)

Source: Adapted from the Applicant submitted SAP Table 5

Abbreviations: IV, intravenous; n, number of subjects; SC, subcutaneous; TNF, tumor necrosis factor

The details of individual adult studies used in the meta-analysis were described in the SAP.

Meta-Analysis Statistical Details and Results

The Applicant proposed to use a fixed-effects model with the ‘inverse-variance’ weighting (weights of each study are equal to one over sample variance of each study) method in the meta-analysis for the historical placebo control rate. A random-effects model allows for heterogeneity in placebo rates across studies, whereas a fixed-effects model assumes the rate is identical across studies. As the variance for a binary outcome is related to the mean of that outcome, in this instance, the use of the inverse-variance method would generally give more weights to studies with a lower placebo rate, which could result in underestimation of the placebo rate. As a result, FDA recommended that the Applicant use a random-effects model with sample size weighting during the IND stage. The meta-analysis for the point estimate of the placebo rate, based on fixed and random effects models with inverse-variance weighting and sample-size weighting are included in [Table 14](#).

Table 14. Placebo Remission Rate Based on Meta-Analysis for Clinical Remission at Week 6

Study (Naïve TNF Population)	Total (n)	Subjects in Clinical Remission (n)	Placebo Point Estimate for Clinical Remission Based on Meta-Analysis (95% CI) Inverse-Variance Weighting		Placebo Point Estimate for Clinical Remission Based on Meta-Analysis (95% CI) Sample-Size Weighting	
			Fixed Effects	Random Effects	Fixed Effects	Random Effects
Week 6	988	89	8.3%	8.6%	9.0%	9.0%
Studies for comparison with the primary endpoint			(6.6%, 10.0%)	(6.5%, 10.8%)	(7.2%, 10.8%)	(6.8%, 11.2%)

Source: Adapted from the Applicant submitted SAP Table 7. Results were verified by the review team.

Abbreviations: CI, confidence interval; n, number of subjects; TNF, tumor necrosis factor

Secondary Endpoints Analysis

The same analysis method was used for the secondary endpoints as for the primary endpoint. For the short-term efficacy secondary endpoints of clinical response at Week 6 and endoscopic healing at Week 6, the Applicant performed post hoc meta-analyses based on the Agency's information request (IR) dated on January 31, 2025. For the long-term efficacy, the Applicant performed a prespecified meta-analysis for the secondary endpoint of clinical remission at Week 54 and post hoc meta-analyses for the secondary endpoints of endoscopic healing at Week 54 and clinical remission at Week 54 for subjects in clinical remission at Week 6 based on the Agency's IR dated on January 31, 2025.

Meta-Analysis for Clinical Remission at Week 54

For the purpose of the meta-analysis for the placebo rate to be descriptively compared with the clinical remission at Week 54, studies were chosen that met the following criteria:

1. Studies that had a similar adult subject population
2. Phase 3, global clinical studies
3. Studies with endpoint ~54 weeks after study start
4. Studies that had a randomized withdrawal design or a treat through design
5. Studies with similar definition for clinical remission from Week 0 to Week 54
6. Studies with population naïve or non-naïve to TNF
7. Studies that used central or local endoscopic assessment
8. Studies that defined the clinical remission with the Full Mayo score (Mayo score ≤ 2 with no individual subscore ≥ 1) or Full Mayo score without PGA

Based on the criteria, the meta-analysis included eight phase 3 studies ([Table 15](#)) with a randomized withdrawal design: golimumab [PURSUIT-M], ustekinumab [UNIFI-M], vedolizumab [GEMINI 1, MLN0002/CCT-101M (Japan), VISIBLE 1], ozanimod [TRUE NORTH], tofacitinib [OCTAVE SUSTAIN], and upadacitinib [U-ACHIEVE]. The meta-analysis for the placebo points estimate for the fixed effects and random effect model are included in [Table 16](#).

Table 15. Characteristics of Past UC Studies in Adult Participants With Moderately to Severely Active UC, Timing of Clinical Remission Endpoint ~54 Weeks After Study Start

Study	Population	Endoscopic Assessment	Trial Design	Timing of Clinical Remission Endpoint	Clinical Remission Definition	Placebo Point Estimate	Point Estimate for Active labeled Dose
Golimumab – PURSUIT-M	Naïve to TNF	Local	Randomized withdrawal	Week 54	Full Mayo score	22.1% (n=154)	33.1% for 50 mg (n=151) 33.8% for 100 mg (n=151)
Ustekinumab – UNIFI-M	Non-naïve to TNF	Central	Randomized withdrawal	Week 52	Full Mayo score	24.0% (n=175)	38.4% for 90 mg every 12 weeks (n=172) 43.8% for 90 mg every 8 weeks (n=176)
Vedolizumab – GEMINI 1	Non-naïve to TNF	Local	Randomized withdrawal	Week 52	Full Mayo score	15.9% (n=126)	41.8% for every 8 weeks (n=122) 44.8% for every 4 weeks (n=125)
Vedolizumab – MLN0002/CCT-101M (Japan)	Non-naïve to TNF	Local	Randomized withdrawal	Week 60	Full Mayo score	30.9% (n=42)	56.1% (n=41)
Vedolizumab – VISIBLE 1	Non-naïve to TNF	Central	Randomized withdrawal	Week 52	Full Mayo score	14.3% (n=56)	46.2% for SC (n=106) 42.6% for IV (n=54)
Ozanimod – TRUE NORTH	Non-naïve to TNF	Central	Randomized withdrawal	Week 52	Full Mayo score without PGA	18.5% (n=227)	37% (n=230)
Tofacitinib – OCTAVE SUSTAIN	Non-naïve to TNF	Central	Randomized withdrawal	Week 60	Full Mayo score	11.1% (n=198)	34.3% for 5 mg (n=198) 40.6% for 10 mg (n=197)

Study	Population	Endoscopic Assessment	Trial Design	Timing of Clinical Remission Endpoint	Clinical Remission Definition	Placebo Point Estimate	Point Estimate for Active labeled Dose
Upadacitinib – U-ACHIEVE	Non-naïve to TNF	Central	Randomized withdrawal	Week 60	Full Mayo score without PGA	12.1% (n=149)	42% for 15 mg (n=148) 52% for 30 mg (n=154)

Source: Adapted from the Applicant submitted SAP Table 6

Abbreviations: IV, intravenous; n, number of subjects; PGA, physician's global assessment; SAP, statistical analysis plan; SC, subcutaneous; TNF, tumor necrosis factor; UC, ulcerative colitis

Table 16. Placebo Remission Rate Based on Meta-Analysis for Clinical Remission at Week 54

Study (Naïve TNF Population)	Total (n)	Subjects in Clinical Remission (n)	Placebo Point Estimate for Clinical Remission Based on Meta-Analysis (95% CI) Inverse-Variance Weighting		Placebo Point Estimate for Clinical Remission Based on Meta-Analysis (95% CI) Sample-Size Weighting	
			Fixed Effects	Random Effects	Fixed Effects	Random Effects
Week 54 Studies for comparison with the secondary endpoint of clinical remission at Week 54	1127	199	16.4% (14.3%, 18.6%)	17.5% (13.6%, 21.5%)	17.7% (15.5%, 19.9%)	17.7% (13.6%, 21.8%)

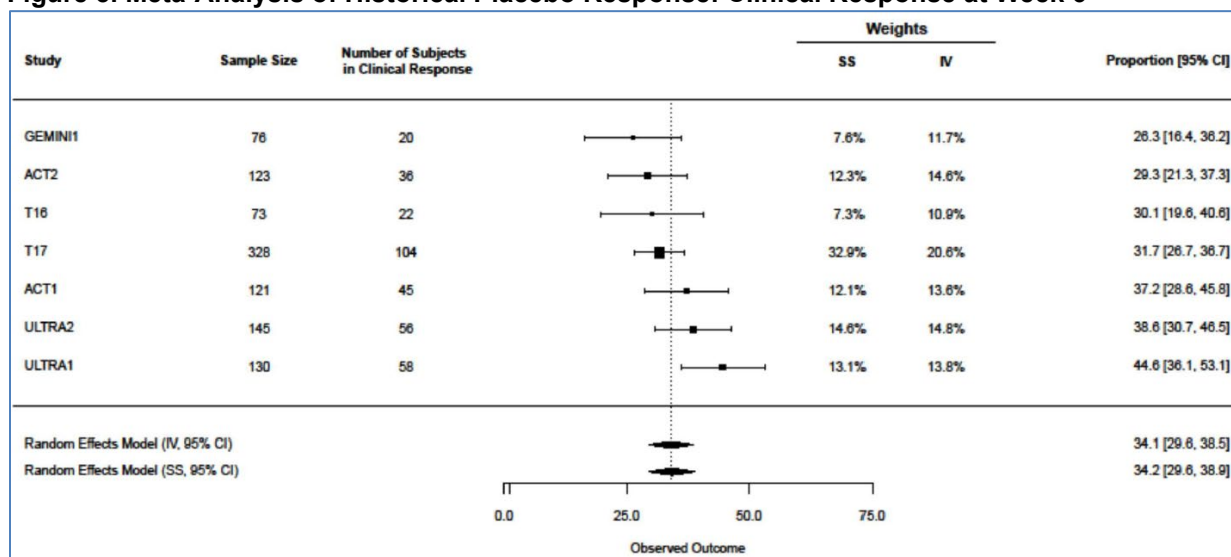
Source: Adapted from the Applicant submitted SAP Table 7. Results were verified by the review team.

Abbreviations: CI, confidence interval; n, number of subjects; SAP, statistical analysis plan; TNF, tumor necrosis factor

Additional Meta-Analysis for Secondary Endpoints

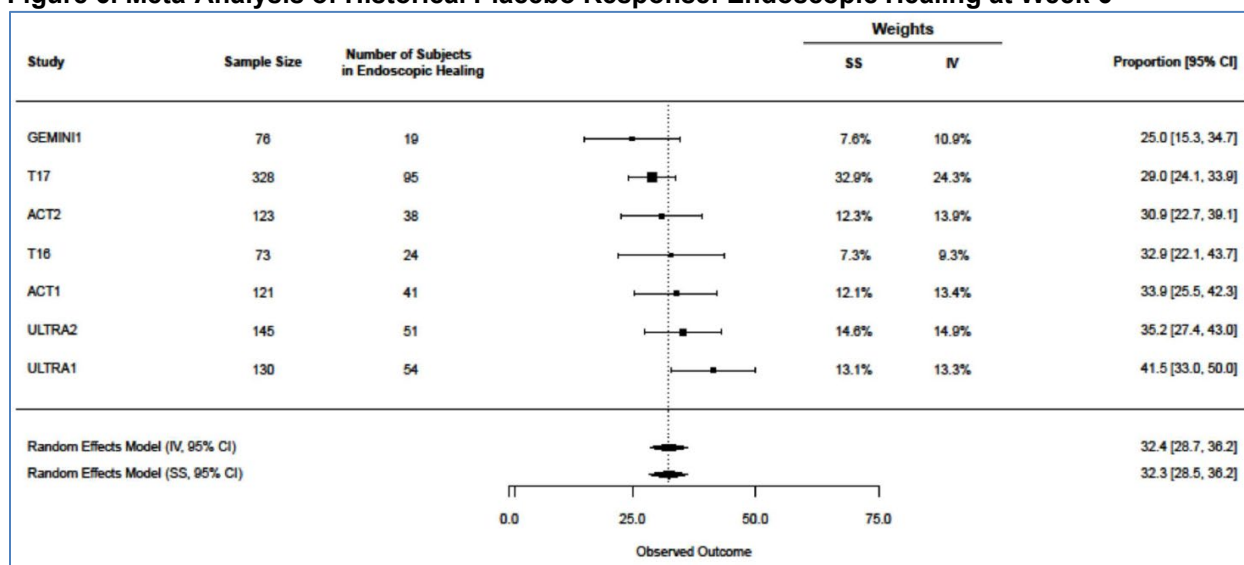
In their responses submitted on February 11, 2025, to the FDA comments in the IR dated on January 31, 2025, the Applicant stated that they had conducted additional meta-analyses of the placebo response for four secondary endpoints. These endpoints were selected based on the availability of data. The historical adult placebo rates for all four additional secondary endpoints were estimated using random effects meta-analysis with 1) sample-size weighting and 2) inverse-variance weighting. The placebo rates and associated 95% CIs of the meta-analyses for the four additional secondary endpoints are shown in [Figure 5](#) to [Figure 8](#).

Figure 5. Meta-Analysis of Historical Placebo Response: Clinical Response at Week 6

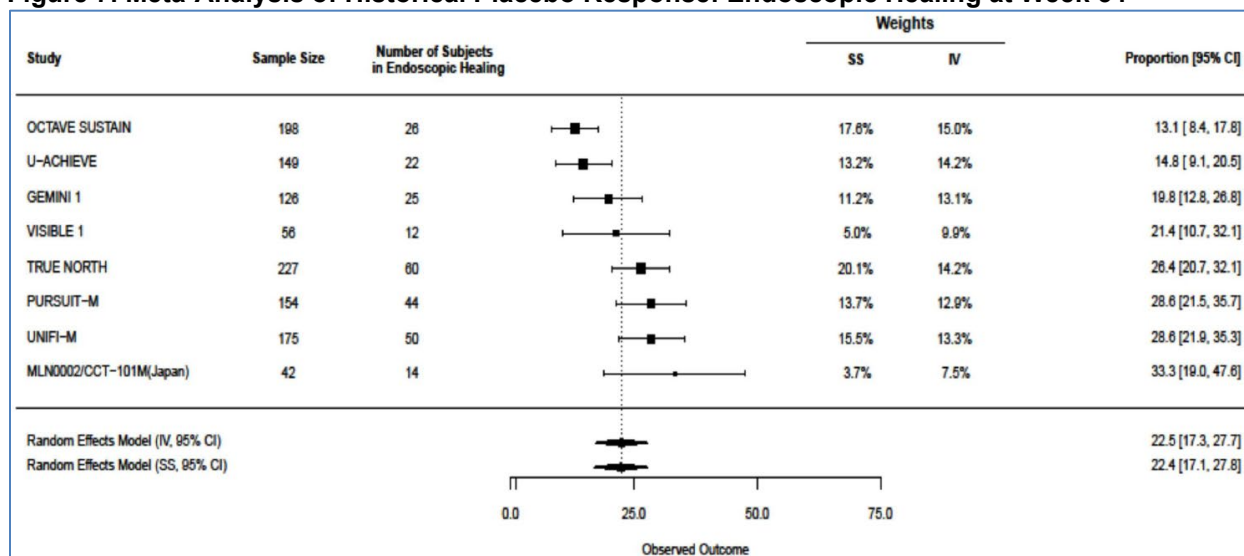


Source: The Applicant's responses submitted on February 11, 2025. Results were verified by the review team.
Abbreviations: CI, confidence interval; IR, information request; IV, inverse-variance; SS, sample-size

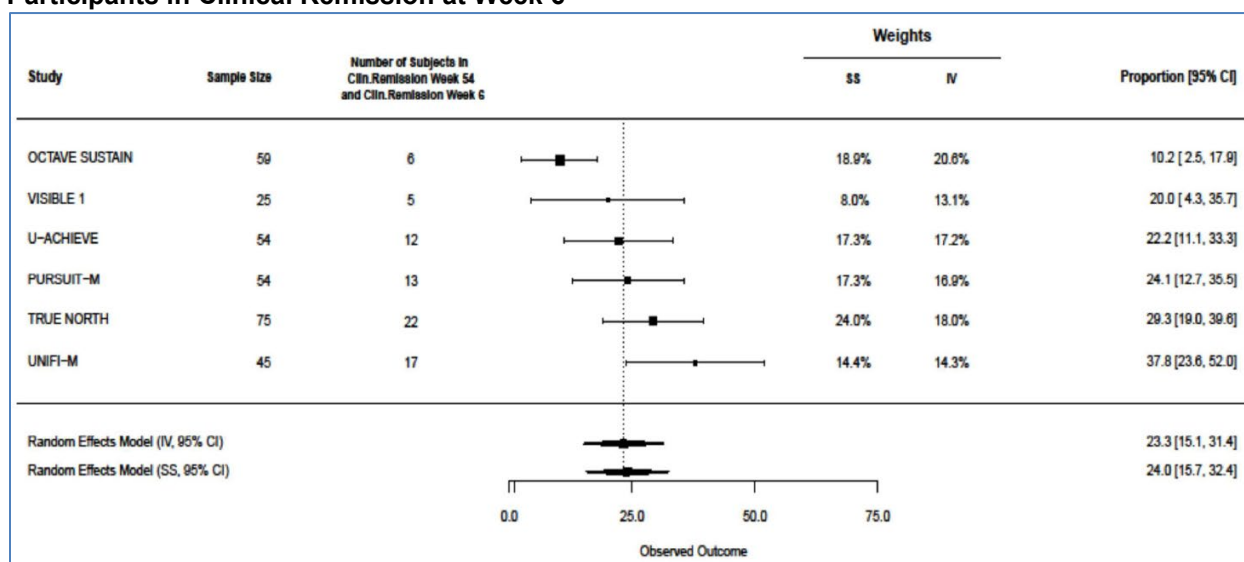
Figure 6. Meta-Analysis of Historical Placebo Response: Endoscopic Healing at Week 6



Source: The Applicant's responses submitted on February 11, 2025. Results were verified by the review team.
Abbreviations: CI, confidence interval; IR, information request; IV, inverse-variance; SS, sample-size

Figure 7. Meta-Analysis of Historical Placebo Response: Endoscopic Healing at Week 54

Source: The Applicant's responses submitted on February 11, 2025. Results were verified by the review team.
Abbreviations: CI, confidence interval; IR, information request; IV, inverse-variance; SS, sample-size

Figure 8. Meta-Analysis of Historical Placebo Response: Clinical Remission at Week 54 for Participants in Clinical Remission at Week 6

Source: The Applicant's responses submitted on February 11, 2025. Results were verified by the review team.
Abbreviations: CI, confidence interval; IR, information request; IV, inverse-variance; SS, sample-size

Analysis Methods

The primary analysis for the secondary endpoints using the same method as the primary analysis for the primary endpoint. That is, 90% CIs using the asymptotic formula based on the normal approximation to the binomial distribution were provided and compared with the corresponding efficacy thresholds established by the meta-analyses described above for each secondary endpoint.

Protocol and SAP Amendments

Protocol for Study UCO3003 was initially submitted on May 22, 2018.

The protocol was amended six times. The key modifications are summarized below.

Table 17. Protocol Amendments, Study UCO3003

Amendment #	Date	Key Changes
1	July 9, 2018	Corrected an error (move inclusion criterion #18 in Section 5.1 to Section 5.2, Exclusion Criteria)
2	May 22, 2019	Added sensitivity analyses on endpoints of remission and clinical responses based on the Modified Mayo score Added symptomatic remission at Week 54 and clinical remission at Week 54 as the first and second major secondary endpoints
3	August 1, 2019	No statistically related changes mentioned Inclusion criteria were modified regarding prior and/or current medication history and failures, concomitant medications, and the stability of enteral nutrition (parenteral nutrition no longer permitted). Deleted intravenous corticosteroids from concomitant medication.
4	April 7, 2021	Discontinued further enrollment into the infliximab arm All newly enrolled subjects to receive golimumab Inclusion criteria regarding TB screening, immunizations, the screening of measles and varicella titers (no longer required) were modified. Exclusion criteria regarding COVID-19 infection, prior <i>C. difficile</i> infection, TB testing and potential infection, history of serious infections were modified.
5	October 20, 2022	Reduced sample size from 90 to 60 golimumab-treated subjects Stopped enrollment of new subjects
6	October 24, 2023	No statistically related changes mentioned Schedule of Activities modified to not that information will be collected up to and including Week 90 to assess safety and efficacy. After Week 90, safety laboratory assessments will be collected annually to reduce participant burden.

Source: Review team generated summary based on multiple BLA 125289 submissions

Abbreviations: COVID-19, coronavirus disease 2019; TB, tuberculosis

Table 18. SAP Amendments

SAP	Date	Key Changes
Original submission	May 22, 2019	Included FDA recommended sensitivity analyses on endpoints of remission and clinical responses based on the Modified Mayo score Addition of symptomatic remission and clinical remission at Week 54 as major secondary endpoints
Version 2.0	March 8, 2023	Discontinued further enrollment into the infliximab arm All newly enrolled subjects to receive golimumab Reduction in sample size Added details of how adult UC studies were identified for the meta-analysis to estimate the historical placebo rate for the primary endpoint of clinical remission at Week 6 Added a logistic regression model and a Bayesian logistic model as supportive analyses for comparing pediatric and historical adult placebo remission rates Expanded endoscopy window and added multiple imputation for missing data due to COVID-19
Version 3.0 (final)	March 8, 2024	Added systematic review and meta-analysis for estimating the Week 52/54 placebo clinical remission rate Removal of requirement for similar route of administration in meta-analysis inclusion criteria Added use of sample-size weighting method in meta-analysis Confirmed database lock date of April 11, 2024

Source: Review team generated summary based on multiple BLA 125289 submissions

Abbreviations: COVID-19, coronavirus disease 2019; SAP, statistical analysis plan; UC, ulcerative colitis

8.1.2. Study Results

Compliance With Good Clinical Practices

The studies were conducted in accordance with the protocols, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, applicable regulations and guidelines governing clinical study conduct, and ethical principles originating in the Declaration of Helsinki.

Financial Disclosure

The Applicant adequately disclosed financial arrangements with the clinical investigators. These arrangements do not raise concern over the integrity of the data. See Section [15.2](#) for further discussion and tables detailing financial disclosures.

Data Quality and Integrity

The data were of sufficient quality to permit a substantive review.

Patient Disposition

A total of 69 subjects enrolled and received at least one dose of golimumab. Three (3) subjects were identified to have not met disease severity inclusion criteria of moderately to severely active UC upon Study UCO3003 enrollment and, therefore, are excluded from all efficacy analyses presented in this review unless otherwise stated. A summary of treatment disposition for the remaining 66 study subjects is presented in [Table 19](#). Thirty-one (47.0%) treated subjects discontinued golimumab from Week 0 through the final study visit. The most common reasons for discontinuation of golimumab were AE (22.7%) and lack of efficacy (15.2%). From Week 0 through Week 6, 6/66 (9.1%) treated subjects discontinued golimumab, and the most common reason for discontinuation was AE (6.1%). From Week 6 through Week 54, 25/60 (41.7%) treated subjects discontinued golimumab, and the most common reasons for discontinuation were AE (18.3%) and lack of efficacy (15.0%). Of note, in the study overall the most common treatment-emergent adverse events (TEAEs) were related to worsening of UC.

A summary of the subjects who terminated study participation prematurely in study UCO3003 is shown in [Table 20](#). The reasons for study termination are the same as the reasons for the treatment discontinuations except for two cases. Two subjects who discontinued treatment due to lack of efficacy terminated study participation for reasons reported as either lost to follow-up or AE.

Table 19. Treatment Disposition, All Golimumab-Treated Subjects, Study UCO3003

Disposition Outcomes	Week 0 Through Week 6 (Induction) n (%)	Week 6 Through Week 54 (Maintenance) n (%)	Week 0 Through Final Study Visit (Overall) n (%)
Subjects treated	66	60	66
Discontinued treatment	6 (9.1)	25 (41.7) ^a	31 (47.0)
Adverse event	4 (6.1)	11 (18.3)	15 (22.7)
Initiated prohibited medication	0	1 (1.7)	1 (1.5)
Lack of efficacy	1 (1.5)	9 (15.0)	10 (15.2)
Other ^b	1 (1.5)	1 (1.7)	2 (3.0)
Physician decision	0	1 (1.7)	1 (1.5)
Protocol deviation	0	1 (1.7)	1 (1.5)
Withdrawal by parent/guardian	0	1 (1.7)	1 (1.5)

Source: Review team generated analysis using SAS 9.4 on the Applicant submitted data ADLX.xpt.

^a Includes subjects who were discontinued due to not achieving partial Mayo response at Week 14. These subjects are listed as discontinuing treatment due to various reasons in the ADLX.xpt dataset.

^b "Other" reasons for treatment discontinuation include the following: "PI decision, disease progression" (induction) and "No mucosal healing achieved" (maintenance).

Abbreviations: n, number of subjects with given treatment disposition; PI, principal investigator

Table 20. Study Disposition, All Golimumab Treated Subjects, Study UCO3003

Disposition Outcomes	Week 0 Through Week 6 (Induction) n (%)	Week 6 Through Week 54 (Maintenance) n (%)	Week 0 Through Final Study Visit (Overall) n (%)
Subjects treated	66	60	66
Terminated study	6 (9.1)	23 (38.3) ^a	31 (47.0) ^b
Adverse event	4 (6.1)	11 (18.3)	16 (24.2)
Initiated prohibited medication	0	1 (1.7)	1 (1.5)
Lack of efficacy	1 (1.5)	7 (11.7)	8 (12.1)
Lost to follow-up	0	1 (1.7)	1 (1.5)
Other ^c	1 (1.5)	0	2 (3.0)
Physician decision	0	1 (1.7)	1 (1.5)
Protocol deviation	0	1 (1.7)	1 (1.5)
Withdrawal by parent/guardian	0	1 (1.7)	1 (1.5)

Source: Review team generated analysis using SAS 9.4 on the Applicant submitted data ADSL.xpt.

^a Includes subjects who were discontinued due to not achieving partial Mayo response at Week 14. These subjects are listed as discontinuing treatment due to various reasons in the ADSL.xpt dataset.

^b The Applicant reported that 3 of 31 subjects discontinued the study after Week 54; however, one of the 3 subjects received their last dose at Week 38 and did not have a Week 54 visit. This subject is considered to have been discontinued from the study in this reviewer generated table.

^c "Other" reasons for treatment discontinuation include the following: "PI decision, disease progression" (induction) and "No mucosal healing achieved" (maintenance).

Abbreviations: n, number of subjects with given treatment disposition; PI, principal investigator

Protocol Violations/Deviations

The Applicant reported a total of 83 protocol deviations which occurred in 42 golimumab treated subjects during the Study UCO3003. Forty-nine (59.0% of 83) protocol deviations for 32 (46.4% of 69) golimumab treated subjects were classified as major and 34 (41.0% of 83) protocol deviations for 23 (33.3% of 69) Golimumab treated subjects were classified as minor. All the 34 minor protocol deviations are COVID-19 related. The summary of major protocol is shown in [Table 21](#).

Table 21. Summary of Major Protocol Deviation Frequency and Subjects, Study UCO3003

Major Protocol Deviations	Number of PDs	Number of Subjects
	n (% of Total Events)	With PDs n (% of Total Subjects)*
Total	49 (100.0)	32 (46.4)
Entered but did not satisfy criteria	7 (14.3)	7 (10.1)
Received a disallowed concomitant treatment	3 (6.1)	3 (4.3)
Received wrong treatment or incorrect dose	3 (6.1)	3 (4.3)
Other	36 (73.5)	27 (39.1)
Missed visit/assessment due to COVID-19	5 (10.2)	5 (7.2)
Did not complete the final safety visit	5 (10.2)	5 (7.2)
Missed assessment/assessment was completed outside of window	7 (14.3)	7 (10.1)
SAE not reported/completed within 24 hours/not sent in GMS/not reported to GMS on-time	7 (14.3)	7 (10.1)
Dose was administrated outside of window	5 (10.2)	4 (5.8)
Subject received rescue medication but did not meet criteria for flare/disease flare considered by PI may not comply with disease flare protocol definition.	4 (8.2)	3 (4.3)
Endoscopy performed out of window	3 (6.1)	3 (4.3)

Source: Review team generated analysis using SAS 9.4 on the Applicant submitted data DV.xpt.

* Subjects may appear in more than one category

Abbreviations: COVID-19, coronavirus disease 2019; GMS, Global Medical Safety system; n, number of subjects or events; PD, protocol deviation; PI, principal investigator; SAE, serious adverse event

Among the seven subjects who were enrolled but did not satisfy the eligibility criteria, five subjects did not meet the inclusion criteria ([Table 22](#)), one subject's test for varicella antibodies was not performed, and in one subject the consent process and informed consent form was not performed appropriately (not signed by patient's father who registered the child). The five subjects who had selection criteria violations are summarized in [Table 22](#). Three subjects did not meet the inclusion criterion #4 and #5. The review team had concerns with these three subjects because they did not have moderately or severely active UC based on either their Mayo score or endoscopy subscore. The review team determined these three subjects should be excluded from the efficacy analyses. One subject did not meet the inclusion criterion #7 (concomitant medication stability criteria prior to first administration). The Applicant reported that the subject did not have stable oral steroid dosing for the 2 weeks prior to Week 0 but had a stable dose for daily 5-ASA prior to Week 0. The review team does not have concerns with this subject and agreed to include this subject in the efficacy analysis. One subject did not meet the inclusion criterion #14 (during screening, blood sample to evaluate serum pregnancy has not been collected). The review team does not have concerns with including this subject in the efficacy analyses and more information was provided for this subject (her urine pregnancy test had been performed at week 0 and it was negative).

Table 22. Summary of Subjects Who Did Not Meet Inclusion Criteria, Study UCO3003

Criteria	Number of Subjects Who Did Not Meet Inclusion Criteria n (% of Total Subjects)
Total	5 (7.2)
UC disease criteria (inclusion criterion #4 and #5 not met)	3 (4.3)
Medication criteria (inclusion criterion #7 not met)	1 (1.4)
Laboratory criteria (inclusion criterion #14 not met)	1 (1.4)

Source: Review team's analysis using SAS 9.4 on the Applicant submitted data DV.xpt.

Inclusion #4: Must have moderately to severely active UC (as defined by baseline Mayo score of 6 through 12 [endoscopy {sigmoidoscopy or colonoscopy} subscore assigned by local endoscopist], inclusive).

Inclusion #5: Must have a Mayo endoscopy (sigmoidoscopy or colonoscopy) subscore ≥ 2 (subscore assigned by local endoscopist) at baseline endoscopy (indicative of moderately to severely active UC). Baseline endoscopy (sigmoidoscopy or colonoscopy) must be performed with study software and occur no more than 2 weeks before first study intervention administration.

Inclusion #7: Must meet concomitant medication dose stability prior to the first administration of study intervention.

Inclusion #14: All girls of childbearing potential must have a negative serum pregnancy test at screening.

Abbreviations: n, number of subjects; UC, ulcerative colitis

Three subjects with major protocol deviations received a disallowed concomitant treatment and three subjects received the wrong treatment or incorrect dose. The 36 other protocol deviations included: missed visit/assessment due to COVID-19 (n=5), did not complete the final safety visit (n=5), missed assessment/assessment was completed outside of window (n=5), serious adverse event (SAE) not reported/completed within 24 hours/not sent in GMS/not reported to GMS on-time (n=7), dose was administered outside of window (n=5), subject received rescue medication but did not meet criteria for flare or disease flare considered by principal investigator may not comply with UC flare protocol definition (n=4), endoscopy performed out of window (n=3). The review team does not have concerns regarding the rest of the major protocol deviations.

Golimumab Administration Deviations

The Applicant reported 49 golimumab administration deviations for 18 golimumab treated subjects during the study UCO3003. Two subjects missed their administrations at one of their study visits. Three subjects received five incorrect doses. Fifteen subjects received scheduled administration outside the protocol-specified window at totally 42 study visits. The results of the golimumab administration deviations are summarized in [Table 23](#). In general, these deviations are unlikely to have a major impact on efficacy or safety outcomes.

Table 23. Summary of Protocol Deviations in Study Agent Administration and Subjects With Protocol Deviations in Study Agent Administration, Study UCO3003

Protocol Deviations in Study Agent Administration	Number of Protocol Deviations n (% of Total Events)	Number of Subjects With PDs n (% of Total Subjects)^a
Total	49 (100.0)	18 (26.1)
Missed an administration	2 (4.1) ^b	2 (2.9)
Received incorrect dose	5 (10.2)	3 (4.3) ^c
Received scheduled administration outside protocol-specified window	42 (85.7)	15 (21.7)

Source: Review team's analysis using SAS 9.4 on the Applicant submitted data ADEX.xpt.

^a Subjects may appear in more than one category

^b both subjects subsequently received the "missed" dose later at a rescheduled visit, though just outside of the protocol-permitted window, and are also counted in that category.

^c Three subjects each received a lower than protocol-specified dosage on one occasion each.

Abbreviations: n, number of subjects or events; PD, protocol deviation

Demographic Characteristics

The demographic characteristics of the 66 golimumab treated subjects (excluding 3 subjects who did not meet the inclusion criteria on the severity of the UC) are summarized in [Table 24](#). As expected based on the epidemiology of pediatric UC, the majority of subjects were adolescents and weighed ≥ 45 kg. The youngest study subject was a 4-year-old subject, and there were only two subjects between age of 2 and 5. There were 8 subjects (12.1%) with a baseline weight less than 30 kg. The majority, 63 (95.5%) of the subjects, were enrolled outside the United States.

Table 24. Demographics and Baseline Characteristics, Study UCO3003

Characteristic	Golimumab Total N=66
Sex, n (%)	
Female	35 (53.0)
Male	31 (47.0)
Age, years	
Mean (SD)	13.4 (3.3)
Median (min, max)	14 (4, 17)
Age group, years, n (%)	
2 to 5	2 (3.0)
6 to 11	12 (18.2)
12 to 17	52 (78.8)
Weight, kg	
Mean (SD)	52.6 (17.9)
Median (min, max)	51.4 (16.4, 106.8)
Weight categories, kg, n (%)	
<30	8 (12.1)
≥ 30 to <45	8 (12.1)
≥ 45	50 (75.8)

Characteristic	Golimumab Total N=66
Race, n (%)	
American Indian or Alaska Native	2 (3.0)
Asian	12 (18.2)
Black or African American	2 (3.0)
Multiple	1 (1.5)
White	47 (71.2)
Missing	2 (3.0)
Ethnicity, n (%)	
Hispanic or Latino	16 (24.2)
Not Hispanic or Latino	48 (72.7)
Not reported	2 (3.0)
Country of participation, n (%)	
Brazil	11 (16.7)
Israel	10 (15.2)
Italy	8 (12.1)
Korea	12 (18.2)
Poland	16 (24.2)
Others	9 (13.6)
Is in United States, n (%)	
United States	3 (4.5)
Non-United States	63 (95.5)

Source: Adapted from the Applicant's responses submitted on June 27, 2025, to FDA IR Table TSIDEM05c and verified by the review team using SAS 9.4 on the Applicant submitted data DM.xpt, VS.xpt, and ADSL.xpt.

Abbreviations: IR, information request; N, total number of subjects; n, number of subjects with given characteristic; SD, standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Baseline disease characteristics for the golimumab treated group are summarized in [Table 25](#). The median (range) duration of disease was 1.45 (0.21, 7.84) years. Based on Mayo score, most subjects (93.9%) had UC of moderate severity. Thirty (45.5%) subjects had disease limited to the left side of the colon. Disease extent was based on endoscopy findings and the investigator could choose between colonoscopy and sigmoidoscopy for the assessment.

Table 25. Baseline UC Disease Characteristics, Study UCO3003

Baseline Disease Characteristic	Golimumab
UC disease duration, years	
N	66
Mean (SD)	1.94 (1.69)
Median (min, max)	1.45 (0.21, 7.84)
UC symptoms duration prior to diagnosis, months	
N	66
Mean (SD)	9.2 (20.8)
Median (min, max)	3 (0, 149)
Mayo score	
N	66
Mean (SD)	7.7 (1.5)
Median (min, max)	8 (6, 11)

Baseline Disease Characteristic	Golimumab
Severity of disease by Mayo score, n (%)	
N	66
Mild disease: ≥ 3 - ≤ 5	0
Moderate disease: ≥ 6 - ≤ 10	62 (93.9)
Severe disease: > 10	4 (6.1)
Extent of disease ^a , n (%)	
N	66
Limited to left side of colon	30 (45.5)
Extensive	36 (54.5)
C-reactive protein (CRP), mg/L	
N	65
Mean (SD)	7.67 (15.13)
Median (min, max)	1.59 (0.1, 92.4)
Fecal calprotectin concentrations, mg/kg	
N	60
Mean (SD)	3289.3 (5458.2)
Median (min, max)	1588 (36, 3600)
Fecal calprotectin	
N	60
Normal (≤ 250 mg/kg)	7 (11.7)
Abnormal (> 250 mg/kg)	53 (88.3)

Source: Adapted from the Applicant's responses submitted on June 27, 2025, to FDA IR Table SIDEM05d and verified by the review team using SAS 9.4 on the Applicant submitted data ADBDC.xpt.

^a Based on local endoscopy

Abbreviations: N, number of subjects with given characteristic; SD, standard deviation; UC, ulcerative colitis

The summary of UC-related concomitant medications at baseline is in [Table 26](#). At baseline, a majority of subjects (97.0%) were receiving UC-related medications (corticosteroids, immunomodulators, and 5-ASA); 50.0% of subjects were receiving corticosteroids, and 87.9% were receiving oral 5-ASA.

Table 26. UC-Related Concomitant Medications at Baseline, Study UCO3003

Baseline Concomitant Medications	Golimumab Total N=66 n (%)
Subjects who received any of the following UC medications	64 (97.0) ^a
Corticosteroid use	33 (50.0)
Oral/Parenteral corticosteroid use (excluding budesonide and beclomethasone dipropionate)	24 (36.4)
Rectal corticosteroid use (excluding budesonide and beclomethasone dipropionate)	0
Budesonide ^b	6 (9.1)
Beclomethasone dipropionate ^b	3 (4.5)
Immunomodulatory drugs	31 (47.0)
6-mercaptopurine	0
Azathioprine	31 (47.0)
Methotrexate	0
Oral 5-aminosalicylate	58 (87.9)

Source: Adapted from the Applicant's responses submitted on June 27, 2025, to FDA IR Table TSIDEM05e and verified by the review team using SAS 9.4 on the Applicant submitted data ADBDC.xpt.

^a Note: Subjects may appear in more than one category

^b Including oral or rectal

Abbreviations: IR, information request; N, total number of subjects; n, subjects who received UC-related medications; UC, ulcerative colitis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

During the induction phase, all treated subjects (100%) including the three subjects who did not meet the inclusion criteria received the two scheduled doses of golimumab ([Table 27](#)).

Table 27. Number of Subjects Who Received Scheduled Study Agent Prior to Week 6, Safety Golimumab During the Short-Term Phase Analysis Set, Study UCO3003

Analysis Set	
Week #	Golimumab ^a
Analysis set: Safety golimumab during the short-term phase	69
Subjects receiving a scheduled study agent	
Week 0	69 (100.0%)
Week 2	69 (100.0%)

Source: Adapted from the Applicant's CSR Table TSIX01a on page 758 and verified by the review team using SAS 9.4 on the Applicant submitted data EC.xpt

^a Includes all treated subjects (including three subjects excluded from the efficacy analysis population due to not meeting key inclusion criteria)

Abbreviations: CSR, clinical study report

During the maintenance phase, 98.4%, 72.6%, and 62.9% of subjects including the 3 subjects who did not meet the inclusion criteria received the scheduled dose of golimumab at Week 6, Week 30, and Week 50, respectively ([Table 28](#)).

Table 28. Number of Subjects Who Received Scheduled Study Agent From Week 6 Through Week 54, Safety Golimumab During the Long-Term Phase Analysis Set, Study UCO3003

Analysis Set	
Week #	Golimumab ^a
Analysis set: Safety golimumab during the long-term phase	62
Subjects receiving a scheduled study agent	
Week 6	61 (98.4%)
Week 10	55 (88.7%)
Week 14	52 (83.9%)
Week 18	48 (77.4%)
Week 22	46 (74.2%)
Week 26	46 (74.2%)
Week 30	45 (72.6%)
Week 34	44 (71.0%)
Week 38	42 (67.6%)
Week 42	39 (62.9%)
Week 46	39 (62.9%)
Week 50	39 (62.9%)

Source: Adapted from the Applicant's CSR Table TSIX02a on page 760 and verified by the review team using SAS 9.4 on the Applicant submitted data EC.xpt

^a Includes all treated subjects (including three subjects excluded from the efficacy analysis population due to not meeting key inclusion criteria)

Abbreviations: CSR, clinical study report

Efficacy Results – Primary Endpoint

The efficacy results below exclude the three subjects who did not meet the inclusion criteria on the severity of UC.

The primary endpoint of clinical remission at Week 6, as measured by Mayo score, was defined as a score ≤ 2 points, with no individual subscore > 1 , based on the Mayo endoscopy subscore assigned by the local endoscopist. At Week 6, 31.8% of treated subjects achieved clinical remission as assessed by the Mayo Score ([Table 29](#)).

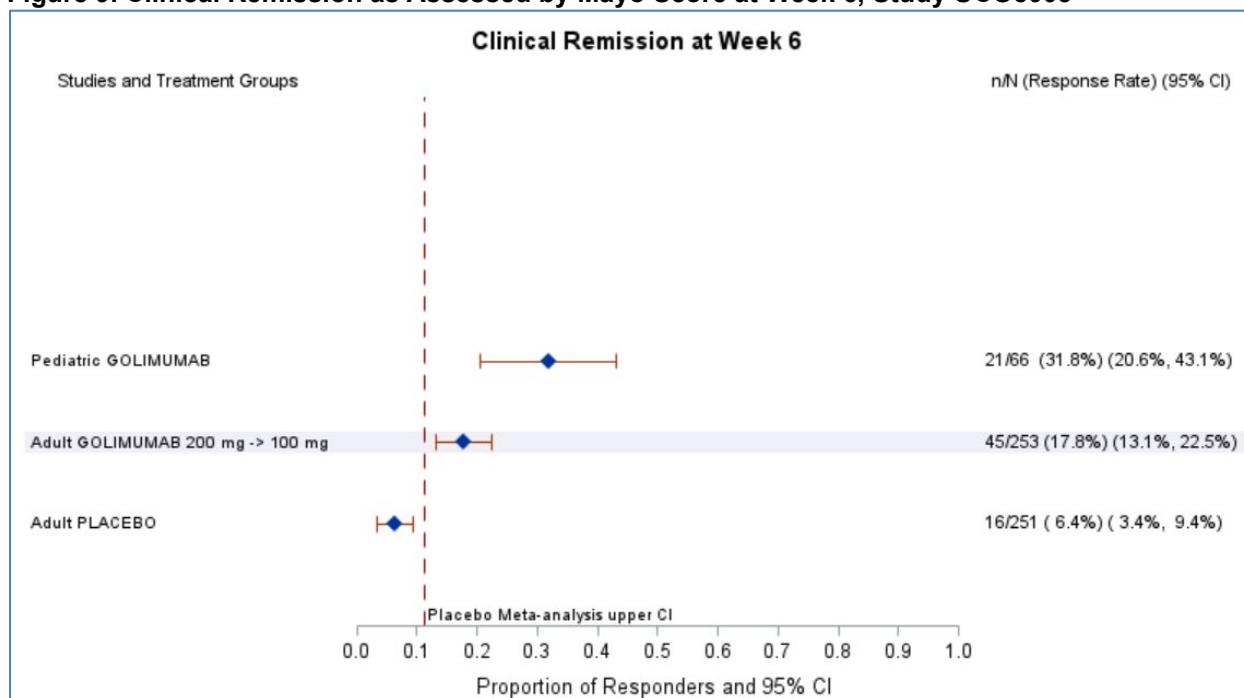
Table 29. Number of Subjects in Clinical Remission at Week 6 as Assessed by the Mayo Score, Study UCO3003

Week 6	Golimumab
N	66
Subjects in clinical remission, n (%)	21 (31.8)
90% CI for proportion of subjects in clinical remission (%)	(22.4, 41.2)
95% CI for proportion of subjects in clinical remission (%)	(20.6, 43.1)

Source: The Applicant's responses submitted on June 27, 2025, to FDA IR Table TEFCREM01za and verified by the review team using SAS 9.4 on the Applicant submitted data QS.xpt, SUPPQS.xpt, ADSL.xpt, and MO.xpt.
The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.
Abbreviations: CI, confidence interval; IR, information request; N, total number of subjects; n, number of subjects in remission

The results meet the prespecified success criteria for the primary efficacy endpoint. The 22.4% lower limit of the 2-sided 90% CI for the proportion of pediatric golimumab treated subjects in clinical remission at Week 6 is greater than the upper limit of the 95% CI for the historical adult placebo control (11.2%), as estimated with a random-effects meta-analysis using sample-size weighting method (the review team's preferred method). The 20.6% lower limit of the 2-sided 95% CI is also above the success criterion (11.2%).

In addition to meeting the above prespecified success criterion, the Mayo clinical remission rate of 31.8% at Week 6 in the pediatric study was also numerically higher than the remission rate for the primary analysis population (golimumab 200 mg $\rightarrow$ 100 mg dose group) in the reference adult golimumab UC induction study [C0524T17, 17.8%, 45/253, 95% CI (13.1%, 22.5%), [Figure 9](#)].

Figure 9. Clinical Remission as Assessed by Mayo Score at Week 6, Study UCO3003

Source: Review team's analysis using SAS 9.4 on the Applicant submitted data ADSL.xpt and ADEFBIN.xpt.

The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.

Abbreviations: CI, confidence interval; N, total number of subjects in treatment group; n, number of subjects in clinical remission

Prior to Week 6, three (4.5%) treated subjects met at least one treatment failure criteria; all whom had a prohibited change in UC medication and discontinued study intervention due to lack of efficacy (1) or an AE of worsening of UC (2). All the three subjects were appropriately considered to be treatment failures for the purpose of the primary analysis.

At Week 6, endoscopies were not performed in four subjects. One subject refused; one subject was due to investigator decision; two subjects were due to scheduling issue related to COVID-19. All the four subjects were not considered to be in clinical remission for the primary analysis.

At Week 6, 62 (93.9%) subjects had completed all components for Mayo scores and 4 (6.1%) subjects were missing 1 Mayo subscore (endoscopies).

Because all the subjects with missing value(s) were considered as "not in clinical remission at Week 6" (i.e., already in the worst case), all the sensitivity analysis performed by the Applicant had either the same results or better results comparing with the results of the primary analysis.

Efficacy Results – Secondary and Other Relevant Endpoints

Because the study UCO3003 is a single arm trial, in this section, only the results for the secondary endpoints with an associated success criterion developed by meta-analysis on the adult placebo subjects are reported, to aid in interpretation of the results. This includes clinical response at Week 6, endoscopic healing at Week 6, clinical remission at Week 54, endoscopic

healing at Week 54, and clinical remission at Week 54 by Mayo score, for participants who had achieved clinical remission at Week 6.

Clinical Response at Week 6 as Assessed by Mayo Score

Clinical response by the Mayo score was defined as a decrease from baseline score of $\geq 30\%$ and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1. At Week 6, 57.6% of treated subjects were in clinical response by Mayo score ([Table 30](#)).

Table 30. Number of Subjects in Clinical Response at Week 6, Study UCO3003

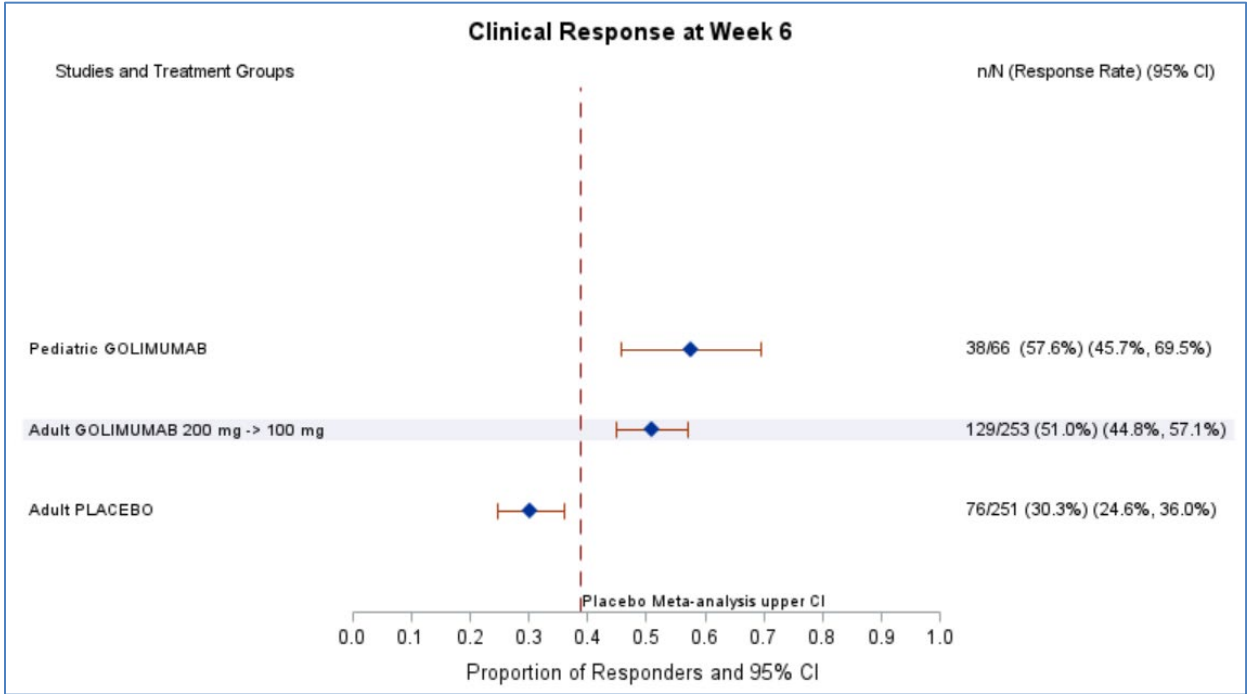
Week 6	Golimumab
N	66
Subjects in clinical response, n (%)	38 (57.6)
90% CI for proportion of subjects in clinical remission (%)	(47.6, 67.6)
95% CI for proportion of subjects in clinical remission (%)	(45.7, 69.5)

Source: The Applicant's responses submitted on June 27, 2025, to FDA IR Table TEFCRES01za and verified by the review team using SAS 9.4 on the Applicant submitted data QS.xpt, SUPPQS.xpt, ADSL.xpt, and MO.xpt.
The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.
Abbreviations: CI, confidence interval; IR, information request; N, total number of subjects; n, number of subjects in clinical response

The results meet the post hoc success criterion performed by the Applicant (requested by FDA via an IR) for this secondary efficacy endpoint. The 47.6% lower limit of the 2-sided 90% CI for the proportion of pediatric golimumab treated subject in clinical response at Week 6 is greater than the upper limit of the 95% CI for the historical adult placebo control (38.9%), estimated with a random-effects meta-analysis using sample-size weighting method. The 45.7% lower limit of the 2-sided 95% CI is also above the success criterion (38.9%).

In addition to meeting the above post hoc success criterion, the Mayo clinical response rate of 57.6% at Week 6 in the pediatric study was also numerically comparable to the response rate for the primary analysis population (golimumab 200 mg → 100 mg dose group) in the reference adult golimumab UC induction study [C0524T17, 51.0%, 129/253, 95% CI (44.8%, 57.1%), [Figure 10](#)].

Figure 10. Clinical Response as Assessed by Mayo Score at Week 6, Study UCO3003



Source: Review team’s analysis using SAS 9.4 on the Applicant submitted data ADSL.xpt and ADEFBIN.xpt. The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution. Abbreviations: CI, confidence interval; N, total number of subjects in treatment group; n, number of subjects in clinical response

Endoscopic Healing at Week 6

Endoscopic healing was defined by the Applicant an endoscopy subscore of 0 or 1 based on local endoscopy. This endpoint is commonly described in labeling as endoscopic improvement. At Week 6, 40.9% of treated subjects achieved endoscopic healing ([Table 31](#)).

Table 31. Number of Subjects in “Endoscopic Healing^a” at Week 6, Study UCO3003

Week 6	Golimumab
N	66
Subjects in endoscopic healing (“endoscopic improvement”), n (%)	27 (40.9)
90% CI for proportion of subjects in clinical remission (%)	(31.0, 50.9)
95% CI for proportion of subjects in clinical remission (%)	(29.0, 52.8)

Source: The Applicant’s responses submitted on June 27, 2025, to FDA IR Table TEFENDO01za and verified by the review team using SAS 9.4 on the Applicant submitted data QS.xpt, SUPPQS.xpt, ADSL.xpt, and MO.xpt.

The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.

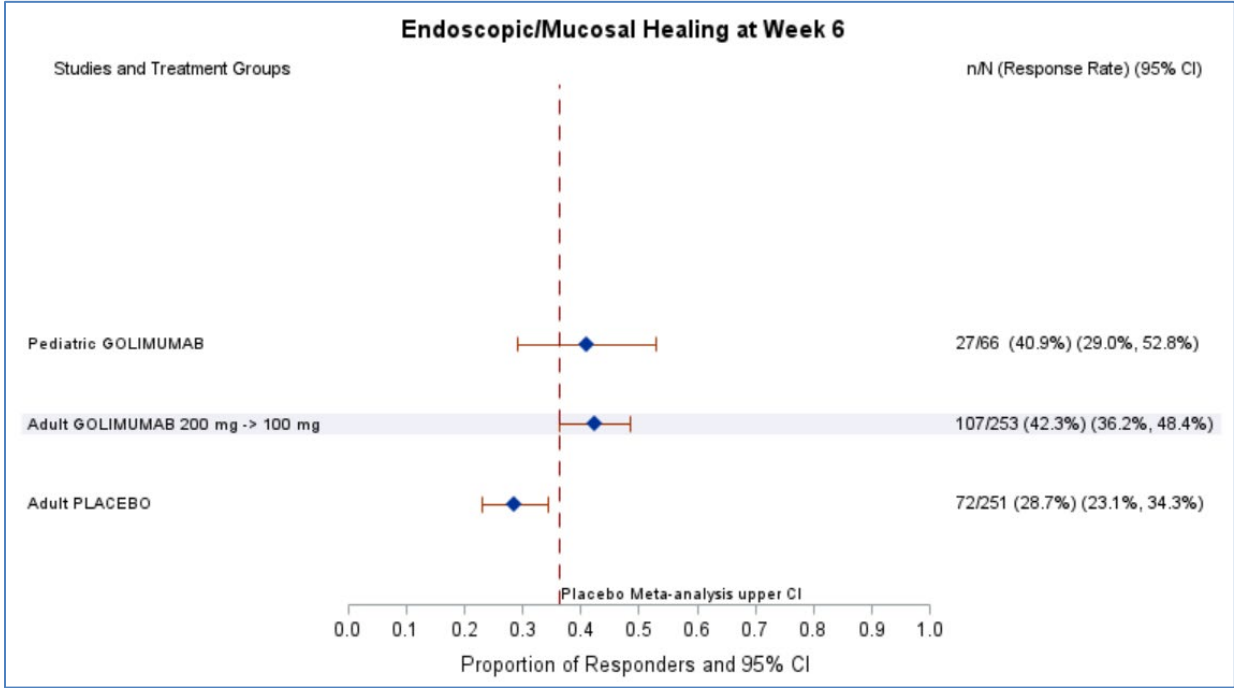
^a This endpoint is typically referred to by the Division as “endoscopic improvement”

Abbreviations: CI, confidence interval; IR, information request; N, total number of subjects; n, number of subjects in endoscopic healing

The results for this endpoint do not meet the post hoc success criterion as performed by the Applicant based on FDA’s request via an IR. The 31.0% lower limit of the 2-sided 90% CI for the proportion of pediatric golimumab treated subject in endoscopic healing at Week 6 is less than the upper limit of the 95% CI for the historical adult placebo control (36.2%), estimated with a random-effects meta-analysis using sample-size weighting method. This overlap may be caused by the wide confidence interval related to the point estimate, secondary to the small sample

size. The point estimate for this endpoint (41%) was numerically similar to that observed (golimumab 200 mg ->100 mg dose group) in the reference adult golimumab UC induction study [C0524T17, 42.3%, 107/253, 95% CI (36.2%, 48.4%), [Figure 11](#)].

Figure 11. “Endoscopic Healing”^a as Assessed by Mayo Score at Week 6, Study UCO3003



Source: Review team’s analysis using SAS 9.4 on the Applicant submitted data ADSL.xpt and ADEFBIN.xpt. The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.
^a This endpoint is typically referred to by the Division as “endoscopic improvement”
Abbreviations: CI, confidence interval; N, total number of subjects in treatment group; n, number of subjects in endoscopic healing

Clinical Remission at Week 54 Assessed by Mayo Score Among Week 6 Clinical Responders

At Week 54, 34.2% of Week 6 clinical responders were in clinical remission by the Mayo score ([Table 32](#)).

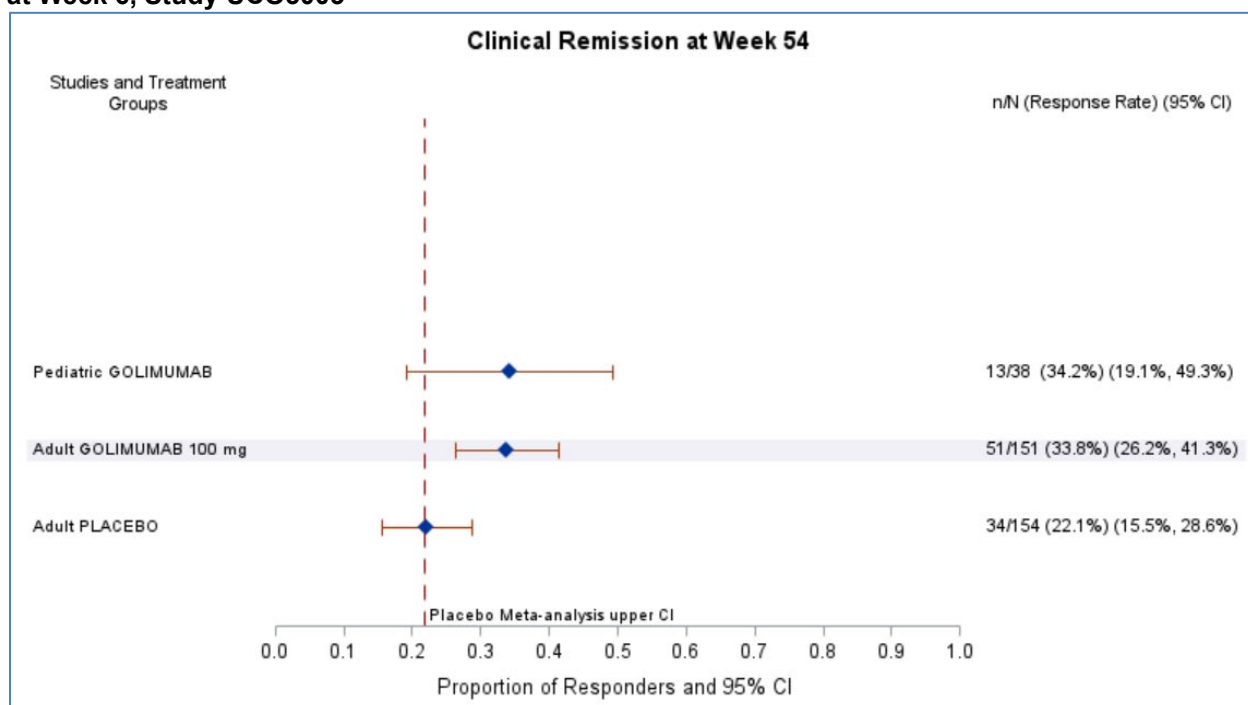
Table 32. Number of Subjects in Clinical Remission at Week 54 Among Clinical Responders at Week 6, Study UCO3003

Week 54	Golimumab
N	38
Subjects in clinical remission, n (%)	13 (34.2)
90% CI for proportion of subjects in clinical remission (%)	(21.6, 46.9)
95% CI for proportion of subjects in clinical remission (%)	(19.1, 49.3)

Source: The Applicant’s responses submitted on June 27, 2025, to FDA IR Table TEFCREM04zb and verified by the review team’s analysis using SAS 9.4 on the Applicant submitted data QS.xpt, SUPPQS.xpt, ADSL.xpt, and MO.xpt. The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.
Abbreviations: CI, confidence interval; IR, information request; N, total number of subjects; n, number of subjects in clinical remission

The results do not meet the prespecified success criterion for this secondary efficacy endpoint. The 21.6% lower limit of the 2-sided 90% CI for the proportion of pediatric golimumab treated subject in clinical remission at Week 54 for clinical responders at Week 6 is less than the upper limit of the 95% CI for the historical adult placebo control (21.8%), estimated with a random-effects meta-analysis using sample-size weighting method. However, the point estimate for this endpoint (34.2%) was numerically similar to that observed (golimumab 100 mg dose group) in the reference adult golimumab UC maintenance study [C0524T18, 33.8%, 51/151, 95% CI (26.2%, 41.3%), [Figure 12](#)].

Figure 12. Clinical Remission as Assessed by Mayo Score at Week 54 Among Clinical Responders at Week 6, Study UCO3003



Source: Review team's analysis using SAS 9.4 on the Applicant submitted data ADSL.xpt and ADEFBIN.xpt. The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution. Abbreviations: CI, confidence interval; N, number of subjects in treatment group; n, number of subjects in clinical remission

In the maintenance phase (after Week 6 and through Week 54), 19/38 (50.0%) Week 6 clinical responders met at least 1 treatment failure criterion: 13 (34.2%) had a prohibited change in UC medication, 10 (26.3%) used a rescue medication after a clinical flare, and 8 (21.1%) discontinued study intervention due to lack of efficacy or worsening of UC. At Week 54, endoscopies were not performed in 12 (31.6%) Week 6 clinical responders due to treatment discontinuation.

“Endoscopic Healing” at Week 54 Among Clinical Responders at Week 6

At Week 54, 39.5% of Week 6 clinical responders achieved “endoscopic healing” ([Table 33](#)).

Table 33. Number of Subjects in “Endoscopic Healing^a” at Week 54 Among Clinical Responders at Week 6, Study UCO3003

Week 54	Golimumab
N	38
Subjects in clinical remission, n (%)	15 (39.5)
90% CI for proportion of subjects in clinical remission (%)	(26.4, 52.5)
95% CI for proportion of subjects in clinical remission (%)	(23.9, 55.0)

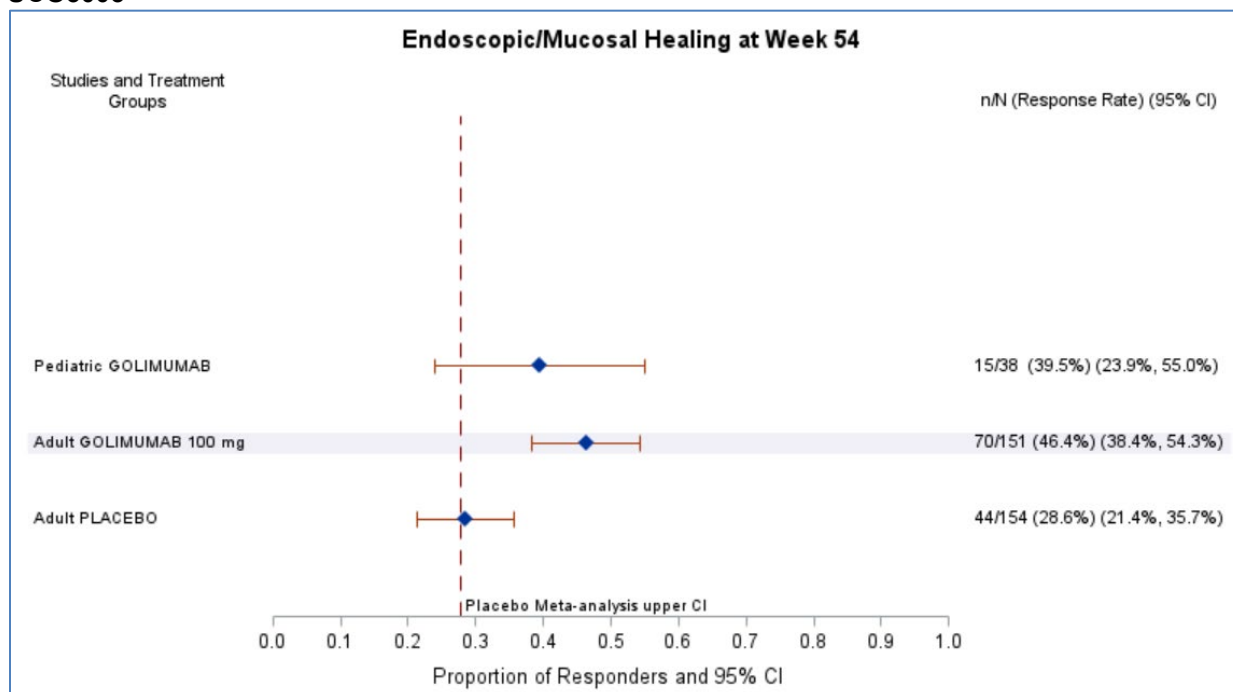
Source: The Applicant's responses submitted on June 27, 2025, to FDA IR Table TEFENDO02zb and verified by the review team's analysis using SAS 9.4 on the Applicant submitted data QS.xpt, SUPPQS.xpt, ADSL.xpt, and MO.xpt.

The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.

^a This endpoint is typically referred to by the Division as “endoscopic improvement”

Abbreviations: CI, confidence interval; IR, information request; N, total number of subjects; n, number of subjects in clinical remission

The results do not meet the post hoc success criterion for this secondary efficacy endpoint. The 26.4% lower limit of the 2-sided 90% CI for the proportion of pediatric golimumab treated subject in endoscopic healing at Week 54 for clinical responders at Week 6 is less than the upper limit of the 95% CI for the historical adult placebo control (27.8%), estimated with a random-effects meta-analysis using sample-size weighting method. The point estimate for this endpoint (39.5%) was numerically less to that observed (golimumab 100 mg dose group) in the reference adult golimumab UC maintenance study [C0524T18, 46.4%, 70/151, 95% CI (38.4%, 54.3%), [Figure 13](#)].

Figure 13. “Endoscopic Healing^a” at Week 54 Among Clinical Responders at Week 6, Study UCO3003

Source: Review team's analysis using SAS 9.4 on the Applicant submitted data ADSL.xpt and ADEFBIN.xpt.

The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.

^a This endpoint is typically referred to by the Division as “endoscopic improvement”

Abbreviations: CI, confidence interval; N, number of subjects in treatment group; n, number of subjects in “endoscopic healing”

Clinical Remission at Week 54 by Mayo Score, for Participants Who Had Achieved Clinical Remission at Week 6 (“Maintenance of Clinical Remission”)

At Week 6, 21 treated participants achieved clinical remission by the Mayo score, and 57.1% of these participants were still in clinical remission by the Mayo score at Week 54 ([Table 34](#)).

Table 34. Number of Subjects in Clinical Remission at Week 54, as Assessed by the Mayo Score, Among Subjects Who Had Achieved Clinical Remission at Week 6, Study UCO3003

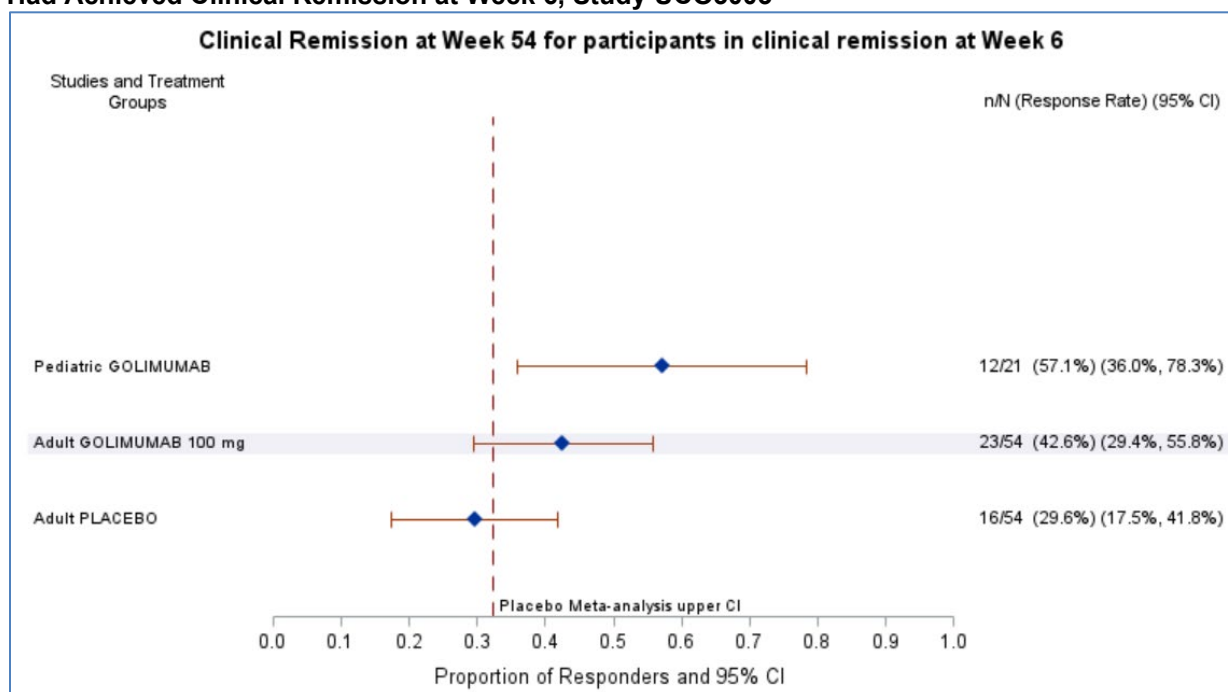
Week 54	Golimumab
N	21
Subjects in clinical remission, n (%)	12 (57.1)
90% CI for proportion of subjects in clinical remission (%)	(39.4, 74.9)
95% CI for proportion of subjects in clinical remission (%)	(36.0, 78.3)

Source: Adapted from the Applicant’s responses submitted on June 27, 2025, to FDA IR Table TEFCREM03za and verified by the review team using SAS 9.4 on the Applicant submitted data QS.xpt, SUPPQS.xpt, ADSL.xpt, and MO.xpt.
The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.
Abbreviations: CI, confidence interval; IR, information request; N, total number of subjects; n, number of subjects in clinical remission

The results of this analysis, which represent what has previously been referred to as “maintenance of clinical remission” meet the post hoc success criterion performed by the Applicant. The 39.4% lower limit of the 2-sided 90% CI for the proportion of pediatric golimumab treated subject in clinical remission at Week 54 for subject who had clinical remission at Week 6 is greater than the upper limit of the 95% CI for the historical adult placebo control (32.4%), estimated with a random-effects meta-analysis using sample-size weighting method. The 36.0% lower limit of the 2-sided 95% CI is also above the success criterion (32.4%).

In addition to meeting the above post hoc success criterion, the Mayo clinical remission rate of 57.1% at Week 54 for subjects who had clinical remission at Week 6 in the pediatric study was also numerically comparable to the response rate for the primary analysis population (golimumab 100 mg dose group) in the reference adult golimumab UC maintenance study [C0524T18, 42.6%, 23/54, 95% CI (29.4%, 55.8%), [Figure 14](#)].

Figure 14. Clinical Remission at Week 54, as Assessed by the Mayo Score, Among Subjects Who Had Achieved Clinical Remission at Week 6, Study UCO3003



Source: Review team's analysis using SAS 9.4 on the Applicant submitted data ADSL.xpt and ADEFBIN.xpt.

The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.

Abbreviations: CI, confidence interval; N, number of subjects in treatment group; n, number of subjects in clinical remission

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (Patient-Reported Outcome) Endpoints

The Applicant assessed (and proposed for inclusion in labeling)

(b) (4)

which are not discussed further here, as these endpoints are not considered fit-for-purpose to support an efficacy assessment in pediatric UC.

Additional Analyses Conducted on the Individual Trial

Additional Bayesian Analyses

For the secondary endpoints, clinical remission at Week 54, “endoscopic healing” at Week 6, and “endoscopic healing” at Week 54, the lower limit of the 90% CI of the pediatric response rate were smaller than the upper limit of the 95% CI based on the meta-analysis of adult placebo response rates. To better understand the efficacy of the investigational product for pediatric use, as it is considered reasonable to use partial extrapolation of efficacy from adult studies, FDA requested the Applicant perform additional Bayesian analyses to determine the minimum amount of adult data that would need to be borrowed in order to show efficacy on these secondary endpoints. For these analyses, the pediatric response rates were estimated using a Bayesian Beta-Binomial analysis with the conjugate Beta distribution used as the prior for the pediatric response rate. The means of the Beta prior were fixed at the estimated adult

golimumab response rate. With the means fixed, the smallest values of effective sample sizes (i.e., the minimum amount of adult data) that would be needed for the lower limit of the 90% credible interval for pediatric subjects to be greater than the upper limit of the adult placebo rate based on the meta-analysis were calculated. The results of these additional Bayesian analyses are summarized in [Table 35](#).

Table 35. Minimum Amount of Golimumab Adult Data That Would Need To Be Borrowed for the Lower Limit of the 90% CrI for the Pediatric Response Rate To Be Greater Than the Upper Limit of the 95% CI for the Adult Placebo Rate (Based on Random Effects Meta-Analysis With Sample Size Weighting), Study UCO3003

Endpoints	Golimumab Pediatric Response Rate (90% CI)	Golimumab Adult Response Rate (95% CI)	Placebo Meta-Analysis (95% CI)	Pediatric Posterior Mean (90% CrI)	Total Size of Borrowing From Golimumab Adult Data
Clinical remission at Week 54	34.2% (13/38) (21.6%, 46.9%)	33.8% (51/151) (26.2%, 41.3%)	17.7% (13.6%, 21.8%)	34.2% (22.3%, 47.0%)	1
Endoscopic healing at Week 54	39.5% (15/38) (26.4%, 52.5%)	46.4% (70/151) (38.4%, 54.3%)	22.4% (17.1%, 27.8%)	40.0% (27.8%, 52.7%)	3
Endoscopic healing at Week 6	40.9% (27/66) (31.0%, 50.9%)	42.3% (107/253) (36.2%, 48.4%)	32.3% (28.5%, 36.2%)	41.8% (36.2%, 47.6%)	137

Source: Adapted from the Applicant's Response dated June 27, 2025, to FDA IR Table 1 on page 6 and verified by the review team using R on the Applicant submitted program.

The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.

The credible interval is calculated based on equal-tailed interquantile on the posterior distribution.

Abbreviations: CI, confidence interval; CrI, credible interval; IR, information request

For the Week 54 endpoints of interest, clinical remission at Week 54 and endoscopic healing at Week 54, the amount of adult data that would need to be borrowed are one subject and three subjects, respectively, in order for the 90% credible interval lower limit in the pediatric response rate to be greater than the upper limit of the 95% CI for the adult placebo response from the meta-analysis. Given the small amount of data that would need to be borrowed to demonstrate success on these endpoints, this study supports long-term efficacy of golimumab in pediatric subjects. For the induction endpoint of endoscopic healing at Week 6, the minimum amount of adult data that would need to be borrowed is 137, more than double the size of the pediatric study. This amount of excessive borrowing from the adult data would lead to overweighting of the adult data in posterior estimates and, therefore, the pediatric study is not sufficient to demonstrate efficacy for this endpoint.

Reanalysis of the Primary and Secondary Endpoints Using the Current Definitions in FDA Guidance

The review team performed analyses on the six efficacy endpoints (i.e., the primary endpoint and five secondary endpoints with associated success criteria) using the definitions in the FDA pediatric IBD guidance. The difference of the endpoint definitions between the Applicant used in Study UCO3003 and the FDA pediatric IBD guidance are summarized in [Table 36](#).

Table 36. Endpoints Definition Comparison

Endpoints	Study UCO3003	FDA Guidance
Clinical remission	Total Mayo score ≤ 2 points, with no individual subscore > 1 .	Modified Mayo score of 0 to 2, including SF = 0 or 1, RB = 0, centrally read endoscopy = 0 or 1 (score of 1 modified to exclude friability)
Clinical response	Decrease from baseline in the total Mayo score by $\geq 30\%$ and ≥ 3 points, with either a decrease from baseline in the RB subscore of ≥ 1 or RB subscore of 0 or 1.	Decrease from baseline in the mMS of ≥ 2 points and at least a 30% reduction from baseline, and a decrease in RB subscore of ≥ 1 or RB subscore of 0 or 1
“Endoscopic healing”/ improvement	“Endoscopic healing” was defined by an endoscopy subscore (based on local read) of 0 or 1.	Endoscopic improvement is defined as a centrally read endoscopy subscore of 0 or 1 (score of 1 modified to exclude friability)

Source: Created by review team

Abbreviations: mMS, modified Mayo score; RB, Rectal Bleeding; SF, Stool Frequency

The results of the re-analyses based on the FDA pediatric IBD guidance are summarized in [Table 37](#) along with the results of the Applicant’s UCO3003 study, the approved adult studies on the Golimumab group and placebo group. The results based on the current FDA definition, shown in the second column, are either similar or a little bit worse than the results of UCO3003 study; however, the interpretation of these comparisons is limited due to the differing definitions used in the adult studies and the rates might not be directly comparable.

Table 37. Analysis Results Using FDA Pediatric IBD Guidance Along With the Analysis Results in Placebo and Golimumab in Adults, Study UCO3003

Endpoints	Pediatric Golimumab FDA Definition n/N (Response Rate) (95% CI) ¹	Pediatric (UCO3003) Golimumab n/N (Response Rate) (95% CI) ¹	Adult (T17/T18) Golimumab n/N (Response Rate) (95% CI) ¹	Adult (T17/T18) Placebo n/N (Response Rate) (95% CI) ¹
Clinical remission at Week 6	16/66 (24.2%) (13.9%, 34.6%)	21/66 (31.8%) (20.6%, 43.1%)	45/253 (17.8%) (13.1%, 22.5%)	16/251 (6.4%) (3.4%, 9.4%)
Clinical response at Week 6	31/66 (47.0%) (34.9%, 59.0%)	38/66 (57.6%) (45.7%, 69.5%)	129/253 (51.0%) (44.8%, 57.1%)	76/251 (30.3%) (24.6%, 36.0%)
Endoscopic healing at Week 6	20/66 (30.3%) (19.2%, 41.4%)	27/66 (40.9%) (29.0%, 52.8%)	107/253 (42.3%) (36.2%, 48.4%)	72/251 (28.7%) (23.1%, 34.3%)
Clinical remission at Week 54	10/31 (32.3%) (15.8%, 48.7%)	13/38 (34.2%) (19.1%, 49.3%)	51/151 (33.8%) (26.2%, 41.3%)	34/154 (22.1%) (15.5%, 28.6%)
Endoscopic healing at Week 54	10/31 (32.3%) (15.8%, 48.7%)	15/38 (39.5%) (23.9%, 55.0%)	70/151 (46.4%) (38.4%, 54.3%)	44/154 (28.6%) (21.4%, 35.7%)
Clinical remission at Week 54 for subjects in clinical remission at Week 6	7/16 (43.8%) (19.4%, 68.1%)	12/21 (57.1%) (36.0%, 78.3%)	23/54 (42.6%) (29.4%, 55.8%)	16/54 (29.6%) (17.5%, 41.8%)

Source: Review team’s analysis using SAS 9.4 on the Applicant submitted data QS.xpt, SUPPQS.xpt, ADSL.xpt, and MO.xpt.

¹ The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.

Abbreviations: CI, confidence interval; N, number of participants in each group; n, number of responders

Long-Term Efficacy Analyses Based on Week 14 Partial Mayo Score Responders

The review team also performed long-term efficacy analyses on the dataset containing both clinical responders at Week 6 (n=38) and 13 additional responders at Week 14 based on the partial Mayo score. The partial Mayo response is defined as a decrease from the Week 0 partial Mayo score of at least 3 points. The analyses were performed on the two endpoints of clinical remission at Week 54 and endoscopic healing at Week 54 for further evaluating the long-term efficacy. The analysis results are summarized in [Table 38](#), along with the results of the Applicant's UCO3003 study, the approved adult studies on the Golimumab group and placebo group. The estimated response rates for the two endpoints are a little bit worse than the estimates based on clinical responders at Week 6 only.

Table 38. Long-Term Efficacy Results Based on Both Clinical Responders at Week 6 and Responders Based on Partial Mayo Score at Week 14 Along With the Analysis Results for Placebo and Golimumab in Adults, Study UCO3003

Endpoints	Pediatric Golimumab Including Partial Mayo Responders n/N (Response Rate) (95% CI)¹	Pediatric (UCO3003) Golimumab n/N (Response Rate) (95% CI)¹	Adult (T17/T18) Golimumab n/N (Response Rate) (95% CI)¹	Adult (T17/T18) Placebo n/N (Response Rate) (95% CI)¹
Clinical remission at Week 54	17/51 (33.3%) (20.4%, 46.3%)	13/38 (34.2%) (19.1%, 49.3%)	51/151 (33.8%) (26.2%, 41.3%)	34/154 (22.1%) (15.5%, 28.6%)
Endoscopic healing at Week 54	19/51 (37.3%) (24.0%, 50.5%)	15/38 (39.5%) (23.9%, 55.0%)	70/151 (46.4%) (38.4%, 54.3%)	44/154 (28.6%) (21.4%, 35.7%)

Source: Review team's analysis using SAS 9.4 on the Applicant submitted data QS.xpt, SUPPQS.xpt, ADSL.xpt, and MO.xpt.

¹ The confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution.

Abbreviations: CI, confidence interval; N, number of participants in each group; n, number of responders

Efficacy Analyses by Demographic Subgroups

Subgroup analyses were conducted to assess potential differences in clinical remission rates at Week 6 by sex. The clinical remission rate for males was smaller than for females (19.4% vs 42.9%). However, this difference could be explained by the large variability due to small sample sizes with each subgroup (as indicated by the width of the 95% confidence intervals, with a 95% confidence interval of [5.4, 33.3] for males and [26.5, 59.3] for females) as well as potential differences in characteristics between the subgroups that are unrelated to sex. Results should be interpreted with caution due to the lack of a randomized comparator within each subgroup. The sample sizes for racial, ethnic, and age subgroups were too small to reliably evaluate whether there were any differences in efficacy across these demographic subgroups.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety assessment focuses on the data from the open-label, multicenter, phase 3 Study UCO3003. Included are notable findings from the assessment of the supportive safety data from the completed, open-label phase 1b Study UCO1001. The extension phase of the phase 3 Study UCO3003 is ongoing and is intended to evaluate long-term safety of repeated golimumab administration in pediatric patients with UC who completed Study UCO3003 through Week 54 of treatment.

Study UCO3003 has been ongoing since December 20, 2018, and all enrolled subjects are either in the study extension phase or discontinued the study. A total of 84 subjects were enrolled, with 69 subjects receiving golimumab (17 subjects with body weight <45 kg [including 8 subjects with body weight ≤30 kg] and 52 subjects with body weight ≥45 kg) and 15 subjects previously randomized to infliximab. The safety of the initial infliximab arm of Study UCO3003 is not included in this review since this treatment arm was discontinued with protocol amendment 4 and the very small number of subjects treated in that arm limits the utility of direct comparisons. A total of 31 subjects participated the Study UCO3003 extension phase after Week 54.

The first database lock (DBL) for Study UCO3003 was on April 11, 2024, which included screening through Week 54, and the final study visit for subjects who discontinued prior to Week 54 or completed Week 54 and did not enter the study extension. The clinical data from Study UCO3003 and Study UCO1001 were submitted to support the filing of the sBLA. In the 120-day safety update report, the Applicant provided analyses of 8 months of additional data accrued in the ongoing open-label extension of Study UCO3003 using a DBL of December 2, 2024.

The safety evaluation of the submitted clinical studies in the pediatric UC population was conducted within the safety population of patients who received at least one dose of study treatment (Safety Golimumab Analysis Set) until the final safety visit. Because Study UCO3003 is a treat-thru study without rerandomization of induction responders to the maintenance phase of the study, the safety evaluation focuses primarily on the safety findings assessed from Week 0 up to the final safety visit. Additionally, data from the first 6 weeks [short-term treatment (Week 0 to Week 6, “induction”)] are summarized separately. The final safety visit refers to the final visit for subjects who have discontinued the study prior to or at Week 54, or to subjects who completed Week 54 but did not enter the study extension and then returned 16 weeks later for a final safety visit.

There are limitations of evaluating safety results from an open-label, single arm study that included a relatively small number of subjects. The lack of blinding within the open-label studies creates a concern for the introduction of potential biases, while the lack of a concurrent

comparator treatment group makes the interpretation of the safety data difficult to determine whether safety events can be attributed to the study drug or to the underlying disease process.

In addition to the clinical safety data from the pediatric, phase 3 Study UCO3003, additional data to help establish the safety profile are included from the phase 1b Study UCO1001, the prospective, observational safety registry Study C0168Z02 (DEVELOP) in pediatric patients <17 years of age with IBD, and postmarketing data that were included in support of the sBLA submission. The known safety profile of golimumab in adults (per the approved prescribing information, which includes data from the phase 3 program in adult subjects with UC [Studies C0524T16, C0524T17, and C0524T18] was used to identify several adverse events of special interest (AESIs), which were systematically assessed during the pediatric UC trials. The AESIs are discussed in Section [8.2.5.1](#).

8.2.2. Review of the Safety Database

8.2.2.1 Overall Exposure

The Applicant submitted safety data from 69 subjects evaluated in the safety population of Study UCO3003, representing a limited primary safety database. As noted in the regulatory background in Section [3](#), the Division stated that a clinical trial safety database including at least 60 subjects enrolled in the phase 3 trial would be acceptable to support filing for this application, if supplemented by supportive safety data derived from multiple sources including postmarketing data and data from pediatric IBD registries.²²

Patients in the Study UCO3003 safety population were enrolled at 26 investigative sites in the United States, Korea, Belgium, Poland, France, Italy, Spain, Brazil, and Israel, with approximately 58% (40/69) of the subjects completing the maintenance phase of the study.

At the time of the DBL date of April 11, 2024, approximately 75% (41 of 55 patients) were still participating in Study UCO3003, and the majority of patients received golimumab for at least 50 weeks. Of the 40 subjects who completed the maintenance phase of Study UCO3003, 31 enrolled in the open-label extension phase of Study UCO3003 at 11 sites.

The overall mean duration of golimumab exposure for the 69 patients who received at least one dose of golimumab of Study UCO3003 was 50 weeks, for a total of 46 patient-years of exposure. See [Table 39](#) for the number of patients included in the safety database and the extent of overall golimumab exposure in the safety population.

²² Refer to IND 100181 meeting minutes dated August 1, 2016 (Ref ID 3966307)

Table 39. Extent of Overall Golimumab Exposure, Study UCO3003

Parameter	Golimumab Total N=69
Duration of treatment, weeks	
Mean (SD)	34.8 (20)
Median (Q1, Q3)	50 (13.9, 50.3)
Min, max	2.1, 55.9
Total exposure (person years)	46
Subjects treated, by duration, n (%)	
<6 weeks	9 (13.0)
≥6 weeks	60 (87.0)
≥12 weeks	52 (75.4)
≥18 weeks	48 (69.6)
≥24 weeks	46 (66.7)
≥30 weeks	45 (65.2)
≥36 weeks	42 (60.9)
≥42 weeks	39 (56.5)
≥48 weeks	39 (56.5)
≥54 weeks	1 (1.4)

Source: Reviewer amended table generated by CDS using data submitted by the Applicant in BLA 125289/S-157, datasets adex.xpt and adsl.xpt, module 5.3.5.1. Golimumab Total includes observations from Week 0 through Week 54 with the addition of data from subjects with final safety visit data. Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

120-Day Safety Update

The 120-Day Safety Update for the phase 3 Study UCO3003 provides extended safety information for pediatric patients with UC treated with golimumab. This update encompasses data from the induction, maintenance, and extension phases of the study, with a data cut-off date of December 2, 2024. This represents an extension of approximately 8 months beyond the Week 54 DBL date of April 11, 2024.

Key findings from this update include an increased mean duration of golimumab exposure to 90.5 weeks. The total exposure for the 69 patients who received at least one dose of golimumab in Study UCO3003 (from Week 0 through December 2, 2024) amounted to approximately 120 patient-years. Additionally, the average duration of follow-up in the extension study was 103 weeks. This extended safety data provides information on the longer-term safety profile of golimumab in pediatric patients with UC, offering insights into potential adverse events that may occur with prolonged use of the medication in this population.

8.2.2.2 Relevant Characteristics of the Safety Population

As required under 21 CFR 314.50(d)(5)(vi)(a), this review considered relevant characteristics of the population such as baseline demographic data (e.g., age, sex, race, and ethnicity), geographic region, disease spectrum, and comorbidities, when conducting the safety evaluation. The baseline efficacy (N=66) and safety (N=69) populations of Study UCO3003 are very similar. Refer to Section [8.1.2](#) for a summary of the study population's demographic and disease characteristics.

The phase 3 study UCO3003 enrolled a limited number of patients in the youngest and lowest body weight groups (n=2 for subjects ages 2 to <6 years; n=8 for subjects weighing <30 kg). Baseline UC disease characteristics were similar across different age and body weight groups except for more subjects with severe UC by Mayo score (>10) in the older (12 to 17 years) and higher body weight (≥45 kg) subgroups. At baseline, a majority of subjects (97%) were receiving UC-related medications (corticosteroids, immunomodulators, and 5-ASA); 52% of subjects were receiving corticosteroids, and 88% were receiving oral 5-ASA. There were more baseline corticosteroid users in subjects of older ages (12 to 17 years: 56%; 2 to 11 years: 40%) and higher weights (≥45 kg: 60%; <45 kg: 29%). Subjects with prior exposure to anti-TNF medication were not enrolled.

Additionally, subjects investigated in Study UCO3003 were predominantly ≥12 years of age, white, and enrolled primarily from Europe (46%) and were racially and ethnically homogenous (i.e., white, European, and non-Hispanic), in comparison to the U.S. population. Secondary to the underrepresentation of Asian, Black, and Hispanic patients with UC in Study UCO3003, there is some concern over the generalizability of the results to U.S. patients and to these racial and ethnic groups in particular. However, the disease characteristics of those enrolled in the study appear to be similar to moderately to severely active patients with UC in the United States, providing some assurance that the clinical study results are generalizable to U.S. patients. Recruitment of a diverse patient population in IBD trials has been challenging to date, even in much larger adult studies.

The safety of golimumab for the treatment of pediatric UC in the clinical studies was overseen by an "Anticipated Event Review Committee (ARC)," established to perform reviews of prespecified anticipated events at an aggregate level. The ARC was a safety committee within the Applicant's organization that is independent of the Applicant's study team. The ARC met to aid in the recommendation to the Applicant's study team as to whether there is a reasonable possibility that an anticipated event is related to the study intervention.

As previously noted, the number of pediatric patients and duration of exposure appear adequate to characterize the safety of golimumab in pediatric patients with moderately to severely active UC. The limitations of the safety database include the open-label nature of the study, limited representation of diverse racial and ethnic groups, and patients in the lowest body-weight groups (<30 kg). There were inherent limitations present in conducting this study, as a result of the changing landscape of pediatric IBD treatments that may have negatively affected trial enrollment. Ultimately, in the context of a long history of golimumab use across many indications that provided supportive data, the submitted safety database is considered adequate to support expanding the indication for pediatric patients with UC.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

8.2.3.1 Issues Regarding Data Integrity and Submission Quality

In general, the submitted data are of acceptable quality, based on the overall organization, ease of finding information, and completeness. The quality of the safety data was evaluated by the clinical data scientists and clinical and statistical reviewers.

8.2.3.2 Categorization of Adverse Events

All TEAEs for the safety analysis datasets were summarized using primary system organ classes (SOCs) and dictionary-derived preferred terms (PTs) from the Medical Dictionary for Regulatory Activities, version 26.1. This standardized approach ensures consistency in reporting and categorizing adverse events across the study.

An AE was defined as any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether a causal relationship with that product was established. This broad definition encompasses any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal (investigational) product.

In the protocol of Study UCO3003A, TEAEs were specifically defined as "Intervention-emergent" adverse events. These events either had their onset during the intervention phase or were a consequence of a preexisting condition that had worsened since baseline. The protocol required that AEs were recorded up to 16 weeks after the last dose of golimumab. TEAEs were evaluated per treatment phase, and each subject was counted once for a particular AE within a treatment phase, regardless of the number of times they experienced that specific preferred term.

Adverse events of special interest, considered to be potential safety issues for golimumab, were prespecified and are discussed in Section [8.2.5.3](#). In addition to AE reporting, safety evaluations also included assessments of laboratory parameters and vital signs, providing a comprehensive overview of the treatment's safety profile.

8.2.3.3 Recoded Treatment-Emergent Adverse Event²³ Preferred Terms

During the safety review process, the FDA review team, consisting of clinical data scientists (CDS) and the clinical reviewer, undertook a recoding effort of several preferred terms (PTs)

²³ TEAEs are synonymous with adverse events (AEs), per the Applicant and the review team, and are considered to have occurred following the initial administration of golimumab treatment.

initially used by the Applicant. This recoding was performed to ensure accuracy and consistency in the adverse event reporting.

The review team identified certain treatment-emergent adverse events (TEAEs) that were "split" among various preferred terms. To address this issue, these TEAEs were consolidated and renamed under a single, more appropriate category. This categorization was achieved using either OND custom medical queries (i.e., FDA medical query [OCMQ]) or a specific query defined by the clinical reviewer (Reviewer's Medical Query). [Table 40](#) provides a comprehensive list of these recoded TEAEs, showing how they were consolidated from multiple PTs into more cohesive and representative categories. This recoding effort enhances the clarity and consistency of the safety data, allowing for a more accurate assessment of the treatment's safety profile.

Table 40. Recoded TEAEs Definitions, Study UCO3003

Review Team's Recoded Terms	Applicant's AE Code (Preferred Terms)
Abdominal pain (reviewer's medical query)	Abdominal pain, Abdominal pain upper
Anemia (OCMQ)	Anemia, Anemia macrocytic, Iron deficiency anemia, Hemoglobin decrease
COVID-19 infection (reviewer's medical query) ¹	COVID-19, SARS-CoV-2 antibody test positive
Cough (OCMQ)	Cough, Productive cough, Allergic cough
Fatigue (OCMQs)	Fatigue, Asthenia
Fungal infection (OCMQs)	Oral candidiasis, Fungal foot infection, Fungal infection, Fungal test positive, Onychomycosis
Hemorrhage (OCMQs)	Epistaxis, Hematochezia, Hematoma, Rectal hemorrhage, Contusion
Leukopenia (reviewer's medical query)	Leukopenia, Lymphopenia, Monocytopenia
Local administration reaction (OCMQs)	Injection site erythema, Injection site rash
Upper respiratory tract infection (URTI) (reviewer's medical query) ²	Nasopharyngitis, Pharyngitis, Rhinitis, Laryngitis, and URTI, and Viral URTI
Viral infection (reviewer's medical query) ³	COVID-19, Gastroenteritis viral, Viral infection, Infectious mononucleosis, Nasal herpes, Oral herpes, Rotavirus infection, Cytomegalovirus colitis, Influenza
Worsening UC (reviewer's medical query)	Colitis ulcerative, ⁴ Colitis

Source: Reviewer generated table using data submitted by the Applicant in BLA 125289/S-157, datasets adex.xpt and adsl.xpt, module 5.3.5.1. Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; OCMQ, OND custom medical query; PT, preferred term; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TEAE, treatment-emergent adverse event; UC, ulcerative colitis

¹ COVID-19 infection is defined as PTs of Covid-19 (under the SOC of Infections and infestations) and SARS-CoV-2 antibody test positive (under the SOC of Investigations)

² "URTI" Query includes PTs of Nasopharyngitis, Pharyngitis, Rhinitis and Laryngitis, as adapted from Table 1 of the BLA 125289 Simoni (golimumab) labeling: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125289s155.125433s036lbl.pdf (dated April 18, 2025); additionally, the reported PTs of Upper respiratory tract infection and Viral URTI from Study UCO3003 are included in this query

³ "Viral Infection" Query includes PTs that are similar to the adverse drug reaction (ADR) of "Viral Infection" in Table 1 of the Simoni (golimumab) labeling: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125289s155.125433s036lbl.pdf (dated April 18, 2025)

⁴ "Colitis ulcerative" (i.e., Worsening UC) was recorded by the Applicant as an AE; however, this PT is considered to be worsening of subjects' underlying UC disease, which may be a result of the potential lack of treatment efficacy

8.2.3.4 Routine Clinical Tests

Study activities, laboratory parameters collected, and categorization of TEAE abnormalities based on the National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0 are tabulated in Section [15.4](#).

The timing and clinical laboratory parameters evaluated to assess patient safety during the clinical studies were reasonable and adequate for the intended patient population.²⁴ The Applicant assessed clinical laboratory parameters at multiple study visits. Blood draws were to be performed after all clinical assessments and questionnaires, and vital sign determinations were performed before study drug administration during a visit. A certified central laboratory was utilized to process and conduct the clinical laboratory tests. All abnormal laboratory tests considered clinically significant by the investigator were to be followed to a satisfactory resolution. Blood samples for golimumab and antibodies and neutralizing antibodies to golimumab assays were also collected at multiple, prespecified time points.

8.2.4. Safety Results: Pediatric UC, Phase 3 Study UCO3003

8.2.4.1 Deaths

No deaths were reported in the pediatric study up to the 4-month safety update submission.

8.2.4.2 Overall Treatment-Emergent Adverse Events

A majority of the subjects, 97% (67/69), experienced at least one TEAE with any golimumab exposure during the pediatric phase 3 Study UCO3003 (DBL of April 11, 2024). [Table 41](#) provides an overview of the types and frequencies of TEAEs reported in the study.

²⁴ Full listing of the parameters assessed and schedule for collecting required laboratory tests appear in [Table 60](#) in the Appendix

Table 41. Overview of TEAE Types, Study UCO3003

Event Category	Week 0 Through Week 6 N=69 n (%)	Week 6 Through Week 54 N=62 n (%)	Week 0 Through Final Study Visit N=69 n (%)
Any TEAE	47 (68.1)	58 (93.5)	67 (97.1)
Any SAEs	10 (14.5)	21 (33.9)	28 (40.6)
Any severe of AEs	10 (14.5)	15 (24.2)	22 (31.9)
Any TEAE leading to discontinuation of study drug	5 (7.2)	9 (13.0)	14 (20.3)
AE leading to interruption of study drug	0	1 (1.6)	1 (1.4)
Any TEAE with reasonable possibility of being related to study drug ²⁵	8 (11.6)	9 (13.0)	15 (21.7)

Source: Reviewer amended (using JMP 18.0) table generated by CDS using data submitted by the Applicant in BLA 125289/S-157, datasets adex.xpt and adsl.xpt, module 5.3.5.1. Applicant's submission. ds.xpt and adsl.xpt. Total includes observations from Week 0 through Week 54 with the addition of data from subjects with final safety visit data. Treatment-emergent adverse events defined as any AE with onset after the first administration of study drug. Severity as assessed by the investigator. Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

Below, [Table 42](#) summarizes the most common treatment-emergent AEs reported in the safety population, using logical groupings of similar terms where appropriate.

Table 42. TEAEs by SOC Reported by ≥10% of the Safety Population

SOC	Week 0 Through Week 6 N=69 n (%)	Week 6 Through Week 54 N=62 n (%)	Week 0 Through Final Study Visit N=69 n (%)
Gastrointestinal disorders	18 (26.1)	45 (72.6)	55 (79.7)
Infections and infestations	19 (27.5)	37 (59.7)	44 (63.8)
Skin and subcutaneous tissue disorders	6 (8.7)	14 (20.3)	19 (27.5)
General disorders and administration site conditions	11 (15.9)	8 (12.9)	16 (23.2)
Blood and lymphatic system disorders	2 (2.9)	14 (22.6)	18 (26.1)
Nervous system disorders	6 (8.7)	8 (12.9)	12 (17.4)
Investigations	19 (27.5)	37 (59.7)	11 (15.9)
Respiratory, thoracic, and mediastinal disorders	5 (7.2)	7 (11.3)	11 (15.9)
Musculoskeletal and connective tissue disorders	1 (1.4)	7 (11.3)	8 (11.6)

Source: Reviewer amended table generated by CDS using data submitted by the Applicant in BLA 125289/S-157, datasets adex.xpt and adsl.xpt, module 5.3.5.1. Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

Below, [Table 43](#) summarizes the most common treatment-emergent AEs reported in the safety population, using logical groupings of similar terms where appropriate.

²⁵ Per the Study UCO3003 Clinical Study Report, a reasonably related AE was defined as any event with the relationship to study intervention as 'very likely,' 'probable,' or 'possible' on the AE eCRF page, or if the relationship to study intervention was missing.

Table 43. Most Common TEAEs Reported by ≥10% of the Safety Population

Preferred Term, Grouped Query, Narrow OND Custom Medical Query, or Clinical Reviewer's Queries	Week 0 Through Week 6 (Induction) N=69 n (%)	Week 6 Through Week 54 (Maintenance) N=62 n (%)	Week 0 Through Final Study Visit (Overall) N=69 n (%)
Worsening UC (reviewer's medical query)	11 (15.9)	34 (54.8)	43 (62.3)
Viral infection (reviewer's medical query)	8 (11.6)	19 (27.5)	27 (39.1)
COVID-19 infection (reviewer's medical query)	5 (7.2)	9 (14.5)	14 (20.2)
Upper respiratory tract infection (URTI) (reviewer's medical query)	21 (30.4)	4 (6.5)	22 (31.2)
Anemia (OCMQ)	2 (2.9)	10 (16.1)	14 (20.3)
Headache (PT)	6 (8.7)	8 (12.9)	12 (17.4)
Hemorrhage (OCMQ)	1 (1.4)	9 (14.5)	10 (14.5)
Abdominal pain (reviewer's medical query)	3 (4.3)	7 (11.3)	9 (13.0)
Acne (PT)	2 (2.9)	4 (6.5)	7 (10.1)
Diarrhea (PT)	1 (1.4)	6 (9.7)	7 (10.1)
Hematochezia (PT)	0	7 (11.3)	7 (10.1)
Pyrexia (PT)	4 (5.8)	4 (6.5)	7 (10.1)

Source: Reviewer amended table generated by CDS using data submitted by the Applicant in BLA 125289/S-157, datasets adex.xpt and adsl.xpt, module 5.3.5.1. Software: R; JMP 18.0. Refer to OCMQ, GQ, and reviewer's queries as noted in above Section 8.2.3.3. Based on approved Simponi labeling, URTI consists as PTs of Nasopharyngitis, Pharyngitis, Rhinitis, and Upper respiratory tract infections (no cases of laryngitis were reported). Abbreviations: AE, adverse event; CDS, clinical data scientist; COVID-19, coronavirus disease 2019; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query; PT, preferred term; SOC, system organ class; UC, ulcerative colitis

Study UCO3003: Overall Summary of SOCs and TEAEs (Week 0 to Final Study Visit)

Overall, the SOCs with the highest frequency of TEAEs were Gastrointestinal Disorders in 80% (55/69) and Infections and Infestations in 64% (44/69) of subjects. The most frequently reported TEAE was worsening UC in 62% (43/69) of subjects. It is possible that the reports of worsening UC could be signify the lack of efficacy of golimumab in these subjects, leading to a worsening of their underlying disease state.

The most common infections were viral infections, which consisted of reported events of COVID-19, gastroenteritis viral, viral infection, infectious mononucleosis, nasal herpes, oral herpes, rotavirus infection, cytomegalovirus colitis, and Influenza. Viral infections were reported overall in 39% (27/69) subjects. Most of the viral infections were COVID-19-related [reported in 20% (14/69) of subjects] which is likely explained by the fact that the study was conducted during the COVID-19 pandemic and during a period of enhanced screening/testing for COVID-19. Although the overall rate of viral infections reported was numerically higher than reported in the Simponi clinical trials in adult subjects with UC, this is likely driven by elevated levels of testing and reporting of COVID 19 during the pandemic. No subjects were reported to have tuberculosis infection.

Approximately 24% (17/69) of subjects experienced a TEAE that the investigator considered possibly related to the study drug. Of these, headache was considered by the study investigators to be the most common and “reasonably related” AE²⁶ as reported in 5.8% (4/69) of subjects, and the SOC with the highest frequency of reasonably related AEs was general disorders and administration site conditions in 9% (6/69) of subjects.

In general, the TEAEs in Study UCO3003 in pediatric subjects with UC were similar to those described in the currently approved Simponi labeling for the treatment of adult patients with UC and previously approved indications (i.e., RA, PsA, and AS).²⁷ Per the FDA clinical review of the T18 adult UC maintenance study, there was no clear dose-response relationship of AEs among the Golimumab treatment groups, except for nasopharyngitis.²⁸ Likewise, the incidences of AE and SAEs were generally similar between the pediatric and adult study populations with UC, however, events of worsening UC, viral infections, upper respiratory tract infection (URTI), and COVID-19 infections, are noted to be reported more frequently in the Simponi pediatric UC study population as compared with the adult UC trial population.

The reporting of higher URTI, viral infection, and COVID-19 events in the pediatric study as compared to the adult UC program are not unexpected given that the pediatric study was conducted during the pandemic whereas the adult UC trials were conducted years before the pandemic. Moreover, pediatric patients may also likely experience more mild and frequent viral infections than adults, in general, due to multiple factors including immature immune systems, increased exposure in group and close contact settings (e.g., daycare, schools), age-specific susceptibility to certain viruses, less hand hygiene, etc.²⁹ Therefore, the review team finds that these events are not considered to be necessarily related to golimumab therapy, and that that safety profile of pediatric subjects with UC is relatively similar to adults with UC treated golimumab.

²⁶ Per the Study UCO3003 CSR (submitted December 12, 2024), a reasonably related AE was defined as any event with the relationship to study intervention as ‘very likely’, ‘probable’, or ‘possible’ on the AE eCRF page or if the relationship to study intervention was missing.

²⁷ BLA 125289 Simponi (golimumab) USPI (dated April 18, 2025):

https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125289s155,125433s036lbl.pdf

²⁸ sBLA 125289/S-77, 78, 79, FDA Unireview for Simponi (golimumab) for the treatment of adult patients with UC, by Dr. Erica Wynn. DARRTs reference ID: 3308680 (dated May 15, 2013)

²⁹ Hwang JK, et. al. Age-Specific Characteristics of Adult and Pediatric Respiratory Viral Infections: A Retrospective Single-Center Study. J Clin Med. 2022 Jun 3;11(11):3197

Study UCO3003: Labeling Considerations of Common TEAEs (Occurring in ≥10% of Subjects)

URTI and other viral infections reported in the pediatric study likely represent adverse drug reactions (ADRs), given that Simponi increases the risk of infection. Since similar events of URTI and other viral infections are reported for the adult Simponi trials within the labeling, the review team focused on evaluating the remaining seven TEAEs that occurred in ≥10% of subjects in Study UCO3003 overall (as reported from Week 0 to the final study visit) to determine whether they are reasonably likely to represent treatment related ADRs of golimumab treatment. These TEAEs were anemia, headache, abdominal pain, diarrhea, hematochezia, pyrexia, and acne, as noted in [Table 43](#) above. Because this study was a single-arm and open-label study, the review team recognizes the limitations of the data to determine the relatedness of the event occurrences to golimumab treatment.

Information requests were sent to the Applicant requesting additional information regarding the subject narratives associated with the seven TEAEs noted above, to aid in our determination as to if these events likely represent potential drug-related adverse reactions. In their responses, the Applicant contended that these seven TEAEs do not warrant inclusion into the labeling as new ADRs for various reasons. Specifically, the Applicant attributes TEAEs of anemia, abdominal pain, diarrhea, and hematochezia to the subject's underlying UC disease process, and notes that these events were not frequent occurrences in the non-UC golimumab programs. The Applicant proposed that the events of acne were all in participants who were 12 to 16 years of age at study entry, which is an age range where acne is common. Similarly, for the TEAEs of headache and pyrexia, the Applicant states that limited association exists with dose changes or trial discontinuation for almost all these TEAEs.

While the review team concurs with the Applicant's rationale that the adverse events of anemia, abdominal pain, diarrhea, hematochezia, and acne have other potential causes and are unlikely to represent ADRs (i.e., symptomatology associated with UC disease and subject population age), the review team plans to include the following two TEAEs (headache and pyrexia) into the Simponi labeling. Our considerations and recommendation to include headache and pyrexia in the United States prescribing information (USPI) follows:

TEAEs of Headache

Headache was reported as a common TEAE, occurring in 12 subjects (17%). Of those 12, investigators considered the headaches to be possibly or probably related to drug administration in four cases [5.8% of subjects (4/69), with three cases occurring during the induction phase and one case during the maintenance phase]. As compared to other TEAEs, headache was identified by investigators as the TEAE most related to golimumab treatment. At least one subject (Subject (b) (6)) with headache of moderate intensity led to golimumab treatment interruption, although this event was not considered to be related to study treatment.

The review team notes that headache events are known to be prevalent in the overall pediatric and adult population, with recurrent headache reported in approximately 17% of children, with higher rates in those with comorbid chronic illnesses.^{30,31} However, headache is also recognized as a neurological adverse effect associated with anti-TNF- α therapy in children with inflammatory bowel disease, including UC. In a published retrospective analysis of pediatric IBD patients treated with anti-TNF- α agents, headache was specifically reported as a moderate neurological adverse event, with a median onset of 6 months after initiation of therapy. Most cases resolved completely or partially after discontinuation of the anti-TNF agent, underscoring a likely causal relationship.³²

The Applicant provided detailed information on each subject with reported AE of headache in a response to IR received (b) (6). Our review of these cases determined that while some events were mild, short duration, and self-limited, there were several patients who reported ongoing, intermittent headaches lasting multiple weeks; while none of these resulted in permanent discontinuation of study drug, there was inadequate information available to conclude that golimumab treatment did not cause or worsen a pre-existing chronic headache condition.

Additionally, the Applicant acknowledged that a higher proportion of pediatric subjects in Study UCO3003 reported headache as compared to the subjects in the adult UC trials.

Table 44. Frequencies of Reported Cases of Headache, Studies UCO3003, T17, and T18

Time period	Study UCO3003	Adult trial (Study T17 [CSR C0524T17 2011])		
		Placebo	200mg->100 mg induction	400 mg->200 mg induction
Week 0-6 (vs T17)	8.7%	5.2%	3.0%	4.5%
		Adult trial (Study T18 [CSR C0524T18 2012])		
		Placebo	50 mg	100 mg
Week 6-54 (vs T18)	12.9%	9.0%	7.8%	7.8%

Source: Applicant's IR response to sBLA 124289/s-157, submitted July 23, 2025
Abbreviations: CSR, clinical study report; IR, information request; vs, versus

Furthermore, other TNF blockers (i.e., infliximab and adalimumab) also include headache as an ADR within their labeling. Thus, in the absence of a concurrent control, it is reasonable to consider headache as potential ADR and worthy of inclusion in labeling.

³⁰ Onofri A, et al. Primary Headache Epidemiology in Children and Adolescents: A Systematic Review and Meta-Analysis. The Journal of Headache and Pain. 2023;24(1):8.

³¹ Lateef TM, et al. Headache in a national sample of American children: prevalence and comorbidity. J Child Neurol. 2009 May;24(5):536-43.

³² Bertrand V, et. al. Neurological Adverse Effects Associated With Anti-tumor Necrosis Factor A Antibodies in Pediatric Inflammatory Bowel Diseases. J Pediatr Gastroenterol Nutr. 2020 Jun;70(6):841-848.

TEAEs of Pyrexia

Seven patients reported 12 instances of fever during the study. Per the Applicant, in 8 of the 12 reported TEAEs of pyrexia, there was an associated UC flare or “likely mild intercurrent illness” which may have been the cause of fever. However, in four of the episodes of pyrexia, there was no obvious cause from the records. Although pyrexia is recognized to occur in settings of acute, severe, and/or fulminant colitis, fever is not a frequent symptom in most cases of UC. It is known in the literature that pyrexia can be associated with TNF- α treatment in pediatric patients, most commonly as a manifestation of infection. TNF- α inhibitors increase the risk of a broad spectrum of infections, including bacterial, viral, fungal, and mycobacterial pathogens, and pyrexia is often the presenting symptom of these infections in immunosuppressed children.³³ Therefore, the presence of pyrexia should raise concern for severe disease or complications, such as infections in the setting of immunosuppression secondary to TNF- α treatment. Given the known risks of the development of infections with TNF- α inhibitors which can lead to related pyrexia, the review team concludes that pyrexia should be included into the golimumab labeling as an ADR. Pyrexia is also included in the label for adalimumab, another TNF blocker, and the label for the IV formulation of golimumab (Simponi Aria).

In conclusion, while this study lacked a comparator arm for further interpretation of these event findings, the review team recommends that TEAEs of headache and pyrexia should be including into Simponi labeling as ADRs given their frequency and probable relatedness to golimumab treatment.

8.2.4.3 Serious Adverse Events

In the safety population of Study UCO3003, 41% (28/69) of patients experienced at least one treatment-emergent serious adverse events (SAE) occurring between Week 0 and the Final Study Visit.

Study UCO3003: Overall (Week 0 to Final Study Visit)

The SOC with the highest frequency of SAEs was gastrointestinal disorders in 28% (19/69), and the most frequently reported SAE was colitis ulcerative 26% (18/69). Because hospitalizations result in reporting of an SAE, the higher SAE rates observed in this pediatric study may in part be due to higher rates of hospitalization for IBD reported in pediatric populations as compared with adults with IBD.^{14, 34} As noted above, it is possible that the reports of worsening colitis could be signify the lack of efficacy of golimumab in these subjects, leading to a worsening of

³³ Ardura MI, et al. NASPGHAN Clinical Report: Surveillance, Diagnosis, and Prevention of Infectious Diseases in Pediatric Patients With Inflammatory Bowel Disease Receiving Tumor Necrosis Factor- α Inhibitors. J Pediatr Gastroenterol Nutr. 2016 Jul;63(1):130-55.

³⁴ Silva ACV, Tumelero TJ, Yamamoto DR, Truppel SK, da Silva GS, Ribeiro LBM, et al. Biological therapy, surgery, and hospitalization rates for inflammatory bowel disease: An observational Latin American comparative study between adults and pediatric patients. Gastroenterol Hepatol. 2024;47(8):813-20.

their underlying UC condition. Refer to [Table 45](#) for the details of the Study UCO3003 reported SAEs by SOC and PT.

Table 45. SAEs Reported in Subjects Receiving Golimumab Treatment

System Organ Class Preferred Term	Week 0 Through Week 6 N=69 n (%)	Week 6 Through Week 54 N=62 n (%)	Week 0 Through Final Study Visit N=69 n (%)
Any SAE	10 (14.5)	21 (33.9)	28 (40.6)
Blood and lymphatic system disorders (SOC)	0	1 (1.6)	1 (1.4)
Anemia	0	1 (1.6)	1 (1.4)
Gastrointestinal disorders (SOC)	8 (11.6)	11 (17.7)	19 (27.5)
Colitis ulcerative	8 (11.6)	10 (16.1)	18 (26.1)
Abdominal pain	0	1 (1.6)	1 (1.4)
Infections and infestations (SOC)	1 (1.4)	8 (12.9)	9 (13.0)
Pseudomembranous colitis	1 (1.4)	0	1 (1.4)
<i>Clostridium difficile</i> infection	0	1 (1.6)	1 (1.4)
COVID-19	0	1 (1.6)	1 (1.4)
Fungal test positive (Candida bacteremia), with UC flare**	0	1 (1.6)	1 (1.4)
Cytomegalovirus colitis*	0	2 (3.2)	2 (2.9)
Pneumonia	0	2 (3.2)	2 (2.9)
Stump appendicitis	0	1 (1.6)	1 (1.4)
Injury, poisoning and procedural complications (SOC)	0	1 (1.6)	1 (1.6)
Hand fracture	0	1 (1.6)	1 (1.6)
Musculoskeletal and connective tissue disorders (SOC)	0	1 (1.6)	1 (1.6)
Sacroiliitis	0	1 (1.6)	1 (1.6)
Reproductive system and breast disorders (SOC)	1 (1.4)	0	1 (1.4)
Breast mass	1 (1.4)	0	1 (1.4)
Respiratory, thoracic, and mediastinal disorders (SOC)	0	1 (1.6)	1 (1.6)
Dyspnea	0	1 (1.6)	1 (1.6)

Source: Reviewer amended table generated by CDS using data submitted by the Applicant in BLA 125289/S-157, datasets adex.xpt and adsl.xpt, module 5.3.5.1. Software: R; JMP Clinical 18.2. **Fungal test positive* Candida bacteremia case reclassified to infections and infestations SOC from Investigations SOC.+ Only SAE with relationship to Study drug (noted as “very Likely”). Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; SOC, system organ class; UC, ulcerative colitis

After SAEs of worsening UC, the most common SAEs in Study UCO3003 were occurrences of infections. This is consistent with the safety profile of Simponi. Overall, there are no new safety signals noted in the observed SAEs.

The following abbreviated narrative is the only SAE that was assessed by a study investigator to have a reasonable possibility of being related to investigational drug during Study UCO3003:

- **Subject** (b) (6): 9-year-old female experienced a SAE of “UC flare with positive blood culture” with *Candida famata* that a reported as a PT of “fungal test positive”, occurring on Study Day 61. This SAE was severe in intensity and was concerning for the development of presumed sepsis amid worsening UC. The presence of candida in the blood culture was

categorized as an opportunistic infection. On Study Day 61, the subject was diagnosed with the candida bacteremia during a hospitalization for worsening UC, when the subject presented with fever, vomiting, and frequent bowel movement. She was subsequently presumed to have sepsis requiring an intense antibiotic treatment and red blood cell transfusion. Study Day 72, the blood cultures turned positive for fungi (*Candida famata*) and gram-negative bacilli, requiring intravenous fluconazole antifungal treatment. Study Day 85, the events of fungal test positive and colitis ulcerative were reported as resolved, and the subject was discharged from the hospital. The subject had last received 35 mg of golimumab on Day 43. Treatment with the study intervention was permanently discontinued due to receiving infliximab on Study Day 61. The subject was withdrawn from the study on Day 156 due to the event of fungal test positive and after receiving infliximab on Day 150. The investigator considered this event to have a reasonable possibility of being related to study drug.

The review team concurs that the SAE of serious infections are potentially related to golimumab therapy given the immunosuppressive effects of TNF inhibitors. The Simponi labeling currently includes the risk of infections and no further labeling changes are necessary.

8.2.4.4 Opportunistic Infections

Opportunistic infections are known to occur with the administration of TNF blockers including golimumab. These adverse reactions of special interest are included in the Simponi labeling, within the Boxed Warning and Warning and Precautions, as potential serious infections that may occur with golimumab use. In Study UCO3003 from Week 0 to the final study visit, there was a total of three subjects with TEAES of opportunistic infections. These infections include the case of Candida bacteremia with presumed sepsis (Subject (b) (6)), as discussed in Section 8.2.4.3 above. The following are brief narratives the additional opportunistic infection cases:

- Subject # (b) (6): 17-year-old male experienced a SAE of cytomegalovirus (CMV) colitis of severe intensity on Day 56 of the study. Prior to the opportunistic infection SAE, he received dose of golimumab on Day 50. The study intervention was not changed, and the subject recovered from the infection. The event of CMV colitis was reported as resolved on Study Day 103. The investigator considered the event of CMV colitis to be not related to the study intervention. Of note, the subject also experienced an earlier SAE of worsening UC on Day 36, in association with positive tests for *Clostridioides difficile* infection infections that required hospitalization, which resolved. These events were not considered by the investigators to be related to the study intervention. Both CMV and *Clostridioides difficile* infections are known to occur with greater frequency in IBD patients than the general

population³⁵ and may not be readily attributable to golimumab treatment or other treatment interventions.

- Subject (b) (6): 7-year-old female experienced a SAE of CMV colitis of mild intensity on Day 106 of the study. The subject was hospitalized and treated with ganciclovir. She had received the last dose of golimumab on Day 99. The subject recovered from the infection and was discharged from the hospital on Day 121. The study treatment was discontinued, and the subject was withdrawn from the study on Day 181. It was reported that the event of CMV colitis was a reactivation of prior CMV infection and the investigator considered the SAE to be doubtfully related to the study intervention. This subject also experienced an SAE of anemia with a hemoglobin level of 7.6 g/dL associated with an SAE of worsening UC on Study Day 183. She was treated with red blood cell transfusion and her hemoglobin improved to 10.7 g/dL by Study Day 210. These events were not considered by the investigators to be related to the study intervention. As noted above, CMV infections are known to occur at a higher frequency in patients with IBD. Similarly, due to the underlying disease, anemia as iron deficiency is commonly seen in patients with IBD, particularly during periods of active disease or severe inflammation, secondary to ongoing blood loss.³⁶

8.2.4.5 Additional SAEs of Interest

An additional SAE of interest that the reviewer identified as reasonably attributable to golimumab treatment are two cases of pneumonia requiring hospitalization (Subject (b) (6) and (b) (6)). Although the investigator and Applicant do not agree with this possible causality, golimumab is recognized to be associated with immunosuppression and serious infections, which could have led to the development or worsening of pneumonia necessitating hospitalization.

- Subject (b) (6): 4-year-old female (baseline weight of 16.4 kg), was the youngest and smallest subject of Study UCO3003. During Study UCO3003, this subject experienced multiple TEAEs requiring hospitalization, including SAEs of pseudomembranous colitis on Study Day 33 and pneumonia on Day 103. The subject recovered from these events without undergoing any change in golimumab treatment and completed 54 weeks of the study. Golimumab treatment was not changed during the study and these events were not considered by the investigators to be related to the study intervention.
- Subject (b) (6): 10-year-old female who experienced multiple TEAE, including an SAE of pneumonia of moderate severity on Study Day 273, following an infection with COVID-19. She also had a SAE of dyspnea on Day 380 of moderate severity that required hospitalization. This subject also recovered from these events without undergoing any

³⁵ Sheriff MZ, et al. Opportunistic Infections Are More Prevalent in Crohn's Disease and Ulcerative Colitis: A Large Population-Based Study. *Inflamm Bowel Dis.* 2020 Jan 6;26(2):291-300.

³⁶ DeLoughery TG, et al. AGA Clinical Practice Update on Management of Iron Deficiency Anemia: Expert Review. *Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association.* 2024;22(8):1575-1583.

change in golimumab treatment and completed 54 weeks of the study. These events were not considered by the investigators to be related to the study intervention.

8.2.4.6 Severe Adverse Events

Study UCO3003: Overall (Week 0 to Final Study Visit)

From Week 0 through the final safety visit, 35% (24/69) of subjects reported at least 1 severe AE. The SOC with the highest frequency of severe AEs was Gastrointestinal disorders, and worsening UC was the most common PT at 26% (18/69). Overall, severe AEs led to 28% (19/69) of subjects discontinuing golimumab treatment, although most of the severe AEs were not considered by the investigator to have a reasonable possibility of being related to study drug. Only one subject in the maintenance phase was considered to have a severe AE that was related to golimumab treatment (Subject (b) (6), SAE of Candida bacteremia with worsening UC). This narrative of this subject is included in Section 8.2.4.3 above. Table 46 provides the frequency of severe events per phase of the study. The reviewer notes that most TEAEs were mild to moderate in and that severe AEs were mainly comprised of worsening UC and infection-related events, which are recognized within the known safety profile of golimumab.

Table 46. Severe Adverse Events, Overall (Week 0 to Final Study Visit), Study UCO3003

System Organ Class Preferred Term	Week 0 Through Week 6 (Induction) N=69 n (%)	Week 6 Through Week 54 (Maintenance) N=62 n (%)	Week 0 Through Final Study Visit (Overall) N=69 n (%)
Gastrointestinal disorders	9 (13.0%)	11 (17.7%)	18 (26.1)
Colitis ulcerative	9 (13.0%)	11 (17.7%)	18 (26.1)
Infections and infestations	0	2 (3.2%)	2 (2.9)
Clostridium difficile infection	0	1 (1.6%)	1 (1.4)
Cytomegalovirus colitis	0	1 (1.6%)	1 (1.4)
Investigations	0	1 (1.6%)	1 (1.4)
Fungal test positive (Candida bacteremia)	0	1 (1.6%)	1 (1.4)
Musculoskeletal and connective tissue disorders	0	1 (1.6%)	1 (1.4)
Sacroiliitis	0	1 (1.6%)	1 (1.4)
Reproductive system and breast disorders	1 (1.4%)	0	1 (1.4)
Breast mass	1 (1.4%)	0	1 (1.4)

Source: Reviewer generate using data submitted by the Applicant in BLA 125289/S-157, datasets adex.xpt and adsl.xpt, module 5.3.5.1. Software: JMP Clinical 18.2. Abbreviations: N, number of subjects in treatment arm; n, number of subjects with at least one event

8.2.4.7 Overdose

There was one case of an “overdose” of golimumab in a 4-year-old female (subject (b) (6)). At Week 50, one subject received 60 mg instead of 50 mg of golimumab due to an incorrect weight entry. The investigator performed a safety assessment and determined that the incorrect dose did not impact the subject’s safety.

8.2.4.8 Dropouts and/or Discontinuations Due to Adverse Effects

A total of 46% (32/69) of subjects discontinued treatment participation during Week 0 to the final study visit, with 10% (7/69) in the induction and 40% (25/69) in the maintenance phase of the study, respectively. Overall, from Week 0 through the final safety visit, 23% (16/69) of treated subjects reported at least 1 TEAE leading to discontinuation of golimumab, and the most common reasons for treatment discontinuation was worsening UC and/or “lack of efficacy,” occurring in a total of 19% (13/69) of subjects, respectively.

8.2.4.9 Vital Signs

Overall, no subjects experienced a clinically significant worsening of blood pressure or pulse rate, and the blood pressure and pulse rate evaluation found no consistent or clinically meaningful safety signal. The AEs related solely to vital sign abnormalities were few and did not lead to discontinuation of golimumab.

8.2.4.10 Laboratory Findings

The laboratory parameters in Study UCO3003 were analyzed (mean, change from baseline) in the induction, maintenance treatment, and overall golimumab study (Week 0 to final study visit) periods. National Cancer Institute -Common Terminology Criteria for Adverse Events toxicity grades were used by the Applicant to categorize postbaseline shifts in laboratories. The CDS review team evaluated laboratory data using FDA standardized levels and laboratory cut-offs for the identification of postbaseline laboratory shifts and outliers.³⁷ In addition, analyses of mean changes from baseline to minimum, maximum, and final visit values were conducted. Overall, no new safety signals related to changes in laboratory parameters were noted as compared to prior golimumab clinical investigations.

8.2.4.11 Hematology

[Table 47](#) shows the postbaseline, hematologic laboratory shifts per FDA standardized levels, based on CDS analyses of Study UCO3003 data of subjects treated with golimumab.

Table 47. Hematology Postbaseline Laboratory Shifts*

Laboratory Parameter	Golimumab Induction Phase N=69	Golimumab Maintenance Phase N=62	Golimumab Total N=69
Complete Blood Count	n/N _w (%)	n/N _w (%)	n/N _w (%)
WBC, decreased (10 ³ cells/μL)			
Level 1 (<3.5)	3/61 (4.9)	1/55 (1.8)	4/66 (6.1)
Level 2 (<3)	1/61 (1.6)	0/55 (0)	1/66 (1.5)
Level 3 (<1)	0/61 (0)	0/55 (0)	0/66 (0)

³⁷ CDS-generated threshold levels 1, 2, and 3 are considered to be clinically meaningful and are defined within the [Standard Safety Tables & Figures Integrated Guide](#)

Laboratory Parameter	Golimumab Induction Phase N=69 n/N _w (%)	Golimumab Maintenance Phase N=62 n/N _w (%)	Golimumab Total N=69 n/N _w (%)
Complete Blood Count			
WBC, high (10 ³ cells/μL)			
Level 1 (>10.8)	6/61 (9.8)	12/55 (21.8)	15/66 (22.7)
Level 2 (>13)	4/61 (6.6)	4/55 (7.3)	7/66 (10.6)
Level 3 (>15)	3/61 (4.9)	2/55 (3.6)	4/66 (6.1)
Hemoglobin, decreased (g/dL)			
Level 2 (>1.5 g/dL dec. from baseline)	6/60 (10.0)	12/54 (22.2)	14/64 (21.9)
Level 3 (>2 g/dL dec. from baseline)	5/60 (8.3)	8/54 (14.8)	9/64 (14.1)
Platelets, decreased (10 ³ cells/μL)			
Level 1 (<140)	1/57 (1.8)	1/55 (1.8)	2/64 (3.1)
Level 2 (<125)	1/57 (1.8)	1/55 (1.8)	2/64 (3.1)
Level 3 (<100)	1/57 (1.8)	0/55 (0)	1/64 (1.6)

Source: Reviewer amended table generated by CDS using data submitted by the Applicant in BLA 125289/S-157, dataset adlb.xpt, module 5.3.5.1. Software: R; JMP Clinical 18.2. * Based on FDA standardized levels and cut-offs defined by CDS for the purpose of identifying outliers. FDA Standard Safety Tables and figures: Instruction Manual; Center for Drug Evaluation and Research (CDER) Biomedical Informatics and Regulatory Review Science (BIRRS) Team (July 2023). Abbreviations: CDS, clinical data scientist; dec, decrease; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; WBC, white blood cell

Hemoglobin Postbaseline Shifts

Level 3 anemia postbaseline values (hemoglobin decreases of ≥ 2 g/dL from baseline) were measured in five subjects in the induction phase and nine subjects in the overall study. These episodes of anemia are considered to be related to the underlying UC disease. In general, all of the affected subjects recovered or had stabilized hemoglobin levels at the end of their study participation. Two of these subjects were treated with blood transfusions and their brief narratives are noted below.

- **Subject** (b) (6): A 16-year-old male received golimumab 200 mg on Day 1 and 100 mg on Days 15 and 40. On Day 57, he experienced nonserious mild anemia, treated with ferrous sulfate. By Day 66, the anemia worsened, was considered serious, and led to 1-day hospitalization. On Day 71, the subject experienced a severe UC flare, which led to a second hospitalization. He was treated with antibiotics, steroids, and packed red blood cell transfusion. On Day 82, the UC flare resolved, and the subject was discharged. The study intervention was permanently discontinued due to protocol deviation (IV steroid use). On Day 151, the subject was withdrawn from the study, and the hemoglobin level had normalized to 13.2 g/dL. The investigator deemed the anemia was doubtfully related and the UC flare as not related to the study intervention.
- **Subject** (b) (6): A 12-year-old male received golimumab 200 mg on Day 1 and 100 mg on Day 17. On Day 35, the subject experienced a severe UC flare, leading to hospitalization on Day 37. Despite receiving another 100 mg dose of golimumab on Day 37, the subject's condition worsened, requiring blood transfusion on Day 38 due to decreased hemoglobin levels. The study intervention was permanently discontinued, and the subject was treated with corticosteroids, antibiotics, and iron supplements. The investigator deemed the UC flare unrelated to the study intervention. The event resolved on Day 46, at which point the subject was discharged and withdrawn from the study.

Platelet Postbaseline Shift

A level 3 thrombocytopenia postbaseline value ($<100 \times 10^9$ cells/L) was measured in one subject (Subject (b) (6)) during the induction phase of the study. Notably the subject's platelets decreased from a baseline of 605×10^9 /L at baseline (Day -41) to 74×10^9 /L on Day 43 of the study, preceding an SAE of fungal bacteremia described in Section 8.2.4.3 above. Serious systemic infections can be associated with thrombocytopenia. It is unclear whether the subject's platelet count recovered as there are no additional platelet count laboratory results in the submitted dataset for this subject and is not described by the Applicant in the clinical study report (CSR).

Leukopenia Postbaseline Shifts

A level 3 lymphopenia postbaseline value ($<0.5 \times 10^9$ cells/L) was measured in one subject (Subject (b) (6)) during the maintenance of the phase of the study. This subject was a 16-year-old female who experienced lymphopenia (lymphocyte count of 0.36×10^9 /L) and monocytopenia at Study Day 190. This leukopenia was preceded by and a SAE of worsening UC requiring hospitalization on Day 154, multiple respiratory tract infections, including an URTI on Day 157. The subject's lymphocytes recovered at Week 38 and were reported to be 1.84×10^9 /L. The CSR notes that the study treatment was not changed and that the events resolved.

Leukocytosis Postbaseline Shifts

Alternatively, level 3 leukocytosis postbaseline values ($>15 \times 10^9$ /L) were measured in a total of four subjects in the overall study, with three occurring in the induction and two events occurring during the maintenance phases. All of this postbaseline leukocytosis shifts were related to worsening UC episodes/ UC flares. In the induction phase, postbaseline leukocytosis shift occurred in two subjects, Subjects (b) (6) and (b) (6). A brief narrative for Subject (b) (6) is located below and the narrative for Subject (b) (6) is include under the section "Hemoglobin Postbaseline Shifts" above. In the maintenance phase, Subject (b) (6) was a 15-year-old male who experienced a postbaseline leukocytosis shift in association with UC flare. Subject (b) (6), a 10-year-old female with an SAE with pneumonia, experienced leukocytosis in both the induction and maintenance phases (see Section 8.2.4.4 for the subject narrative).

- **Subject (b) (6)**: A 16-year-old male subject experienced a leukocyte count of 16.7×10^9 /L (from a baseline of 14.9×10^9 /L) at Study Day 134. This was preceded by a total of two doses of golimumab given during the induction phase (last on at Day 17), and a SAE of severe worsening UC from Days 38 to 60. The subject had an early study discontinuation visit on Day 36 and started infliximab on Study Day 42. He subsequently was treated with IV corticosteroids on Day 57 and fluconazole prophylaxis. The participant was withdrawn from the study on Day 133 as per the principal investigator's decision and disease progression (and due to initiation of IV steroids and infliximab, both prohibited medications). There were no additional blood tests recorded. The cause of the leukocytosis could be attributed to multiple factors, including the subject's UC flare, steroid treatment, or other causes, making the potential association with golimumab treatment highly confounded.

8.2.4.12 Chemistry

The postbaseline, chemistry laboratory shifts per FDA standardized levels, based on CDS analyses of Study UCO3003 data of subjects treated with golimumab were evaluated.³⁸ Overall, no level 3 chemistry-related changes were reported. Of note, a level 2 postbaseline hypokalemia value of 2.8 mEq/L on Study Day 244 (decreased from a level of 4.6 mEq/L on Day 183)] was reported for a subject ((b) (6), 7-year-old male). This electrolyte abnormality was reported to be in association with a TEAE of worsening UC, which led to study discontinuation. The incidence of hypokalemia was not reported as a TEAE. The subject received potassium oral supplementation over 36 days, however, there are no additional laboratory values recorded. The last day of golimumab administration was Day 210.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Liver Biochemistry

Overall, most subjects who had normal baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels had maximum postbaseline values that were within the reference range ($\leq 1 \times$ upper limit of normal [ULN]). A total of three (4.3%) subjects had a maximum postbaseline total bilirubin $\geq 2 \times$ ULN. Among the subjects who had elevated ALT postbaseline, 1 (16.7%) had a maximum postbaseline ALT and AST ≥ 5 and $< 8 \times$ ULN, without having elevated bilirubin. In this subject, the ALT and AST elevation returned to normal at Week 14. Among the three subjects who had elevated baseline total bilirubin, two subject with a history of Gilbert's syndrome also had a maximum postbaseline value of $\geq 2 \times$ ULN.

Table 48. Liver Biochemistry, Study UCO3003

Laboratory Parameter	Golimumab Induction Phase N=69 n/N_w (%)	Golimumab Maintenance Phase N=62 n/N_w (%)	Golimumab Total N=69 n/N_w (%)
Alkaline phosphatase, high (U/L)			
Level 1 ($>1.5 \times$ ULN)	0/62 (0)	0/58 (0)	0/69 (0)
Level 2 ($>2 \times$ ULN)	0/62 (0)	0/58 (0)	0/69 (0)
Level 3 ($>3 \times$ ULN)	0/62 (0)	0/58 (0)	0/69 (0)
Alanine aminotransferase (ALT), high (U/L)			
Level 1 ($>3 \times$ ULN)	1/60 (1.7)	0/57 (0)	1/67 (1.5)
Level 2 ($>5 \times$ ULN)	1/60 (1.7)	0/57 (0)	1/67 (1.5)
Level 3 ($>10 \times$ ULN)	0/60 (0)	0/57 (0)	0/67 (0)
Aspartate aminotransferase (AST), high (U/L)			
Level 1 ($>3 \times$ ULN)	1/58 (1.7)	0/58 (0)	1/67 (1.5)
Level 2 ($>5 \times$ ULN)	1/58 (1.7)	0/58 (0)	1/67 (1.5)
Level 3 ($>10 \times$ ULN)	0/58 (0)	0/58 (0)	0/67 (0)

³⁸ FDA Standardized levels: FDA "Standard Safety Tables and figures: Instruction Manual; Center for Drug Evaluation and Research (CDER) Biomedical Informatics and Regulatory Review Science (BIRRS) Team" (July 2023)

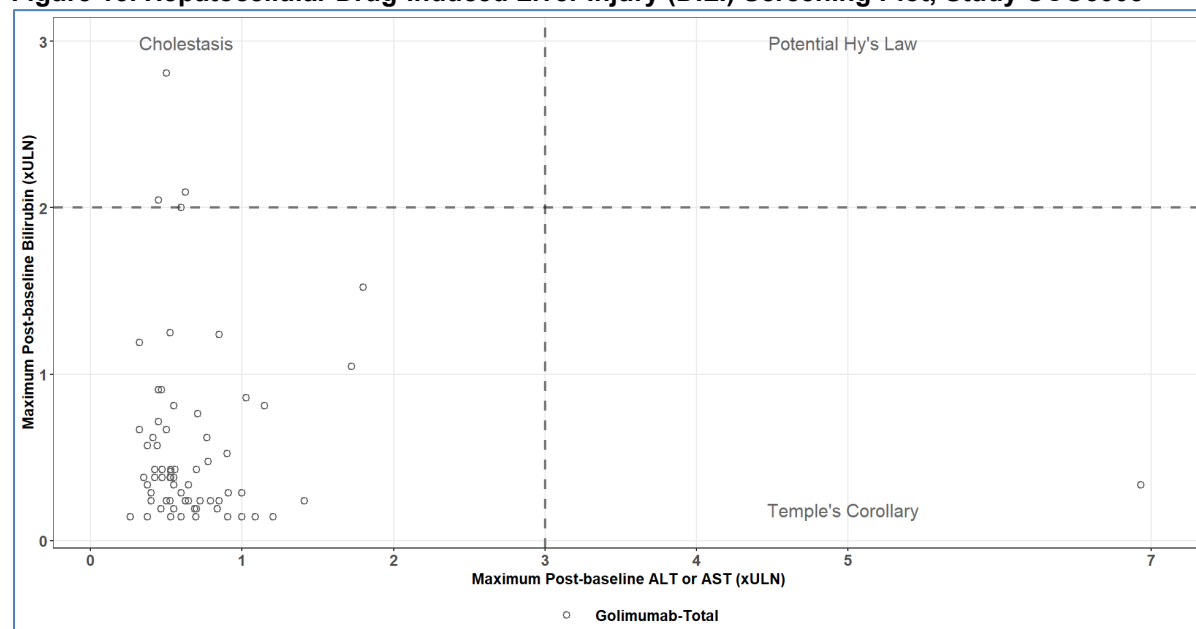
Laboratory Parameter	Golimumab Induction Phase N=69	Golimumab Maintenance Phase N=62	Golimumab Total N=69
	n/N _w (%)	n/N _w (%)	n/N _w (%)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	3/62 (4.8)	4/58 (6.9)	5/69 (7.2)
Level 2 (>2X ULN)	3/62 (4.8)	1/58 (1.7)	3/69 (4.3)
Level 3 (>3X ULN)	0/62 (0)	0/58 (0)	0/69 (0)

Source: Reviewer amended table generated by CDS using data submitted by the Applicant in BLA 125289/S-157, dataset adlb.xpt, module 5.3.5.1. Software: R; JMP Clinical 18.2. *Based on FDA standardized levels and cut-offs defined by CDS for the purpose of identifying outliers. FDA Standard Safety Tables and figures: Instruction Manual; Center for Drug Evaluation and Research (CDER) Biomedical Informatics and Regulatory Review Science (BIRRS) Team (July 2023). Abbreviations: CDS, clinical data scientist; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Evaluation for Potential Hy's Law Cases

None of the subjects with elevated bilirubin also had elevations in ALT or AST at the same time. There were no cases of Hy's Law (ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN) in this study. The hepatocellular drug-induced liver injury screening plot for Study UCO3003 is depicted in [Figure 15](#).

Figure 15. Hepatocellular Drug-Induced Liver Injury (DILI) Screening Plot, Study UCO3003



Source: Reviewer amended table generated by CDS using data submitted by the Applicant in BLA 125289/S-157, dataset adlb.xpt, module 5.3.5.1. Software: R; JMP Clinical 18.2. *Based on FDA standardized levels and cut-offs defined by CDS for the purpose of identifying outliers. FDA Standard Safety Tables and figures: Instruction Manual; Center for Drug Evaluation and Research (CDER) Biomedical Informatics and Regulatory Review Science (BIRRS) Team (July 2023). Golimumab Total includes observations from Week 0 through Week 54 with the addition of data from participants with final safety visit data. Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period. A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN. Those subjects who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red. The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases. All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted. In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDS, clinical data scientist; ULN, upper limit of normal

Table 49. DILI Screening, Study UCO3003

	Golimumab Induction Phase N=69	Golimumab Maintenance Phase N=62	Golimumab Total N=69
Quadrant	n/N_w (%)	n/N_w (%)	n/N_w (%)
Potential Hy's Law (right upper)	0/61 (0)	0/59 (0)	0/69 (0)
Cholestasis (left upper)	3/61 (4.9)	1/59 (1.7)	3/69 (4.3)
Temple's corollary (right lower)	1/61 (1.6)	0/59 (0)	1/69 (1.4)
Total	4/61 (6.6)	1/59 (1.7)	4/69 (5.8)

Source: Reviewer amended table generated by CDS using data submitted by the Applicant in BLA 125289/S-157, dataset adlb.xpt, module 5.3.5.1. Software: R; JMP Clinical 18.2. * Based on FDA standardized levels and cut-offs defined by CDS for the purpose of identifying outliers. FDA Standard Safety Tables and figures: Instruction Manual; Center for Drug Evaluation and Research (CDER) Biomedical Informatics and Regulatory Review Science (BIRRS) Team (July 2023). Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Narratives of Subjects With Abnormal Key Liver Biochemistry

As noted above, the liver biochemistry elevations were not suspected to represent hepatocellular drug induced liver injury. Additional details of the level ≥ 2 elevations in liver biochemistry values, ALT, AST, and bilirubin are provided in the case narratives below.

- Subject (b) (6): 9-year-old male, had elevated ALT/AST levels at Week 6 that resolved by Week 14, with elevated ALT (298 U/L) and AST (263 U/L) on Study Day 50. No specific treatment reported for elevated liver enzymes. ALT and AST levels returned to normal by Study Day 104. Investigator considered these events not related to the study drug (golimumab). Subject Completed study through Week 54.
- Subject (b) (6): 16-year-old male with history of Gilbert's syndrome, had elevated total bilirubin (2.5 mg/dL) on Study Day 378. No formal adverse event was reported for this elevated bilirubin, which was consistent with the subject's history of Gilbert's syndrome. On the same day, the participant had normal ALT (11 U/L), AST (24 U/L), and alkaline phosphatase (196 U/L). No formal adverse event was reported for this elevated bilirubin.
- Subject (b) (6): 14-year-old male with elevated total bilirubin (2.8 mg/dL) at screening and fluctuating elevated levels between 1.5 to 2.6 mg/dL throughout the study. No specific treatment reported. Consistent with subject's underlying Gilbert's syndrome. No investigator assessment of relationship provided, as this was not reported as an adverse event.
- Subject (b) (6): 14-year-old female with a history of Gilbert's syndrome experienced elevated total bilirubin (3.5 mg/dL) on Study Day 40, consistent with subject's known history of Gilbert's syndrome. All other liver function tests were normal. On Study Day 97, the level of bilirubin returned to normal at 0.4 mg/dL. The participant completed Week 54 visit on Study Day 382 and entered the study extension. The last dose received prior to entering the study extension was on Study Day 355. No investigator assessment of relationship provided, as this was not reported as an adverse event.
- Subject (b) (6): 12-year-old male with a history of Gilbert's syndrome experienced elevated bilirubin fluctuating between 1.5 to 2.6 mg/dL, consistent with the participant's underlying Gilbert's syndrome mg/dL). The other liver function parameters (AST, ALT, alkaline

phosphatase) were normal on the same day. Investigator considered liver function test increases to be doubtfully related to golimumab.

- Subject (b) (6): 16-year-old male with ulcerative colitis and primary sclerosing cholangitis had SAE of COVID-19 on Day 45, and on Study Day 156, the subject had a nonserious adverse event of liver function test increased of mild intensity. No action was taken with the study intervention due to this event. No treatment was reported for this event. The investigator considered the event of liver function test increased to be doubtfully related to the study intervention. Of note, consistent with the diagnosis of primary sclerosing cholangitis, the ALT, AST, and gamma-glutamyl transferase levels continued to fluctuate from normal to mildly elevated. On Study Day 184, the subject had mildly elevated ALT and AST (ALT level: 48 U/L, AST level: 53 U/L). On Study Day 270, the subject again had mildly elevated ALT, AST (ALT level: 67 U/L, AST 72 U/L). On Study Day 382, the subject's ALT and AST levels were normal (ALT 21 U/L, AST 23 U/L). Completed study through Week 54.

The elevated bilirubin levels in subjects with Gilbert's syndrome persisted during the study. However, these elevations were not considered to be clinically significant.

8.2.5.2 Study UC03003: 120-Day Safety Update

The Applicant's submitted 120-day safety update for Study UC03003 provided results from the Week 54 dosing up to the cut-off of December 12, 2024, which includes 8 months of data following the initial DBL of April 2024. Out of the 69 pediatric subjects enrolled in the study, 40 subjects completed the Induction and Maintenance periods of the study (i.e., through Week 54) and 31 participants entered the Study Extension period. There were no new study participants. During the study extension period, the 31 subjects had an average follow-up of 103 weeks.

Overall, the most frequently reported AEs included URTI with COVID-19, worsening UC, nasopharyngitis, rash, and abdominal pain, as seen in greater than 10% (or 3 subjects) of the 31 subjects each. During the study extension period, three subjects reported one or more SAEs: worsening UC in two subjects, gastroenteritis with *Escherichia coli* and norovirus infection in one subject (who later had worsening UC), depression in one subject, and hand fracture in another subject.

Injection-site reactions were experienced in three subjects. This included injection site swelling in two subjects and "other" reaction in one subject. During the study extension period, two subjects experienced a TEAE that led to study intervention discontinuation, which included one subject who experienced worsening UC and another subject became pregnant during the study, as described in the following narrative:

Subject (b) (6): 15-year-old female with pregnancy diagnosed on Study Day 585, via urine human chorionic gonadotropin test. The subject did not experience any medical disorders or problems during the pregnancy and delivered a healthy male baby on (b) (6), via vacuum extraction at 39 weeks and 6 days gestation. The treatment with the study drug was permanently discontinued on (b) (6), due to the event of pregnancy. The review team sent an inquiry request was sent to the Applicant for follow-up

information of the infant. The Applicant replied that the most recent follow-up information provided by the site principal investigator was from (b) (6), approximately 4 months after what was described as a healthy delivery. No additional follow-up information was obtained, and the study site has been closed for several years.

The assessed laboratories included changes that were consistent with the main study. No case of Hy's Law was observed, and no Grade 3 or 4 blood chemistry abnormalities were observed. One subject had Grade 3 neutrophil count decreased and Grade 2 abnormalities of anemia and white blood cell decreased were reported in one subject each.

In general, data from this 120-day safety update does not change the previous assessment of the safety of subcutaneous golimumab in pediatric subjects with moderately to severely active UC aged 2 to <18 years as previously described.

8.2.5.3 Adverse Events of Special Interest

AEs designated as AESIs within this program were derived from the Warnings and Precautions of the approved prescribing information. Specifically, the Warnings and Precautions section of the labeling contains specific language for serious infections, malignancies, congestive heart failure, central and peripheral nervous system demyelinating disorders, hematologic cytopenia, autoimmunity, and hypersensitivity reaction.²⁷

In addition to serious infections, including opportunistic infections, and hematologic cytopenias, the following AESIs occurred in Study UCO3003 from Week 0 to the final study visit:

Hypersensitivity Reactions

No serious or severe intensity hypersensitivity reactions occurred. From Week 0 through the final safety visit, 6% (4/69) of treated subjects reported at least one injection-site reaction. Specifically, two subjects had injection site erythema, and one subject each had injection site rash or skin infection. No TEAEs led to anaphylaxis or delayed hypersensitivity reactions. Hypersensitivity reactions were not demonstrated to be clearly related to antidrug antibody formation, though the small numbers limit the evaluation.

Antibodies to Golimumab

Of the 69 subjects treated with golimumab, 15 (21.7%) were positive for antibodies to golimumab, with relatively low titers ($\leq 1:96$). Of these 15 subjects, 3 (20%) tested positive for neutralizing antibodies. The incidence of antibodies to golimumab over time was comparable between pediatric and adult subjects with UC.

Autoimmunity and Autoantibodies

In Study UCO3003, 35% (22/63) of subjects who had negative antinuclear antibody titer at baseline developed a positive ($\geq 1:160$) antinuclear antibody titer at any time during the study.

No subjects were positive for anti-dsDNA (titer >120 IU/ml) nor anti-dsDNA equivocal antibodies at any time during the induction phase or maintenance phase. No lupus-like syndrome events were reported.

8.2.5.4 Safety Analyses by Demographic Subgroups

Overall, the interpretation and conclusions of the safety evaluation of golimumab treatment in pediatric subjects with UC based on demographic subgroups (sex, age, weight, race, and ethnicity) are limited given the small number of subjects enrolled in the study overall and in each subgroup. While interpretation is limited by small sample sizes, the proportions of participants who had one or more AEs, SAEs, AEs that led to study intervention discontinuation, and infections reported from Week 0 of induction through Week 54 of maintenance were fairly similar across most baseline demographic subgroups including sex (male or female), race (white versus nonwhite), age (<12 years or ≥12 years), and weight (<45 kg or ≥45 kg). Refer to [Table 50](#) for additional details on the number of adverse events per study demographics.

Table 50. Proportions of Subjects Reporting at Least 1 TEAE by Demographic Subgroup, Study UCO3003

Characteristic	Golimumab Induction Phase N=69 n/N_s (%)	Golimumab Maintenance Phase N=62 n/N_s (%)	Golimumab Total N=69 n/N_s (%)
Sex			
Female	24/37 (64.9)	32/33 (97.0)	36/37 (97.3)
Male	23/32 (71.9)	26/29 (89.7)	31/32 (96.9)
Age group, years			
2 to 5	2/2 (100)	2/2 (100)	2/2 (100)
6 to 11	8/13 (61.5)	9/10 (90.0)	12/13 (92.3)
12 to 17	37/54 (68.5)	47/50 (94.0)	53/54 (98.1)
Race			
American Indian or Alaska Native	2/2 (100)	2/2 (100)	2/2 (100)
Asian	7/12 (58.3)	10/12 (83.3)	11/12 (91.7)
Black or African American	2/2 (100)	2/2 (100)	2/2 (100)
Multiple	1/1 (100)	1/1 (100)	1/1 (100)
White	34/50 (68.0)	41/43 (95.3)	49/50 (98.0)
Missing	1/2 (50.0)	2/2 (100)	2/2 (100)
Ethnicity			
Hispanic or Latino	14/17 (82.4)	16/16 (100)	17/17 (100)
Not Hispanic or Latino	33/50 (66.0)	40/44 (90.9)	48/50 (96.0)
Not reported	0/2 (0)	2/2 (100)	2/2 (100)
Is in United States			
United States	4/4 (100)	4/4 (100)	4/4 (100)
Non-United States	43/65 (66.2)	54/58 (93.1)	63/65 (96.9)

Source: Reviewer amended table generated by CDS using data submitted by the Applicant in BLA 125289/S-157, dataset adlb.xpt, module 5.3.5.1. Software: R; JMP Clinical 18.2

Abbreviations: N, number of subjects in treatment arm; n, number of subjects reporting at least one TEAE; N_s, number of subjects with given characteristic

Race and Ethnicity Subgroup Evaluation

As aforementioned, there were too few subjects in any racial or ethnic groups, outside of those identified as White and Non-Hispanic, to draw conclusions about potential differences in safety.

Sex-Related Subgroup Evaluation

From Week 0 to the final study visit, as compared to males (n=32), female subjects (n=37) demonstrated a numerically higher proportion of gastrointestinal disorders, including worsening UC, abdominal pain, hematochezia, and others (84% [31/37] versus 75% [24/32]). While there were similar proportions of SAES in both the female and male subgroups (31% [10/32] versus 24% [9/37]), more SAEs of worsening UC were reported in male versus female subjects (31% [10/32] versus 24% [9/37]). There were also more infections and infestation disorders in females as compared to male subjects (68% [25/37] versus 59% [19/32]), and more females than males had pyrexia (16% [6/37] versus 3% [1/32]), headache and paresthesia (22% [8/37] versus 13% [4/32], each), weight decrease (16% [6/37] versus 3% [1/32]). However, males had a slightly higher occurrence of COVID-19 infections as compared to females. Likewise, more males than females reported events of acne (19% [6/32] versus 3% [1/32]).

This finding suggests potential sex-based differences in immune response or infection susceptibility warrant consideration, however, the numbers in each subgroup remain too small to make reliable conclusions.

Age and Weight Subgroup Evaluation

Subjects in the younger age group (4 to <12 years, n=15) exhibited a fairly comparable safety profile compared to adolescents (12 to <18 years, n=54). While the overall rates of SAEs were slightly lower in those weighing <45 kg as compared to those with weight ≥45 kg (35% [6/17] versus 42% [22/52]), there was a higher incidence of worsening UC SAEs in the younger versus older subjects, (53% [8/15] versus 28% [15/54]) and a greater propensity for treatment discontinuation due to adverse events (27% [4/15] versus 15% [8/54]). Both groups showed similar susceptibility to infections and infestations (20% [3/15] versus 28% [15/54]).

Of note, the smallest subject who received golimumab was 4 years of age and weighted 16 kg. The Applicant proposes (b) (6)

8.2.6. Pediatric Phase 1b Study UC01001 Safety Results

This study was a phase 1b open-label trial evaluating the pharmacokinetics, safety, and efficacy of subcutaneous golimumab in pediatric patients ages 2 to 17 years with moderately to severely active ulcerative colitis. The study enrolled 35 patients who received weight-based dosing of golimumab for 14 weeks. Subcutaneous golimumab was generally well tolerated through Week 14 in the pediatric UC population.

Key safety findings in Study UCO1001 include the following:

- 94.3% (34/35) of subjects reported at least one adverse event through Week 14
- 31.4% of subjects reported at least one serious adverse event through Week 14
- 37.1% of subjects reported at least one infection through Week 14
- 17.1% of subjects reported at least one injection-site reaction through Week 14
- No deaths, serious infections, opportunistic infections including tuberculosis, or malignancies were reported through Week 14
- 3 subjects (8.6%) discontinued study agent due to adverse events through Week 14, all due to worsening of UC
- 11 subjects reported serious adverse events through Week 14, the majority of which were associated with worsening of UC
- 6 subjects reported injection-site reactions through Week 14, all of which were mild or moderate
- No possible anaphylactic or serum-sickness like reactions were reported
- Markedly abnormal changes in hematology and chemistry laboratory values were uncommon
- The safety profile was generally consistent across age, weight, and baseline concomitant medication subgroups

Outside of SAEs of worsening UC there was an AE of special interest in one subject. Subject (b) (6) was a 16-year-old female who experienced an SAE of acute pancreatitis on Day 73 of the study. She was hospitalized and treated with IV fluids and recovered after 7 days subject.

In general, the safety profile of golimumab in this pediatric UC population was generally consistent with the safety observed in the adult trials of subjects with UC, pediatric subjects in Study UCO3003, approved golimumab indications, and anti-TNF- α agents for the treatment of pediatric patients with UC (i.e., infliximab and adalimumab).

8.2.7. Safety in the Postmarket Setting

8.2.7.1 Safety Concerns Identified Through Postmarket Experience

Pharmacovigilance

In addition to the clinical study data, the proposed indication for pediatric UC is further supported by real-world evidence submitted by the Applicant. Golimumab is approved for RA, PsA, AS, nonradiographic axial spondyloarthritis, polyarticular course juvenile idiopathic arthritis, and UC and, as of April 6, 2024, golimumab is authorized for use in 104 countries or territories worldwide. Per the Applicant, the worldwide postmarketing patient exposure to Simponi was estimated to be (b) (4) through March 31, 2024. The estimated cumulative postmarketing patient exposure since first approval is (b) (4).

The currently approved golimumab labeling outlines the known safety profile, including updates from postmarketing reports and postapproval safety studies, where relevant. In general, the additional reports provided information on safety consistent with what is already labeled and did not identify new safety concerns.

The Applicant maintains a pharmacovigilance system that continues to monitor safety information for golimumab from clinical studies, registries, and spontaneous postmarketing reports. Periodic Benefit Risk Evaluation Reports generated for golimumab reflect ongoing postmarketing safety surveillance, as well as assessments of all important identified and potential risks. The most recent Periodic Benefit Risk Evaluation Report (reporting period of April 7, 2024, to April 6, 2025) did not identify any new adverse drug reactions.

Golimumab continues to demonstrate a favorable benefit-risk profile in both adult and pediatric patients across all approved indications. Based on the comprehensive evaluation of the available safety data in pediatric UC, no new important identified or potential risks have been identified. The available safety data were consistent with those from the approved indication of UC in adults, suggesting that the overall safety profile is consistent across the UC population.

Safety Registry Study C0168Z02 (DEVELOP)

DEVELOP is a multicenter, global, prospective, observational study examining the long-term safety and clinical status of pediatric patients under 17 years of age with IBD who are treated with Remicade (infliximab). The study also collects data on other medical therapies used for IBD. It began in 2007 as a postmarketing requirement from regulatory authorities for Remicade. Physicians prescribe treatments based on usual clinical practice, with no restrictions on the use of commercially available medications. Enrollment in DEVELOP was completed in November 2017, with a total of 6,069 IBD patients enrolled, including 21 ulcerative colitis patients exposed to golimumab before age 18. Interim analyses of the cumulative data are performed at least annually. All adverse events and serious adverse events are collected approximately every 6 months following a standardized protocol, with planned follow-up of 20 years or until study withdrawal/termination. Adverse events of special interest, including dysplasia, malignancy, serious infections, and new autoimmune diseases, are specifically documented. The data cutoff date for the DEVELOP data included in this application is June 30, 2023.

This registry study provides some supportive long-term safety data for golimumab in pediatric UC patients that appears consistent with its known safety profile. While new safety signals have not been identified, the small sample size and differences in study design limit the ability to draw definitive conclusions.

Expectations on Safety in the Postmarket Setting

In addition to the primary safety data on pediatric UC patients submitted with this application, the safety profile of golimumab is well characterized from its many years of use across multiple indications. In consideration of the information available from multiple sources as outlined

above, no additional postmarketing safety studies are recommended at this time for pediatric UC patients.

8.3. Conclusions and Recommendations

The review team recommends approval of this supplement, to expand the indication for golimumab to include treatment of pediatric patients weighing at least 15 kg with moderately to severely active UC.

The safety profile demonstrated in Study UCO3003 through Week 54 was consistent with the known safety profile of golimumab in adult patients with UC. Additional adverse reactions recommended for inclusion in the labeling are pyrexia and headache, which are consistent with other drugs in class. There were no new or unexpected safety signals identified in this development program. The pediatric UC program evaluated one dose level, which performed acceptably from a safety perspective. The rate of select adverse events known to be associated with active UC (such as worsening UC) observed may be related to allowing nonresponders at Week 6 into the maintenance phase without dose escalation. The higher frequency of serious adverse events as compared to adult studies may be partly due to higher rates of hospitalization for UC flares specifically in pediatric patients as compared with adults.

The efficacy data from Study UCO3003 met the primary endpoint of clinical remission at Week 6 relative to a historical adult placebo control. When evaluated in totality, including comparisons to adult UC data, the available efficacy data is considered adequate to recommend approval. The recommended dosing regimen is designed to generate similar exposures to those observed in adult patients.

Limitations of the data included relatively small sample sizes in some subgroups, such as patients weighing <30 kg. Although some uncertainty remains regarding efficacy in these under-represented subgroups, based on the adult experience, pathophysiology of the disease and its similarity in adults and pediatric patients, and understanding of the mechanism of action, these limitations did not preclude approval.

In conclusion, golimumab provides a new subcutaneously administered treatment option for pediatric patients with moderately to severely active UC. The recommended dosage is a body weight-based regimen. The submitted data demonstrate that the benefits of treatment with golimumab in the intended population outweigh the identified risks.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this application.

10 Pediatrics

Pediatric clinical trials in patients with moderately to severely active UC were the focus of this efficacy supplement. Relevant regulatory history and the efficacy and safety findings of the pediatric UC studies are discussed in the preceding sections of this document.

The Applicant was granted orphan drug designation prior to the approval of golimumab for the treatment of UC in adults, thus no studies were required under the Pediatric Research Equity Act. However, the Applicant agreed to conduct studies for PMCs #4 and #5, as described in Section [3.1](#).

11 Labeling Recommendations

11.1. Prescription Drug Labeling

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the currently approved PI and the Applicant's draft PI) ([Table 51](#)). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 51. Key Labeling Changes and Considerations

1 INDICATIONS AND USAGE	Section 1.4, <i>Ulcerative Colitis</i>: The indicated pediatric population was revised from "(b) (4)" to "pediatric patients weighing at least 15 kg with moderately to severely active UC." The review team determined that weight, "(b) (4)", was most appropriate to define the patient population for the following reasons: - Because the minimum patient age enrolled in the pediatric UC Study UCO3003 was 4 years of age, there are no observed clinical trial data (PK, safety, efficacy) in patients with UC "(b) (4)". - The safety and efficacy profile of golimumab was evaluated in patients with UC weighing at least 15 kg. Recognizing that weight variability is common among patients of similar ages with chronic conditions such as UC, "(b) (4)" ensures that the appropriate population (those weighing at least 15 kg) can receive golimumab "(b) (4)". - Given that the proposed treatment regimen is weight-based, specifying the minimum weight requirement in the Dosage and Administration section provides directly relevant information for appropriate dosing. See Section 6.3.1 for additional details.
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2 DOSAGE AND ADMINISTRATION	Sections 2.3, <i>Recommended Dosage</i>: Pediatric dosing table revised from (b) (4) to weight-based recommendations to align with the indicated population: • Patients ≥ 40 kg: 200 mg at Week 0, 100 mg at Week 2, then 100 mg every 4 weeks • Patients 15 to <40 kg: 100 mg at Week 0, 50 mg at Week 2, then 50 mg every 4 weeks. Section 2.4, <i>Preparation and Administration Instructions</i>: Administration instructions were revised based on DMEPA review of human factors data. The revised instructions allow for pediatric self-injection with the prefilled syringe based on HF data submitted under BLA 761061 (Tremfya) on November 16, 2016, and BLA 125289 (Simponi) on March 2, 2017. An age limitation of 12 years and older for pediatric self-administration of the prefilled syringe was agreed upon with the Applicant based on the HF study as well as precedence of competitor labeling with pediatric self-administration. The labeling will also state that the SmartJect autoinjector has not been evaluated for pediatric self-administration. The applicant requested additional time to evaluate this device in adults before expanding to pediatric use. The Applicant also added the following statement to the proposed labeling: "If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time. This addition is acceptable as it reflects the instructions included in the labeling of similar products, including Simponi Aria.¹
5 WARNINGS AND PRECAUTIONS	The information on Hepatitis B Virus Reactivation, currently part of Section 5.1 Infections was relocated to Section 5.5 as a stand-alone section, which is consistent with other approved TNF blockers (e.g., Cimzia).² The Surveillance, Epidemiology, and End Results (SEER) database was removed as a listed reference from Section 15 and the date of the database (1964 to 2004) was added to Section 5.2 Malignancies to give context to the data presented.
6 ADVERSE REACTIONS:	Section 6.1, <i>Clinical Trials Experience</i>: Added a summary statement at the beginning of this subsection to describe the size and nature of the pediatric safety database and complement the existing statements about the adult safety database. Pediatric safety statement added noting that the frequency and type of adverse reactions in pediatric UC patients were generally similar to those observed in adults. The UC subsection was revised to combine the adult and pediatric data into one general paragraph. The ADRs of headache and pyrexia were noted in pediatric patients in the study (see Section 8.2.4.2 for additional details).

	Section 6.2, <i>Immunogenicity</i>: The information in Section 6.2 Immunogenicity was moved to Section 12.6 Immunogenicity and modified to align with the FDA draft guidance for industry <i>Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling--Content and Format</i> (February 2022).³
8 USE IN SPECIFIC POPULATIONS	Section 8.1, <i>Pregnancy</i>: Modified as recommended by DPMH to include a <i>Clinical Considerations</i> subsection stating that data suggest there are risks to the mother and the fetus associated with RA and UC in pregnancy, which is consistent with other approved biological products approved for UC. Section 8.4, <i>Pediatric Use</i>: This describes the basis of approval for pediatric UC by clarifying efficacy in pediatric patients with UC is supported by evidence from adequate and well-controlled studies in adults with additional data from the pediatric open-label study. The age of pediatric patients studied (4 to 17 years of age) was revised to match the population enrolled in Study UCO3003. A statement was included regarding the similarity of reported adverse reactions between pediatric patients in Study UCO3003 and adults with UC enrolled in previous trials. ADRs of headache and pyrexia (see Section 8.2.4.2 for additional details) were added and the indication was revised to align with the wording in the INDICATIONS AND USAGE section.
10 OVERDOSAGE	This section was removed from labeling because the information did not meet the criteria in 21 CFR 201.57 for toxicity information.
12 CLINICAL PHARMACOLOGY	Section 12.3, <i>Pharmacokinetics</i>: New subsection added for pediatric UC patients. Information was included that the pharmacokinetics of golimumab are predicted to be similar between adult patients and pediatric patients with UC after accounting for the impact of body weight. Also, a statement was added that there is no expected clinically significant difference in golimumab systemic exposure between adult and pediatric patients weighing 15 kg and above who receive the recommended dosage. See Section 6.3.1 for additional details.
14 CLINICAL STUDIES	Section 14.5, <i>Pediatric UC</i>: After the description of the body-surface area dosage regimen used in the trial, a statement was added explaining the difference between the recommended body-weight tiered dosage for pediatric patients weighing 15 to <40 kg and 40 to <45 kg differs from the body surface area-based dosage administered in Study UCO3003 and that there are no anticipated clinically relevant differences in efficacy between recommended and studied pediatric dosages. The efficacy assessment included 66 (not 69) subjects who met Study UCO3003 inclusion criteria of having moderately to severely active UC, based on baseline Mayo scores (3 of the 69 subjects did not have moderate to severely active UC disease). The key demographics of the study population (n=66) were included.

Efficacy results are presented in tabular format for short-term (at Week 6) key efficacy endpoints, including the primary endpoint of clinical remission and the key secondary endpoint of clinical response. Additional secondary endpoints addressing long-term efficacy include clinical remission at Week 54 among patients in clinical response at Week 6, endoscopic improvement at Week 54 among patients in clinical response at Week 6, and clinical remission at Week 54 among subjects in clinical remission at Week 6. The efficacy results on these secondary endpoints were presented descriptively as text below the table to provide meaningful information to providers regarding the anticipated long term efficacy; although the first 2 of these 3 endpoints did not demonstrate superiority to placebo when comparing the lower bound of the 90% confidence interval for the pediatric remission/response rate to the upper bound of the 95% confidence for the adult placebo rate (based a meta-analysis using historical placebo-controlled trials), the results are considered informative based on additional evaluations of the data conducted by the review team (including Bayesian analyses and comparison to adult on-treatment response rates). See Section [8.1.2](#) for additional details.

(b) (4)

(b) (4)

(b) (4)

15 REFERENCES

This section was removed and the reference for the SEER database removed to be consistent with the definition of a listed reference in 21 CFR 201.57.

**17 PATIENT COUNSELING
INFORMATION**

To align with the DOSAGE AND ADMINISTRATION section statements were added that adult and pediatric patients 12 years of age and older may self-inject with the prefilled syringe, and that the SmartJect autoinjector has not been evaluated for pediatric self-administration.

Source: Reviewer table, based upon the Agency's recommended changes to the proposed labeling submitted on July 10, 2025 (under sBLA 125298/s-0572), the review team's labeling revisions communicated to the Sponsor on August 26, 2025, and the Applicant's revised version submitted September 11, 2025.

¹ Simponi Aria (golimumab injection) USPI (dated 4/18/2025):

https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125289Orig1s155,125433Orig1s036Correctedlbl.pdf

² Cimzia (certolizumab pegol) USPI (dated 9/13/2024):

https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125160s275lbl.pdf

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>

Abbreviation(s): PI, Prescribing Information

12 Risk Evaluation and Mitigation Strategies

Because known and potential risks of golimumab for treatment of pediatric UC can be adequately communicated via labeling, a risk evaluation and mitigation strategy is not recommended.

13 Postmarketing Requirements and Commitment

This submitted efficacy supplement fulfills the requirements of PMC #5 (2909-5) issued at the time of sBLA approval for the adult UC indication, as discussed in Section [3.2](#).

No additional postmarketing requirements or commitments are required at this time.

The safety profile of golimumab has been well characterized across multiple indications over many years, and has been updated, when necessary, as evolving safety information was identified from various sources.

Although the primary safety database in pediatric UC is of limited size, the review Division did not issue an additional requirement for long term observational registry study for the following reasons:

1. Informed by the enrollment challenges experienced with the Adult UC registry, increasing accessibility to alternate treatment options, burdens of trial participation, and generally low incidence of pediatric UC, it is not considered feasible to enroll a new cohort of patients into a registry study and generate data in a reasonable timeframe.
2. Further, unique challenges exist in attempting to interpret data derived from a prospective, controlled, observational study in UC patients, including the fact that most pediatric UC patients have prior exposure to other treatments with the same types of risks (malignancy, serious infection, etc.), and are likely to transition from one therapy to another (often within

1 year of starting a TNF blocker), making it difficult to truly isolate any potential additive or new risk that may be incurred from exposure to the study drug.

Routine pharmacovigilance practices are planned, including continued monitoring for potential new safety signals by ongoing postmarketing safety surveillance practices of SAE reports from clinical studies, all safety reports from spontaneous sources, the literature, and ongoing postmarketing registries.

There appears to be sufficient data on the safety of golimumab from the results of extensive studies across multiple indications and postmarketing experience and surveillance activities.

14 Designated Signatory Authority - (Clinical) Comments

I concur with the team's recommendation to approve supplemental BLA 125289/s157 to expand the indication for Simponi (golimumab) to include pediatric patients weighing at least 15kg with moderately to severely active ulcerative colitis.

Efficacy of Simponi in pediatric patients with ulcerative colitis is supported, in part, by extrapolation of efficacy from adequate and well-controlled trials in adults, relying upon the similarity between adults and pediatric patients in disease progression and response to treatment. This sBLA submission included results from Study UCO1001 (a phase 1b, single-arm, open-label study of 35 pediatric UC patients to establish pharmacokinetics and dosing), and Study UCO3003 (a phase 3, single-arm, open-label trial in 69 pediatric patients aged 2 to 17 years). Efficacy was evaluated in 66 subjects who met the inclusion criteria of having moderately to severely active disease of Study UCO3003 based upon clinical remission using the full Mayo score.

The comprehensive evaluation of the efficacy data included a comparison with the results in adult patients with UC that included 1) review of the results of the Applicant's meta-analysis of adult UC studies to derive an external adult placebo rate, and 2) evaluation of similarity between pediatric results and comparable adult results in the similar golimumab treatment exposures. Additionally, the review team utilized a Bayesian approach, borrowing information from adult UC studies to conduct additional analyses, and evaluated exposure-response relationships for efficacy.

The study successfully met its primary efficacy endpoint. At Week 6, 31.8% of patients achieved clinical remission (90% CI: 22.4%-41.2%). This result exceeded the prespecified success criterion (which was defined as the upper bound of the 95% CI of the historical adult placebo rate, 11.2%), derived from a meta-analysis of seven phase 3 adult ulcerative colitis studies conducted using a random-effects model with sample-size weighting. Long-term efficacy was demonstrated with 57.1% of Week 6 remitters maintaining clinical remission at Week 54, meeting the post hoc success criterion for maintenance of remission. The additional evaluations including comparison of response/remission rates between adult and pediatric UC patients,

exposure-response analysis, and Bayesian analyses generally supported the determination of efficacy

Additional population PK modeling and simulations were conducted were conducted to bridge the studied (body surface area based) dosing regimen to the proposed to-be-marketed weight-tiered dosing regimen for subjects (b) (4). There are no anticipated clinically relevant differences in efficacy between the studied dosage regimen administered in the clinical trial and the recommended dosage for pediatric patients at least 15kg. The Applicant initially propose (b) (4)

(b) (4)
An appropriate dosing regimen can be administered to patients weighing at least 15kg using currently approved Simponi 50 mg/0.5 mL and 100 mg/mL PFS and SmartJect autoinjectors.

The safety profile of Simponi in pediatric patients was generally similar to that seen in adults with UC and in trials of other indications; no new safety signals were identified. Additional adverse reactions observed commonly in pediatric patients with UC (headache and pyrexia) were added to the USPI. The Prescribing Information and Medication Guide incorporating pediatric information will be adequate to communicate the potential risks to healthcare providers and patients; a REMS will not be required.

This sBLA submission fulfilled the following PMC issued at the time of sBLA approval for the adult UC indication:

PMC #5 (2909-5): Conduct a study to evaluate the effectiveness and safety of Simponi (golimumab) in pediatric patients 5 to <18 years of age with moderately to severely active UC. The study should be designed to establish that the dose regimen(s) of Simponi (golimumab) identified in PMC #4 is (are) effective and safe for induction treatment, as well as for continued treatment after induction. Pharmacokinetic measurements should be conducted for exposure-response (E-R) analysis. Collect serum samples for immunogenicity testing and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy, and safety.

No additional post-marketing studies will be required or recommended.

15 Appendices

15.1. References

See footnotes.

15.2. Financial Disclosure

As provided in FDA 3455 Forms, the investigator identified below who participated in Study CNT0148UCO3003 holds financial interests that are required to be disclosed.

The details of the investigator with disclosable financial arrangements and interests, per Form FDA 3455, are summarized below:

- (b) (6)

has disclosed significant payments of other sorts from the sponsoring company totaling more than \$25,000, excluding the cost of conducting clinical trials. (b) (6)

(b) (6)) has disclosed significant payments of other sorts from the sponsoring company named on line 1 of this form, the total of which exceeds USD 25,000, excluding the cost of conducting this trial or other clinical trials.

This site enrolled (b) (6) out of 69 total subjects in the study. (b) (6)

Per the Applicant, given the nature of the design and length of this study and the limited number of subjects enrolled by the investigator with financial interests, it is not expected that this financial interest would bias the outcome of the clinical study.

Table 52. Covered Clinical Study (Name and/or Number): Study UCO3003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>229</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>Exceeding \$25,000 (1)</u> Proprietary interest in the product tested held by investigator: <u>none</u>		

Significant equity interest held by investigator in study: 0		
Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.3.1. Pharmacometrics Assessment

15.3.1.1 Pharmacometrics Executive Summary

The PK modeling and simulation adequately support the following dosage for treatment of moderately to severely active UC in adults and pediatric patients (b) (4) weighing 15 kg and above, which is expected to yield no clinically relevant golimumab exposure differences compared to the pediatric dosage studied in pivotal Study UCO3003.

- Pediatric patients with UC weighing 40 kg and above: 200 mg SC at Week 0, followed by 100 mg SC at Week 2, and then 100 mg SC Q4W (hereafter referred to as “200 mg → 100 mg”)
- Pediatric patients with UC weighing 15 to <40 kg: 100 mg SC at Week 0, followed by 50 mg SC at Week 2, and then 50 mg SC Q4W (hereafter referred to as “100 mg → 50 mg”)

Table 53. FDA – Assessment of Model Risk

Element	Details
Question of interest	• Is the dosage administered in Study UCO3003 appropriate for treatment of UC in pediatric patients (b) (4) ? • Is the proposed dosage appropriate for treatment of UC in pediatric patients (b) (4) r?
Consequence of wrong decision	The consequence of approving an inappropriate pediatric golimumab dosage is <u>moderate/high</u> , as inadequate dosage could potentially lead to lack of efficacy while an unnecessarily high dosage could potentially lead to safety issues in pediatric patients with UC.

Element	Details
Context of use	Population PK modeling and simulation analysis was utilized to predict golimumab exposures in pediatric patients with UC following various dosage regimens and assess the appropriateness of various alternative dosage regimens using exposure-matching to the studied dosage in Study UCO3003 Exposure-response and dose-response analyses in pediatric and adult patients with UC were utilized to investigate the potential impacts on clinical efficacy of alternative dosage regimens compared to the studied dosage in Study UCO3003.
Model influence	- The model influence on assessment of dosage administered in Study UCO3003 is <u>low</u>. - Pediatric patients weighing <45 kg received body surface area-based dosage in Study UCO3003 to minimize differences in exposure across body size (i.e., body surface area and body weight). - Pediatric patients weighing 45 kg and above received 200 mg → 100 mg, which is the same as the currently approved recommended adult dosage. - The model influence on assessment of the proposed dosage is <u>moderate/high</u>. - The proposed pediatric dosage is similar to the dosage administered in Study UCO3003 in some proportion of pediatric patients. However, the proposed pediatric dosage is up to 40% lower and up to 40% higher compared to individual dosages studied in UCO3003, depending on the individual body surface area and body weight. - The proposed pediatric dosage regimen was not investigated in a clinical trial. - The appropriateness of the proposed pediatric dosage regimen was assessed by exposure-matching to pediatric patients with UC in Study UCO3003 with additional exposure data from adult patients with UC in Studies T17 and T18.
Model risk	Modeling contributes <u>moderate/high risk</u> to the assessment of golimumab dosage in pediatric patients with UC.

Source: FDA Review

Abbreviations: PK, pharmacokinetic; UC, ulcerative colitis

Table 54. FDA – Evaluation and Criteria Considered in Pharmacometrics Review

Methodology	Objective	Model Evaluation	Section
Population pharmacokinetic modeling and simulation	- To characterize pharmacokinetics following SC administration of golimumab in pediatric patients with UC - To predict golimumab exposure in pediatric patients with UC following various alternative dosage regimens - To assess the appropriateness of alternative dosage regimens using exposure-matching to the studied dosage in Study UCO3003 - To derive individual predicted exposures for E-R efficacy analysis.	- Standard evaluation of Applicant's popPK model - Comparison of exposure across study, age group, and dosage regimen - Exposure-matching to the studied dosage in Study UCO3003	15.3.1.2

Methodology	Objective	Model Evaluation	Section
Exposure-efficacy and dose-efficacy analysis	To investigate the potential impacts on clinical efficacy of alternative dosage regimens compared to the studied dosage in Study UCO3003	- Comparison of efficacy across exposure quartiles and univariate logistic regression - Comparison of exposure-efficacy relationships across different age subgroups and dosage regimens - Intratrial or cross-trial comparison of clinical efficacy rates at Week 6 across dose regimens - Assessment of potential confounding factors impacting E-R analysis	15.3.1.3

Source: FDA Review

Abbreviations: E-R, exposure-response; popPK, population pharmacokinetics; SC, subcutaneous; UC, ulcerative colitis

15.3.1.2 Population PK Modeling and Simulation Assessment

The Applicant's final popPK model was determined to be adequate for the purpose of predicting exposure following SC administration of golimumab in adult and pediatric patients aged 4 years and older weighing 15 kg and above with UC. PopPK modeling and simulation support the appropriateness of the following dosage in pediatric patients with UC:

- Pediatric patients with UC weighing 40 kg and above: 200 mg SC at Week 0, followed by 100 mg SC at Week 2, and then 100 mg SC Q4W (hereafter referred to as "200 mg → 100 mg")
- Pediatric patients with UC weighing 15 to <40 kg: 100 mg SC at Week 0, followed by 50 mg SC at Week 2, and then 50 mg SC Q4W (hereafter referred to as "100 mg → 50 mg")

The final popPK model was developed using PK data in 960 adult patients with UC from Studies C0524T17 and C0524T18. [Table 55](#) summarizes the final parameter estimates of the popPK model. The FDA reviewer was able to run the final model without significant discrepancies from the Applicant's results. The model adequately characterized pharmacokinetics of golimumab following SC administration in adult patients with UC.

Table 55. Parameter Estimates of the Final Refined PopPK Model for SC Administration of Golimumab in Adult Participants With UC, Studies C0524T17 and C0524T18

Parameters, unit	Estimate	RSE (%)	Shrinkage (%)
CL/F (L/day) ^a	0.948	1.61	--
CL/F-Baseline WT (kg)	0.750 FIX	--	--
CL/F-Baseline ALB (g/dL)	-1.14	8.54	--
CL/F-IRP	0.185	15.1	--
V/F (L) ^b	13.5	1.77	--
V/F-Baseline WT	1.00 FIX	--	--
k _a (day ⁻¹)	0.943	10.4	--
IIV of CL/F (%CV)	32.4	3.84	8.61
IIV of V/F (%CV)	28.7	9.67	32.7
Correlation between IIV of CL/F and V/F	0.484	--	--
Proportional residual error (%)	27.4	2.77	--
Additive residual error (µg/mL)	0.121	15.8	--

ALB=albumin; CL/F=apparent clearance; CV=coefficient of variation ($\sqrt{\exp(\text{variance}) - 1} \times 100\%$); exp=exponential; IIV=inter-individual variability; IRP=immune response (antibodies to golimumab) positive (YES=1/NO=0); k_a=first-order absorption rate constant; PopPK=population pharmacokinetics; RSE=relative standard error; SC=subcutaneous; UC=ulcerative colitis; V/F=apparent volume of distribution; WT=body weight.

$$^a \quad CL/F \text{ (L/day)} = 0.948 \times \left(\frac{WT}{70}\right)^{0.75} \times \left(\frac{ALB}{4.2}\right)^{-1.14} \times (1 + 0.185 \times IRP)$$

$$^b \quad V/F \text{ (L)} = 13.5 \times \left(\frac{WT}{70}\right)^1$$

Source: Table 9 in Applicant's Population PK Report (seqn0534)

In the next step of the Applicant's popPK analysis, model parameters were fixed to the values reported in [Table 55](#) and used to predict individual golimumab concentrations in adult patients (n=960) and pediatric patients aged 4 years and older (n=104) with UC. The number of total patients included in popPK modeling and simulation is summarized by study in [Table 56](#), and patient characteristics are summarized in [Table 57](#).

Although data from pediatric patients with UC were not used to fit or refit the popPK model, the model adequately characterized the pharmacokinetics of SC golimumab in adults and pediatric patients with UC aged 4 years and older. There were no clear differences in model fit between pediatric patients and adult patients with UC, as demonstrated in the goodness-of-fit plots stratified by patient population in [Figure 16](#). There were also no clear differences in model fit between clinical studies (Studies C0524T17, C0524T18, UCO1001, or UCO3003), body weight categories (15 to <40 kg, 40 to <90 kg, and 90 kg and above), or age categories (4 to <6 years [n =2], 6 to <12 years, 12 to <18 years, and 18 years and older).

Table 56. Overview of Studies and Data Included in the PopPK Analysis

Study (Phase)	Population	ROA	N ^a	Treatment		PK Data Included	PK Sample Scheme
				Induction (Week 0 and Week 2)	Maintenance (Week 6 and q4w thereafter)		
CNT0148UCO3003 (Phase 3), referred to as Study UCO3003	Pediatric UC (2-17 years)	SC	69	≥45 kg: 200 mg→100 mg <45 kg: 120 mg/m ² →60 mg/m ²	≥45 kg: 100 mg <45kg: 60 mg/m ²	Up to Week 54	Weeks 0, 2, 6, 10, 14, 18, 26, 34, 36, 42, 50, 54 at pre-dose
CNT0148UCO1001 (Phase 1b), referred to as Study UCO1001	Pediatric UC (2-17 years)	SC	35	≥45 kg: 200 mg→100 mg <45 kg: 90 mg/m ² →45 mg/m ²	≥45 kg: 100 mg <45 kg: 45 mg/m ²	Up to Week 54	Week 0 (Day 1 and Day 4) and at pre-dose for Weeks 2, 4, 6, 14, 18, 30, 42, 54
C0524T17 ^b (Phase 2/3), referred to as Study T17 C052T18 ^b (Phase 3), referred to as Study T18	Adult UC	SC	960	(C0524T17) ^c 100 mg→50 mg 200 mg→100 mg 400 mg→200 mg	(C0524T18) ^c 50 mg 100 mg	C0524T17: Completed (Week 6) ^b C0524T18: Up to Week 54 ^b	C0524T17: Weeks 0, 2, 4, and 6 at pre-dose C0524T18: Weeks 0, 4, 8, 12, 20, 28, 36, and 44 at pre-dose A random sample was taken between Weeks 16 and 24, and at Weeks 30 and 54.

N=number of participants; PK=pharmacokinetic(s); PopPK=population PK; q4w=every 4 weeks; ROA=route of administration; SC=subcutaneous; UC=ulcerative colitis.

^a PopPK analysis population.

^b The participants were initially enrolled in Study T17 to receive 2 induction doses at Week 0 and Week 2, and successively enrolled in Study T18 to receive the maintenance dose starting from Week 6 of Study T17 (=Week 0 of Study T18). The PK data up to Week 54 of Study T18 (=60 weeks after the first induction dose in Study T17) were included in the analyses (See Section 3.2).

^c The participants were allocated to either dose arm listed.

Source: Table 1 in Applicant's PopPK Report

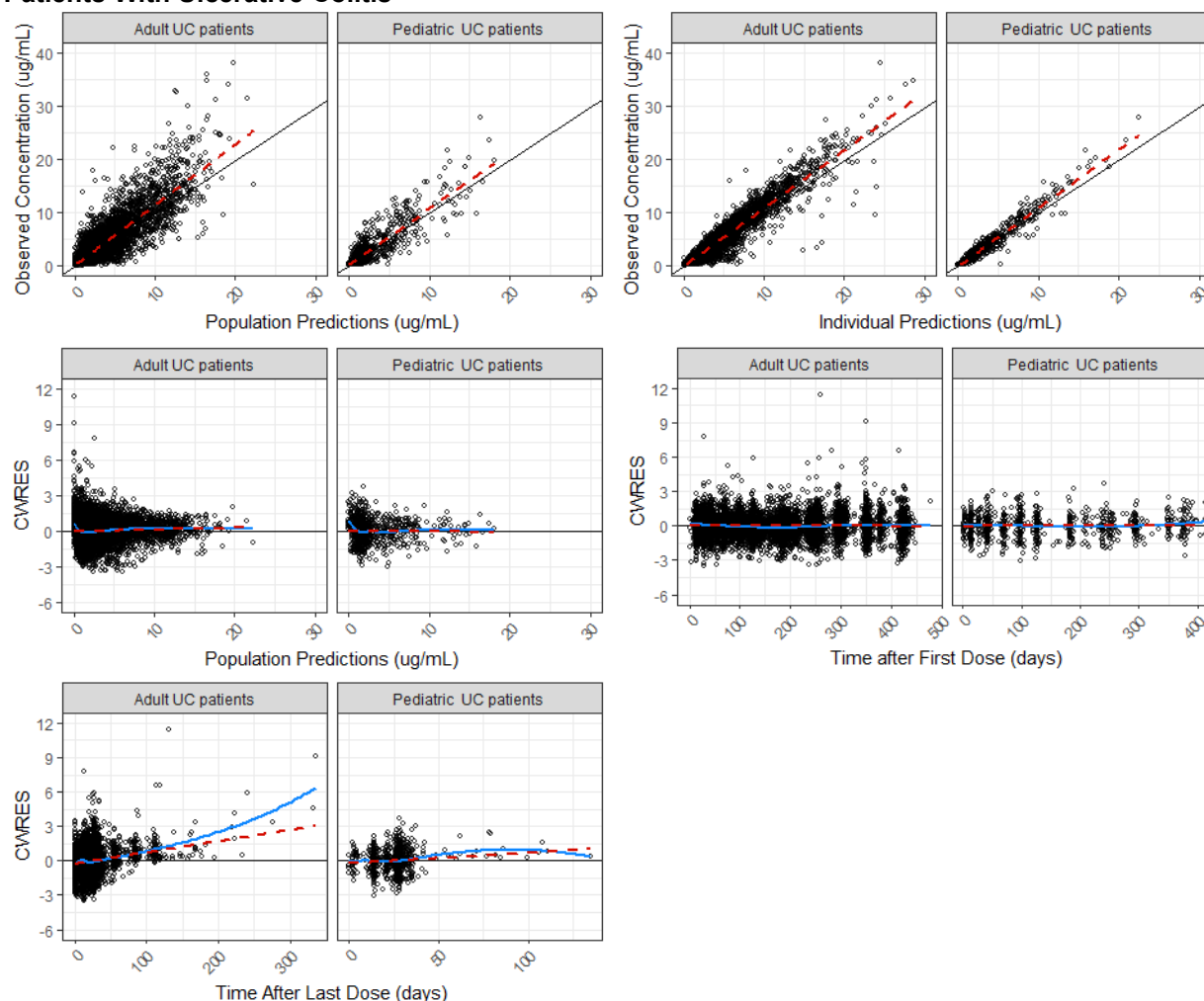
Table 57. Summary of Covariates in Patients With PK Data Following SC Golimumab Administration

Covariate	Category/Statistic	Studies C0524T17 and C0524T18	Study UCO1001	Study UCO3003	Overall
		N=960	N=35	N=69	N=1064
Age category	2 to <6 years [n (%)]	0	0	2 (2.9%)	2 (0.2%)
	6 to <12 years [n (%)]	0	10 (28.6%)	13 (18.8%)	23 (2.2%)
	12 to <17 years [n (%)]	0	20 (57.1%)	45 (65.2%)	65 (6.1%)
	17 years and older [n (%)]	960 (100%)	5 (14.3%)	9 (13%)	974 (91.5%)
Baseline age (years)	Mean (SD)	40.2 (13.3)	13.4 (3.2)	13.4 (3.3)	37.6 (14.9)
	Median	38.5	15	14	37
	Min - max	18-78	6-17	4-17	4-78
Baseline body surface area (m ²)	Mean (SD)	1.86 (0.25)	1.49 (0.38)	1.51 (0.33)	1.83 (0.28)
	Median	1.85	1.52	1.52	1.83
	Min - max	1.17-2.75	0.79-2.63	0.69-2.38	0.69-2.75
Baseline weight (kg)	Mean (SD)	73.8 (17.71)	51.7 (22.7)	52.4 (17.6)	71.7 (19.0)
	Median	72.1	50.6	51.2	70
	Min - max	33-149.7	19.7-134	16.4-106.8	16.4-149.7
Sex	Female [n (%)]	418 (43.5%)	18 (51.4%)	37 (53.6%)	473 (44.5%)
	Male [n (%)]	542 (56.5%)	17 (48.6%)	32 (46.4%)	591 (55.5%)
Baseline creatinine clearance (mL/min)*	Mean (SD)	110.47 (32.3)	106.4 (59.8)	131.4 (37.7)	112.3 (33.3)
	Median	105.9	113.0	128.5	107.0
	Min - max	32.8-270.5	0-262.8	52.1-241.6	32.8-270.5
Baseline albumin (g/L)	Mean (SD)	4.19 (0.43)	3.05 (1.74)	4.45 (0.39)	4.2 (0.44)
	Median	4.2	3.8	4.5	4.3
	Min - max	2.5-5.3	0-4.7	2.9-5.2	2.5-5.3
Subject-level ADA status	ADA positive [n (%)]	201 (20.9%)	4 (11.4%)	15 (21.7%)	220 (20.7%)
	Not ADA positive [n (%)]	750 (78.1%)	31 (88.6%)	54 (78.3%)	835 (78.5%)
	Unevaluable [n (%)]	9 (0.9%)	-	-	9 (0.8%)

Source: Reviewer's analysis of Applicant's "pooled-pkpd-09aug2024-csv.xpt" dataset, seqn 0534

* Creatinine clearance was estimated for patients aged 2 to <12 years using the Schwartz equation. Creatinine clearance was estimated for patients aged 12 years and older using the Cockcroft-Gault equation.

Abbreviations: ADA, antidrug antibody; N, number of patients in study; n, number of patients meeting criteria; PK, pharmacokinetic; SC, subcutaneous; SD, standard deviation

Figure 16. Goodness-of-Fit of the Applicant's Final Population PK Model in Adult and Pediatric Patients With Ulcerative Colitis

Source: Reviewer Analysis of Applicant's population PK data and model ("CNT0148_run04aEBE.mod") submitted with seqn 0534
 LOESS in solid blue; linear regression in dashed red.

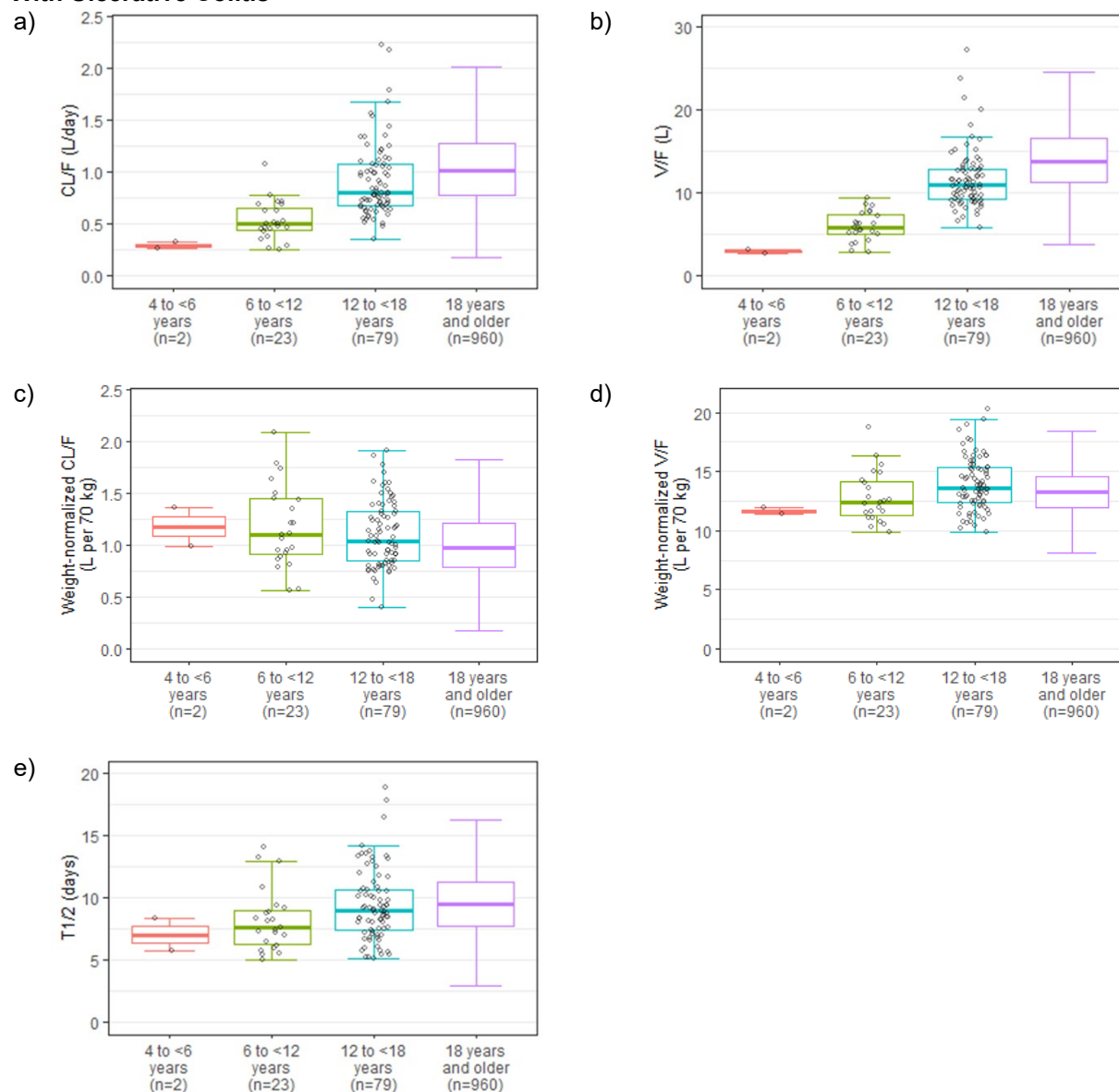
Abbreviations: CWRES, conditional weighted residuals; PK, pharmacokinetic; UC, ulcerative colitis

The popPK model indicates that higher apparent clearance (CL/F) was associated with higher body weight, lower serum albumin, and positive subject-level antidrug antibody status. Higher apparent volume of distribution (V/F) was associated with higher baseline body weight. Fixed allometric scaling exponents of 0.75 and 1.0 were used for CL/F and V/F, respectively.

Due to the association between lower body weight and younger age groups, CL/F and V/F were generally higher in older subgroups compared to younger subgroups (see [Figure 17a](#) and [Figure 17b](#) for CL/F and V/F, respectively). There were no clear differences in body weight-normalized CL/F, body weight-normalized V/F, or elimination half-life across age group ([Figure 17c](#), [Figure 17d](#), and [Figure 17e](#), respectively). Therefore, no clear PK differences were observed according to age or age group after accounting for differences in body weight.

The youngest patient with golimumab PK data following golimumab SC administration was 4 years old at baseline. The pharmacokinetics of golimumab SC is not expected to differ in patients aged 2 to <4 years compared to patients aged 4 years and older after accounting for body weight. The pharmacokinetics of golimumab SC has not been characterized in patients younger than 2 years of age or weighing less than 15 kg.

Figure 17. Individual Predicted Golimumab PK Parameters According to Age Group in Patients With Ulcerative Colitis



Source: Reviewer's analysis of Applicant's model control file "CNT0148_run04aEBE.mod", seqn 0534

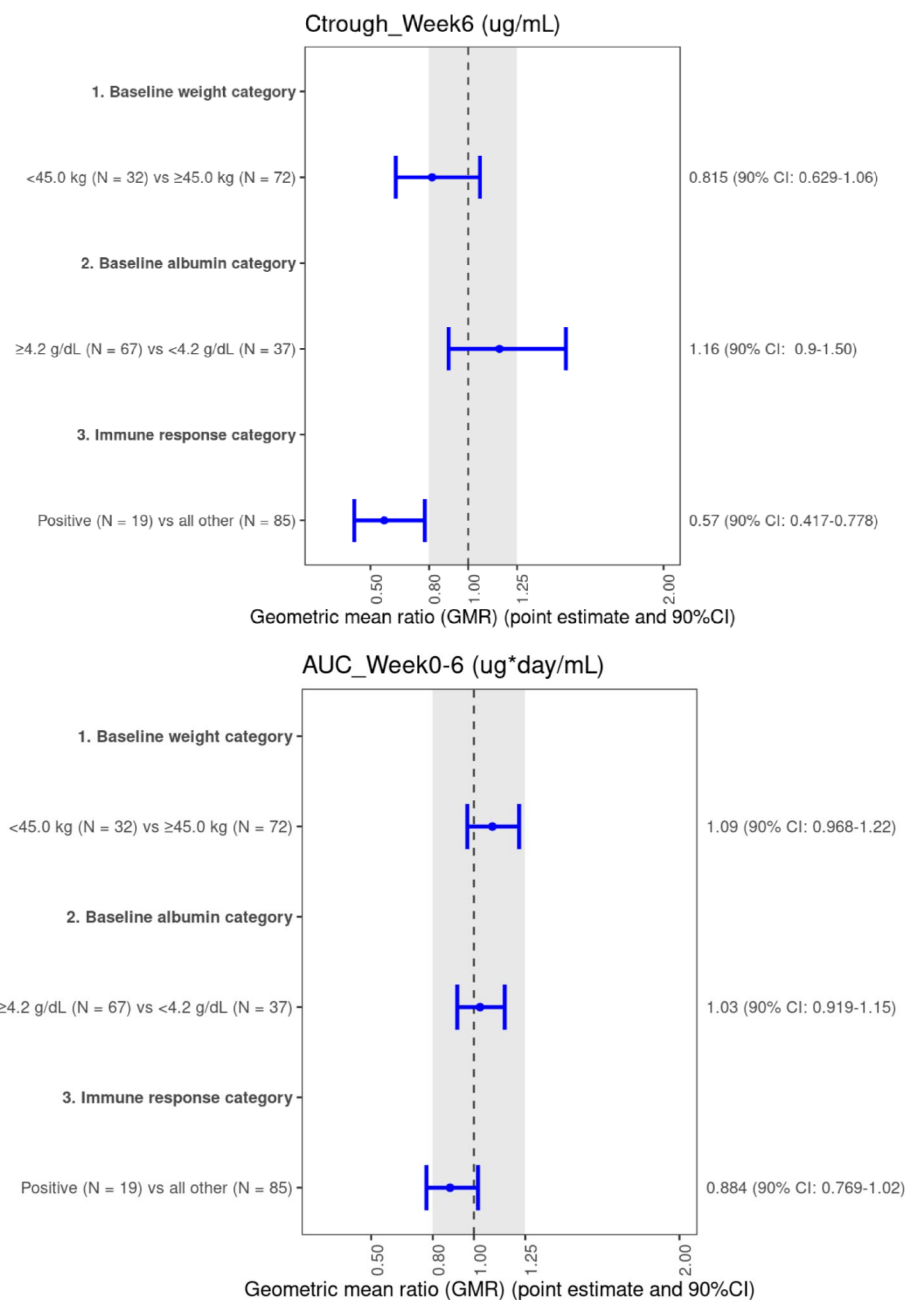
Black points = individual predicted parameter values in pediatric patients. Individual parameter values not displayed for adult patients.

Abbreviations: CL/F, apparent clearance; n, number of patients in age group; PK, pharmacokinetic; T1/2, elimination half-life; V/F, apparent volume of distribution

The final popPK model was used to predict exposure in pediatric patients following the planned Study UCO3003 dosage regimen (i.e., 200 mg → 100 mg in patients weighing ≥ 45 kg and 120 mg/m² → 60 mg/m² in patients weighing < 45 kg). Forest plots of covariate effects on Week 0 to 6 exposure are displayed in [Figure 18](#).

Pediatric patients with higher albumin at baseline (≥ 4.2 g/dL) are predicted to have 16% higher geometric mean Week 6 trough concentration (C_{trough}) and 3% higher geometric mean Week 0 to 6 AUC compared to pediatric patients with baseline albumin below 4.2 g/dL. The impact of baseline albumin on golimumab exposure is not expected to result in any clinical efficacy or safety differences.

Pediatric patients with a positive ADA sample are predicted to have 43% lower geometric mean Week 6 C_{trough} and 11.6% lower geometric mean Week 0 to 6 AUC compared to subjects without any positive ADA samples. Potential associations between ADA and clinical outcomes are evaluated in Section [6.2.2](#).

Figure 18. Forest Plot of Golimumab Week 0 to 6 Exposure by Covariate Subgroup in Pediatric Participants Following Planned Study UCO3003 Dosage

Source: Figure 6 and Attachment 13 in Applicant's PopPK Report

All participants were assumed to receive golimumab doses as instructed in Study UCO3003 (i.e., 200 mg at Week 0 and 100 mg at Week 2, and 100 mg Q4W starting at Week 6 for participants weighing ≥45 kg; 120 mg/m² at Week 0 and 60 mg/m² at Week 2, and 60 mg/m² Q4W starting at Week 6 for participants weighing <45 kg).

Abbreviations: AUC_Week0 to 6, area under the concentration-time curve from Week 0 to Week 6; CI, confidence interval; C_{trough_Week0-6}, trough concentration at the end of Week 0 to Week 6; GMR, geometric mean ratio; N, number of participants; Q4W, every 4 weeks

The reviewer calculated individual predicted exposures in pediatric and adult patients with UC using actual dosing records, which are summarized according to study and dosage regimen in [Table 58](#).

The PK modeling and simulation suggest that the studied phase 3 dosage in pediatric patients weighing <45 kg (i.e., 120 mg/m² → 60 mg/m²) resulted in somewhat higher C_{max} and AUC during induction treatment compared to the approved adult dosage (i.e., 200 mg → 100 mg) in adult patients with UC. The largest median difference occurred with the first dose (i.e., Week 0 to 2). Compared to adults who received 200 mg → 100 mg, pediatric patients who received 120 mg/m² → 60 mg/m² had 51% higher C_{max} (18.3 versus 11.8 µg/mL), 52% higher AUC (139 versus 91.4 µg·day/mL), and 37% higher C_{trough} (10.9 versus 8.0 µg/mL) from Week 0 to 2. However, [Table 58](#) shows that pediatric patients who received 120 mg/m² → 60 mg/m² had lower exposures than adult patients in Study C0524T17 who received 400 → 200 mg. FDA assessment previously determined that there were no clear safety differences between the 400 mg → 200 mg and 200 mg → 100 mg induction treatment cohorts in Study C0524T17 adult patients with UC (*source: 15 May 2013 FDA Clinical Review of sBLA 125289 supplements 77, 78, and 79 [Reference ID: 3308680]*) and so no safety concerns were identified based on PK exposure following the Study UCO3003 pediatric dosage.

Table 58. Individual Predicted Exposure in Adult and Pediatric Patients With Ulcerative Colitis by Study and Dosage

Parameter	Statistics	Study UCO1001		Study UCO3003		Study C0524T17	
		90 → 45 mg/m ² in Patients Weighing <45 kg	200 → 100 mg in Patients Weighing ≥45 kg	120 → 60 mg/m ² in Patients Weighing <45 kg	200 → 100 mg in Patients Weighing ≥45 kg	200 → 100 mg in Adult Patients	400 → 200 mg in Adult Patients
Week 0 to 2	N	15	19	17	52	325	327
C _{max} (µg/mL)	Geo mean (CV%)	12.4 (26.1%)	13.3 (31.1%)	18.3 (21%)	14.1 (28.1%)	11.8 (28.9%)	23 (28.9%)
	Median	12.3	13.5	18.3	14.4	12.1	22.3
	Min - max	9.2-18.9	5.8-22.5	11.2-27.1	6.7-23.1	5.2-24.8	11.9-65.3
C _{trough} (µg/mL)	Geo mean (CV%)	7.1 (34.3%)	9.4 (32.8%)	11 (19.4%)	8.8 (32.5%)	7.8 (33%)	15.2 (34.5%)
	Median	6.6	10.1	10.9	8.9	8	14.9
	Min - max	4.5-12.8	3.8-14.8	7.7-16	3.9-17.3	3-17.1	4.9-48.3
AUC (µg·day/mL)	Geo mean (CV%)	92.4 (27.8%)	105 (31.1%)	137.7 (19.6%)	107.3 (28.6%)	91.5 (29.2%)	177.9 (29.6%)
	Median	92.6	107.9	138.7	111	91.4	174.7
	Min - max	67.2-143.7	44.9-174.2	88-203.5	51.2-180.3	43.3-194.6	87.1-521.6
Week 0 to 6	N	15	19	17	52	325	327
C _{trough} (µg/mL)	Geo mean (CV%)	1.4 (166.5%)	2.8 (78.3%)	2.1 (104.6%)	2.1 (108.2%)	1.8 (102.5%)	3.4 (103.6%)
	Median	1.2	3.5	2	2.2	2	4
	Min - max	0.3-6.2	0.7-7.6	0.4-10.7	0.3-9.3	0-12.3	0-31.9
AUC (µg·day/mL)	Geo mean (CV%)	243.1 (34%)	345.1 (34.3%)	381.2 (19.9%)	311.5 (33.9%)	275.7 (34.5%)	538.8 (36.3%)
	Median	227.4	362.9	393.6	307.1	277.1	528.3
	Min - max	151.2-464.5	129.4-510.8	272.8-539.4	139.2-657	107-606.8	192.5-1823.2
Week 50 to 54	N	7	7	7	32	-	-
C _{max} (µg/mL)	Geo mean (CV%)	8.6 (23.3%)	8.9 (22.7%)	11.9 (20.4%)	8.5 (30.1%)	-	-
	Median	8.7	9	12.1	8.8	-	-
	Min - max	6.6 - 12.3	5.9-11.3	8.8-16.7	3.8-14.6	-	-
C _{trough} (µg/mL)	Geo mean (CV%)	1 (81.6%)	2.5 (44.6%)	1.6 (61.7%)	1.4 (69.5%)	-	-
	Median	1.1	3	1.7	1.4	-	-
	Min - max	0.3-3.5	1-3.3	0.7-3.4	0.3-6.1	-	-
AUC (µg·day/mL)	Geo mean (CV%)	114.3 (35.9%)	153.3 (28.3%)	162.7 (23.1%)	122.3 (38.5%)	-	-
	Median	107	158.9	159.4	128.2	-	-
	Min - max	69.3-211.6	84.9-195.2	124.1-226.3	45.5-285.4	-	-

Source: Reviewer's analysis

The following notation is used to describe dosage: e.g., patients who received 200 → 100 mg were administered 200 mg at Week 0, 100 mg at Week 2, and then 100 mg at Week 6 and Q4W thereafter.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; C_{trough}, trough concentration; CV, coefficient of variation; N, number of subjects in treatment group;

Q4W, every 4 weeks

The PK modeling and simulation adequately support the weight-tiered dosage described in [Table 4](#) of Section [6.1](#) for the treatment of moderately to severely active UC in pediatric patients weighing 15 kg and above. Refer to Section [6.3.1](#) for the assessment of alternative golimumab dosage in pediatric patients with UC.

15.3.1.3 Exposure-Response Assessment

The final popPK model (refer to [Table 55](#) in Section [15.3.1.2](#)) was used to derive individual exposure in patients with UC from Studies C0524T17, C0524T18, UCO1001, and UCO3003. [Table 59](#) summarizes the number of patients with E-R data according to study and dosage. Overall, the E-R efficacy analysis did not identify any concerns with the golimumab dosage in [Table 4](#) in Section [6.1](#) from a clinical pharmacology perspective.

Table 59. Overview of Studies and Data Included in the Exposure-Response Analysis

ER Endpoints	Study	Treatment of Golimumab		Number of Participants
		Induction dose regimen (Week 0 and Week 2)	Maintenance dose regimen (Week 6 and thereafter)	
Week 6 (Induction)	UCO1001 (pediatric)	≥45 kg: 200→100 mg	-	19
		<45 kg: 90→45 mg/m ²	-	15
	UCO3003 (pediatric)	≥45 kg: 200→100 mg	-	52
		<45 kg: 120→60 mg/m ²	-	17
	T17 ^a (adult)	200→100 mg	-	250
		400→200 mg	-	255
Week 54 (Maintenance)	UCO3003 (pediatric)	(≥45 kg: 200→100 mg)	≥45 kg: 100 mg q4w	23
		(<45 kg: 120→60 mg/m ²)	<45 kg: 60 mg/m ² q4w	6
	T18 ^b (adult)	(100→50 mg, 200→100 mg, or 400→200 mg)	50 mg q4w	88
			100 mg q4w	84

Source: Table 5 in Applicant's PopPK/E-R Report

Data from study sites 6706, 7257, and 7407 in Studies T17 and T18 were excluded due to findings of investigator misconduct. The sites were also excluded from the efficacy analyses (Clinical Study Reports Correction T17 2013; T17 2010; T18 2016). For the ER analysis in the induction phase (i.e., Week 6), the model-derived Week 0 to 6 C_{trough} was used as exposure variable. The ER analysis was conducted on the dichotomous efficacy variables (clinical remission, clinical response, and mucosal healing, as assessed by Mayo score at Week 6). For the ER analysis in the maintenance phase (i.e., Week 54), the model-derived Week 50 to 54 C_{trough} was used as exposure variable. The ER analysis was conducted on the dichotomous efficacy variables (clinical remission, and mucosal healing, as assessed by the Mayo score at Week 54).

^a Data at 100 mg→50 mg induction treatment group in Study T17 were not included in the efficacy analysis sets, thus not included in the ER analysis population.

^b The participants were initially enrolled in Study T17 to receive 2 induction doses, and successively enrolled in Study T18 to receive the maintenance dose. The participants received an induction dose of either 100 mg→50 mg, 200 mg→100 mg, or 400 mg→200 mg.

Abbreviations: C_{trough}, trough concentration; ER, exposure-response; q4w, every 4 weeks

E-R Efficacy During Induction Treatment (Week 0 to 6)

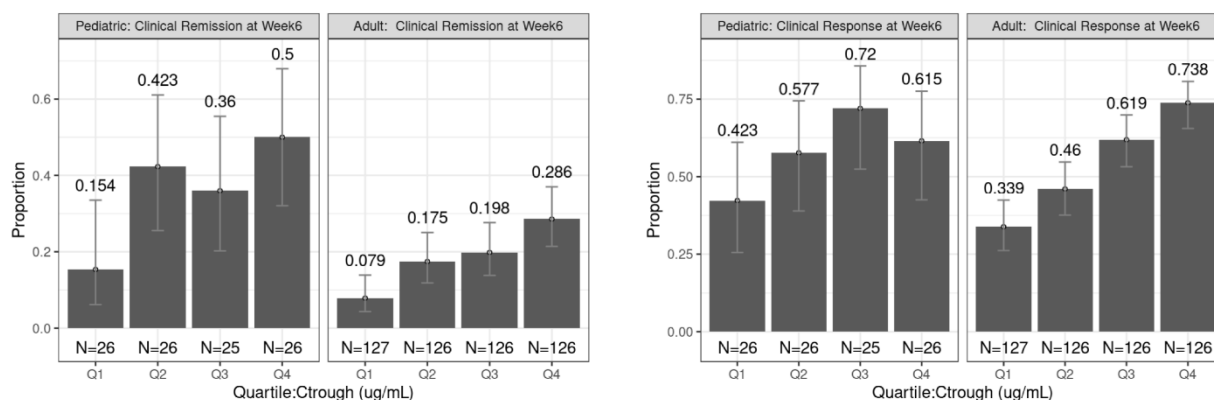
The E-R and dose-response analyses of induction efficacy support the dosage of 100 mg→50 mg for the treatment of moderately-to-severely active UC in pediatric patients weighing 15 kg to <40 kg, and 200 mg→100 mg for the treatment of moderately-to-severely active UC in pediatric patients weighing 40 kg and above.

Both adult and pediatric patients with higher Week 0 to 6 C_{trough} tended to have higher probabilities of clinical response, clinical remission, and endoscopic healing at Week 6. The apparent positive trends between higher C_{trough} quartile and higher rates of efficacy are presented in [Figure 19](#). Similar apparent trends were identified with Week 0 to 2 C_{trough} , Week 0 to 2 AUC, and Week 0 to 6 AUC.

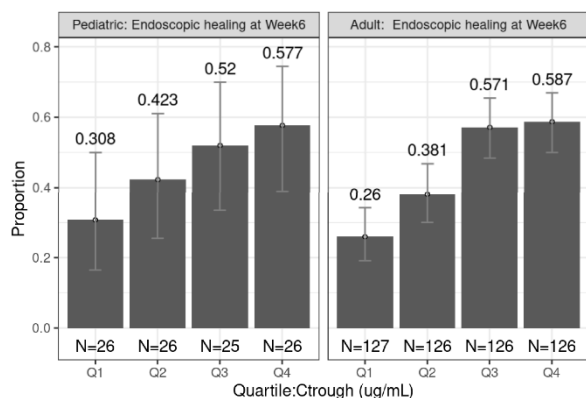
Figure 19. Clinical Endpoints vs. C_{trough} at Week 6 in Pediatric and Adult Patients With UC

(a) Clinical remission based on Mayo score at Week 6

(b) Clinical response based on Mayo score at Week 6



(c) Endoscopic healing at Week 6



$C_{trough, W6}$ range (ug/mL)	Q1	Q2	Q3	Q4
Pediatric (UCO3003 + UCO1001)	(0-0.916)	[0.916-1.82)	[1.82-2.75)	[2.75-9.29)
Adult (T17)	(0-1.28)	[1.28-2.40)	[2.40-4.06)	[4.06-24.1)

Source: Figure 9 in Applicant's PopPK/E-R Report

For each panel block by efficacy endpoint, the left panel is for pediatric participants and the right panel is for adult participants. Error bars indicate the 95% CI of the calculated proportion. Quartile ranges were independently calculated for the pediatric studies and adult studies. The numerical summaries are provided in the tables beneath the figures (Round brackets and square brackets indicate including and excluding the value, respectively).

Abbreviations: CI, confidence interval; C_{trough} , trough concentration; $C_{trough, W6}$, Week 0 to 6 trough concentration; E-R, exposure-response; N, number of participants by quartile; popPK, population pharmacokinetics; Q1, 1st quartile of C_{trough} ; Q2, 2nd quartile of C_{trough} ; Q3, 3rd quartile of C_{trough} ; Q4, 4th quartile of C_{trough} ; UC, ulcerative colitis

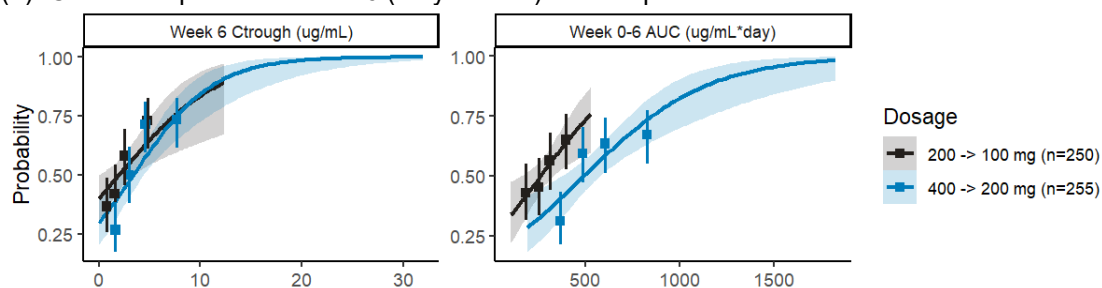
The univariate E-R efficacy trends may be at least partially explained by confounding factors such as target-mediated and time-dependent clearance in the investigated induction dose range. For instance, [Figure 20](#) shows that efficacy is predicted to differ depending on dosage cohort (i.e., 200 mg → 100 mg or 400 mg → 200 mg) in Study C0524T17 despite positive E-R efficacy associations within each cohort and large overlap in exposures between the cohorts. Differences in point estimates of efficacy at a given exposure value were also observed between the 90 mg/m² → 45 mg/m² or 120 mg/m² → 60 mg/m² dosages in Study UCO1001 and UCO3003 pediatric patients, although uncertainty is higher in the pediatric analysis due to smaller sample sizes and cross-trial comparison. Although popPK of golimumab was described adequately by a linear time-independent clearance process (see final popPK model in [Table 55](#) in Section [15.3.1.2](#)), target-mediated or time dependent clearance may still contribute to interindividual and intraindividual variability.

Dose-response analysis did not identify any clinical efficacy differences across the investigated dose levels. Dose-response analysis was somewhat limited by the relatively narrow dose ranges and small pediatric sample sizes, but the results are informative given the lower risk of confounding in dose response trends compared to exposure-response. Within adult patients with UC from Study C0524T17, there were no clinical efficacy differences at Week 6 between the 200 mg → 100 mg (n=257) and 400 mg → 200 mg (n=258) cohorts.³⁹ A cross-trial comparison in pediatric patients with UC who received 90 → 45 mg/m² (n=15) or 120 → 60 mg/m² (n=17) also found no clinical efficacy differences at Week 6, as presented in [Table 11](#) in Section [6.3.1](#). Golimumab exhibits dose proportional pharmacokinetics following doses between 50 mg to 400 mg SC (source: currently approved USPI), and so 25% lower golimumab doses would yield roughly 25% lower exposure. The exposure-response and dose-response assessments both support the conclusion that efficacy following the proposed 100 mg → 50 mg dosage will not differ from efficacy observed in Study UCO3003. There are no efficacy concerns with the golimumab dosage described in [Table 4](#) in Section [6.1](#) for the proposed indication.

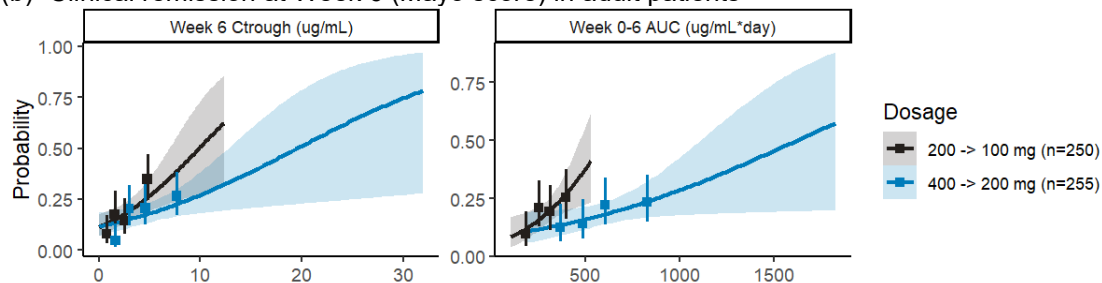
³⁹ FDA Clinical Review of sBLA 125289 supplements 77, 78, and 79. DARRTS Reference ID: 3308680. Dated May 15, 2013.

Figure 20. Probability of Efficacy at Week 6 vs. Exposure in Adult Patients With UC According to Dosage Regimen

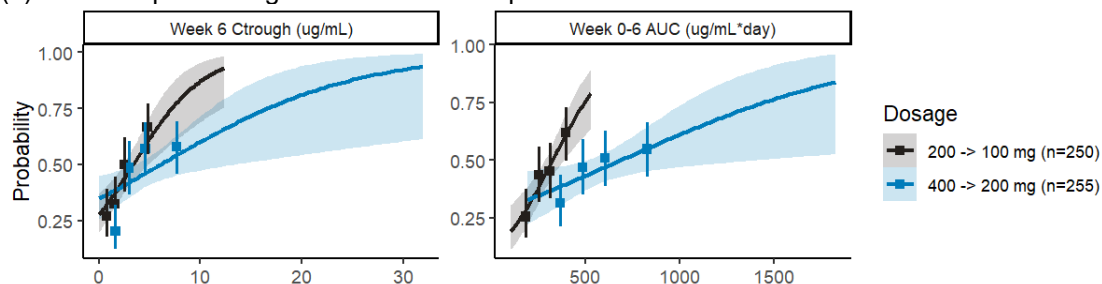
(a) Clinical response at Week 6 (Mayo score) in adult patients



(b) Clinical remission at Week 6 (Mayo score) in adult patients



(c) Endoscopic healing at Week 6 in adult patients



Source: Reviewer's analysis of the Applicant's E-R efficacy datasets (seqn 0534)

Data displayed for adult patients from Study C0524T17 in the Applicant's E-R efficacy datasets.

Squares and error bars = observed efficacy (95% confidence interval) within each exposure quartile.

Abbreviations: AUC, area under the concentration-time curve; C_{trough} , trough concentration; E-R, exposure-response; UC, ulcerative colitis

The SC golimumab pediatric dosage (100 mg → 50 mg for the treatment of moderately-to-severely active UC in pediatric patients weighing 15 kg to <40 kg and 200 mg → 100 mg for the treatment of moderately-to-severely active UC in pediatric patients weighing 40 kg and above) is supported by E-R and dose-response analyses of efficacy in patients with UC. This pediatric dosage is not expected to yield any clinical outcome differences compared to the dosage administered in the pivotal pediatric study UCO3003.

E-R Efficacy During Maintenance Treatment (Week 6 Onward)

No Week 54 E-R efficacy relationships were identified in adults or pediatric patients with UC based on the limited data available, but exploratory conclusions from the E-R maintenance assessment are uncertain due to the following issues:

- Week 54 E-R efficacy data were not available in a relatively large proportion of patients who received golimumab treatment. For instance, Week 54 E-R efficacy data were unavailable in 40 out of 69 pediatric patients in Study UCO3003.
- Adult patients in Study T18 had previously received various induction dosages which may have different impacts on outcomes during the maintenance treatment phase (refer to [Table 59](#)).

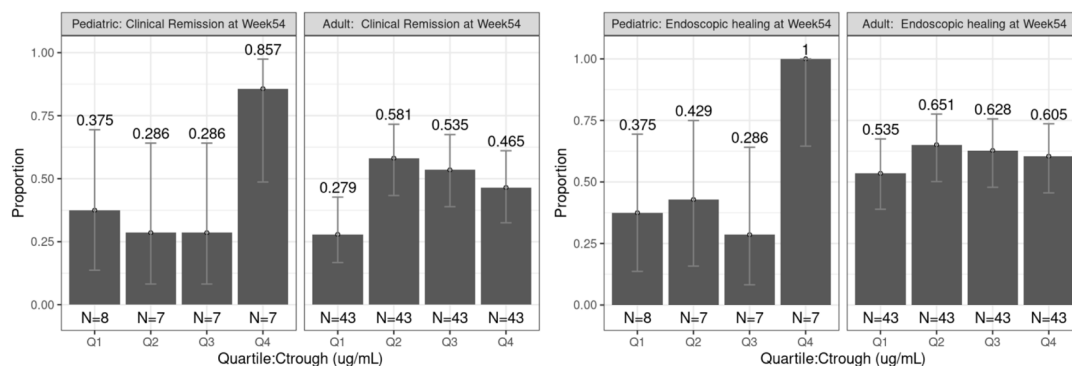
The Applicant's E-R efficacy analysis for maintenance treatment is presented in [Figure 21](#). There were no clear E-R efficacy associations with Week 54 C_{trough} in 29 pediatric patients or 172 adult patients with data at Week 54. Although the highest exposure quartile showed a numerically higher rate of efficacy at Week 54 in pediatric patients with UC, multiple dose levels were not evaluated in Study UCO3003, and the variability showed large overlap across quartiles due to the small sample size.

No significant Week 54 E-R efficacy trends were identified, although there was a relatively large proportion of patients with missing Week 54 E-R efficacy data which introduces uncertainty and potential bias. For example, patients with more favorable efficacy outcomes may have been more likely to receive treatment longer and provide data at Week 54.

Figure 21. Relationships Between Clinical Remission and Endoscopic Healing in the Maintenance Phase and Week 54 C_{trough} in Pediatric and Adult Patients With UC

(a) Clinical remission at Week 54

(b) Endoscopic healing at Week 54



$C_{trough, W54}$ ($\mu\text{g/mL}$)	Q1	Q2	Q3	Q4
Pediatric (UCO3003)	(0.279-0.827)	[0.827-1.69)	[1.69-2.36)	[2.36-8.16)
Adult (T18)	(0-0.672)	[0.661-1.12)	[1.12-1.68)	[1.68-7.01)

Source: Figure 11 in Applicant's PopPK/E-R Report

Notes: In Study T18, the efficacy assessment during the maintenance phase was conducted at Week 54 of Study T18, which corresponds to 60 weeks after the first induction dose in Study T17. The last golimumab dose before the Week 54 efficacy assessment was given at Week 52 of Study T18. In the plots, the efficacy data at Week 54 of Study T18 and the predicted exposure at Week 52 of Study T18 (i.e., 60 and 58 weeks after the first induction dose in Study T17) were used. For each panel block by efficacy endpoint, the left panel is for pediatric participants and the right panel is for adult participants. Error bars indicate the 95% CI of the calculated proportion. Quartile ranges were independently calculated for the pediatric studies and adult studies. The numerical summaries are provided in the tables beneath the figures (Round brackets and square brackets indicate including and excluding the value, respectively).

Abbreviations: CI, confidence interval; $C_{trough, W54}$, trough concentration at Week 54; E-R, exposure-response; N, number of participants; popPK, population pharmacokinetics; Q1, 1st quartile of C_{trough} ; Q2, 2nd quartile of C_{trough} ; Q3, 3rd quartile of C_{trough} ; Q4, the 4th quartile of C_{trough} ; UC, ulcerative colitis

15.4. Clinical Appendices

Table 60. Study Schedule of Activities From Screening Through Week 54, Study UCO3003

Visit	Screening	Week 0	Week 2	Week 6	Week 8	Week 10 ^{cc}	Week 14	Week 18 ^{cc}	Week 22	Week 26 ^{cc}	Week 30	Week 34 ^{cc}	Week 36 ^{cc}	Week 38	Week 42 ^{cc}	Week 46	Week 50 ^{cc}	Week 54	Early Term ^{ad}	Final Safety Visit ^e
Study Procedures ^{a,b,c,d}																				
Screening/ Administrative																				
Informed consent/assent	X																			
Inclusion/exclusion criteria	X	X																		
Medical history and demographics	X																			
Sigmoidoscopy ^g	X																			
Confirmation of prestudy diagnostic UC biopsy results ^h	X																			
QuantiFERON [®] -TB or T-Spot [®] test ⁱ	X																			
Chest radiograph ^j	X																			
Primary tuberculosis screening ⁱ	X	X																		
Stool study including <i>Clostridium difficile</i> toxin ^k	X																			
Screening for up-to-date immunizations per local guidelines ^l	X																			
Hepatitis B testing ^m	X																			
HCV testing	X																			
HIV testing ⁿ	X																			
Serum pregnancy test	X																			

Visit	Screening	Week 0	Week 2	Week 6	Week 8	Week 10 ^{ac}	Week 14	Week 18 ^{ac}	Week 22	Week 26 ^{ac}	Week 30	Week 34 ^{ac}	Week 36 ^{ac}	Week 38	Week 42 ^{ac}	Week 46	Week 50 ^{ac}	Week 54	Early Term ^{df}	Final Safety Visit ^e
Study Procedures ^{a,b,c,d}																				
Study intervention administration ^g																				
Administer SC golimumab ^{h,i}		X	X	X		X	X	X	X	X	X	X		X	X	X	X	X ^p		
Administer IV infliximab ^{q,bb,cc}		X	X	X	X ^r		X		X		X			X		X				
Safety Assessments																				
Physical examination	X						X							X				X	X	X
Vital signs ^s	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study intervention injection-site evaluation		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		
Tuberculosis evaluation ⁱ	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Urine pregnancy test ^l		X	X	X	X ^l	X ^l	X	X ^l	X	X ^l	X	X ^l		X	X ^l	X	X ^l	X	X	
Concomitant medication review	X ^u	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments																				
Sigmoidoscopy ^g				X														X	X	
Mayo Patient Diary Completed ^v	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Mayo score calculation		X		X														X	X	
Partial Mayo score calculation			X		X	X	X	X	X	X	X	X	X	X	X	X	X			
PUCAI score	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IMPACT III ^w		X		X			X				X							X	X	

Visit	Screening	Week 0	Week 2	Week 6	Week 8	Week 10 ^{ac}	Week 14	Week 18 ^{ac}	Week 22	Week 26 ^{ac}	Week 30	Week 34 ^{ac}	Week 36 ^{ac}	Week 38	Week 42 ^{ac}	Week 46	Week 50 ^{ac}	Week 54	Early Term ^{df}	Final Safety Visit ^e
Study Procedures^{a,b,c,d}																				
TUMMY - UC/Observer TUMMY-UC ^x		X		X			X				X							X	X	
CRP		X		X			X						X					X	X	
Fecal calprotectin		X		X			X						X					X	X	
Clinical Laboratory Assessments																				
Hematology, Chemistry	X			X			X			X ^{di}				X				X	X	X
ANA and anti-dsDNA antibodies		X		X						X ^{di}			X					X	X	X
Pharmacokinetics/Immunogenicity																				
Golimumab concentration ^y		X	X	X		X	X	X		X		X	X		X		X	X	X	X
Infliximab concentration ^y		X	X	X	X		X		X		X			X		X		X	X	X
Antibodies to golimumab ^y		X		X			X						X					X	X	X
Antibodies to infliximab ^y		X		X			X											X	X	X
Biomarkers																				
Colonic biopsy (RNA, histology) ^z	X			X														X	X	
Blood RNA ^{aa}	X		X	X														X	X	
Fecal biomarkers		X		X														X	X	

- a. Screening for eligible participants will be performed within 6 weeks before administration of the study intervention.
- b. All participants should return for a final visit, 16 weeks after the last administration of golimumab or 8 weeks after last infliximab administration.
- c. All assessments are to be completed prior to study intervention administration, unless otherwise specified. Visit window should be ± 7 days for each visit up to and including the Week 54 visit.
- d. If there is an early discontinuation of study intervention (before Week 54) these study assessments should be collected. In the case of study termination refer to Section 7.
- e. Participants who discontinue study intervention prior to Week 14 but do not terminate study participation should return for protocol-specified procedures and evaluations up to and including the Week 14 visit. These participants should also return for the final safety visit 16 weeks after the last administration of golimumab or 8 weeks after the last administration of infliximab.
- f. Prior to withdrawal of consent, participants who terminate study participation prior to Week 14 should complete assessments indicated at Week 14.
- g. Should be performed within 2 weeks prior to the administration of study intervention at Week 0, within 2 weeks prior to Week 54, and within 7 days prior to study intervention for Week 6. All study endoscopies (sigmoidoscopy preferred unless colonoscopy clinically indicated) must be performed with study software to permit central reads and scoring in addition to local site study scoring. A colonoscopy will replace a sigmoidoscopy if screening for dysplasia is required. The Sponsor suggests that at least 48 hours must elapse between a colonoscopy with polypectomy or multiple biopsies and the study intervention administration (Week 0) visit.
- h. Previous assessment must be consistent with a diagnosis of UC (eg, crypt distortion, crypt abscess, goblet cell depletion, and continuous distribution).
- i. A tuberculin skin test is required if the QuantiFERON-TB or T-Spot test is not approved/registered in that country, OR the tuberculin skin test is mandated by local health authorities.
- j. Chest radiograph should be obtained during the screening period unless one was obtained within 6 months before screening and the findings recorded in the study source documents. Chest radiographs should be reviewed to assess for potential undiagnosed pulmonary pathologies that may include manifestations of IBD, malignancies, and prior or current infection (eg, latent TB). Chest radiographs must be obtained in all cases when the QuantiFERON-TB or T-Spot test and/or the tuberculin skin test for TB is positive or repeatedly indeterminate.
- k. Stool studies for enteric pathogens, including a stool culture and *Clostridium difficile* toxin assay, that have been performed at a local laboratory during the current episode of disease exacerbation and within 4 months prior to Week 0 may be used for screening. Additional testing such as ova and parasite or *E. coli* 0157:H7 assessments may be performed at the investigator's clinical discretion by the central laboratory. If previous results are unavailable, the central laboratory should be used to perform the tests at screening.
- l. Refer to local immunization guidelines for immunosuppressed participants prior to Week 0.
- m. For additional details, refer to [Appendix 15](#) (Section 10.15).
- n. HIV testing in study participants who are less than 6 years of age is not universally required. It is required in those study participants who are less than 6 years of age and the birth history is unknown (ie, adopted) or has exposure risks (parents with HIV or with risk factors) or at the discretion of the study investigator. In subjects who are less than 6 years of age where testing would be required, if there is a record of a negative HIV test at birth this is acceptable at the discretion of the study physician as long as it is entered into the study record.
- o. Participants' golimumab or infliximab doses for Weeks 0 through 10, inclusive, will be based on the participants' height and weight at Week 0 or, if not available, the most recent height and weight from screening. The same height and weight should be used through Week 10 for golimumab administrations, and the same weight should be used through Week 8 for infliximab administrations. For all dose administrations after Week 10, weight and height at the current visit or the last recorded data will be used to determine study intervention dosage. For AHA of golimumab administrations after Week 54, dosages will be based on the most recent recorded height and weight obtained by the investigator during scheduled office visits.
- p. Golimumab is to be administered only if the participant is eligible and will be participating in the study extension (see [Table 2](#)).
- q. Participants should be evaluated for vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) before and approximately 30 minutes after every SC golimumab administration. Vital signs will be obtained before, approximately every 30 minutes during, and twice (at approximately 30-minute intervals) after completion of the IV infusion(s) of infliximab.
- r. Only if decision is made to escalate the dose of infliximab to 10 mg/kg q8w, and only if participant was given 5 mg/kg Week 6, may the participant receive a dose at Week 8 of infliximab at 5 mg/kg, with subsequent doses of 10 mg/kg starting at Week 14. Infliximab infusions are capped at 1 gm maximum per administration. Additional details are available in [Section 4](#), Study Design. If participant receives infliximab infusion at Week 8, they will need a urine pregnancy test in addition to the other assessments collected from all study participants.
- s. Temperature, pulse/heart rate, respiratory rate, and blood pressure.

- t. All girls of childbearing potential must have a negative urine pregnancy test prior to all study site administration of study intervention. If the visit does not include study intervention administration, a urine pregnancy test is not required unless it is the Week 54 or early discontinuation visit.
- u. Concomitant medications administered up to 30 days before first dose of study intervention must be recorded at screening.
- v. Mayo Patient Diary is completed for 7 continuous days within the 14 days prior to the screening visit. For the screening visit, the Mayo diary will be provided at screening and collected at the Week 0 visit.
- w. Required only if participant is ≥ 10 years of age at Week 0.
- x. Participants will record TUMMY-UC questionnaire data daily for 5 days before the study site visit in a participant diary. For participants less than 8 years old, their caregiver will complete the Observer TUMMY-UC questionnaire. The version used at the Week 0 assessment will be used at all subsequent assessments regardless of participant age.
- y. At drug administration visits, blood samples should be collected prior to study intervention administration (for both golimumab and infliximab) and 1-hour postinfusion (only for infliximab at Weeks 0, 2, 6, and 46). The same blood draw can be used to collect serum samples for measuring study intervention concentration and antibodies to study intervention. Blood sampling in participants with a body weight of 10 kg to 24 kg must be divided between visits during the screening period. Contact Sponsor for details of recommended sampling sequence.
- z. Should be performed within 2 weeks prior to the administration of study intervention at Week 0 and Week 54, and within 7 days for Week 6.
- aa. The RNA blood sample should not be collected at any time point for any participant who at screening has a body weight of 10 kg to <12.3 kg, even if the weight increases to above 12.3 kg during the study. For participants who weighed more at screening but whose body weight falls to between 10 kg to <12.3 kg, the RNA blood sample should not be collected, and blood draws are not to exceed 8.0 mL at any one visit for this weight group.
- bb. At visits during which the participant does not receive an administration of infliximab, the following evaluations do not need to be performed: urine pregnancy and injection-site evaluation.
- cc. For infliximab patients only: Visits at Week 10, 18, 26, 34, 36, 42, 50 and associated study procedures are optional, and only required if investigator implements flexible dosing and is administering infliximab at these time points.
- dd. Infliximab participants who do not have a dosing visit at Week 26 should have hematology, chemistry, ANA, and anti-dsDNA antibodies performed at Week 22 visit.

Source: Applicant's submission, Clinical Protocol Study UCO3003 Amendment 6, pg. 18-25/209, Table 1

Abbreviations: AE, adverse event; AHA, at home administration; ANA, antinuclear antibody; CRP, C-reactive protein; dsDNA, double-stranded DNA; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IV, intravenous; PUCAI, Pediatric Ulcerative Colitis Activity Index; q8w, every 8 weeks; RNA, ribonucleic acid; SC, subcutaneous; TB, tuberculosis; UC, ulcerative colitis

Table 61. Study Schedule of Activities for the Study Extension for Participants Who May Benefit From Continued Treatment: Golimumab Arm, Study UCO3003

	Every 4 Weeks starting Week 54 for participants who receive study intervention administrations at site	Every 12 weeks starting Week 66 for those participants who will perform AHA ⁿ	Every 6 months starting Week 66 through and including Week 90 for all participants	Every year after Week 90 (starting at Week 114) for all participants	Final Safety Visit for the Study ^a
Study Procedures^{b,c,d}					
Study intervention administration					
Administer study intervention ^{e,j,l}	X	X ^m			
Safety Assessments					
Physical examination (including skin examination)			X		X
Vital signs ^f	X	X			X
Height	X	X			X
Weight	X	X			X
Study intervention injection-site evaluation ^{f,j}	X				
Tuberculosis evaluation ^{g,j}	X	X			X
Urine pregnancy test ^h	X	X			
Concomitant medication review ^{j,k}	X	X			X
AE review ⁱ	X	X			X
Efficacy Assessments					
PUCAI score ^p			X		
Clinical Laboratory Assessments					
Hematology, Chemistry			X ^o	X ^o	X
ANA and anti-dsDNA antibodies			X ^o		X

	Every 4 Weeks starting Week 54 for participants who receive study intervention administrations at site	Every 12 weeks starting Week 66 for those participants who will perform AHA ⁿ	Every 6 months starting Week 66 through and including Week 90 for all participants	Every year after Week 90 (starting at Week 114) for all participants	Final Safety Visit for the Study ^a
Pharmacokinetics/Immunogenicity					
Golimumab concentration ⁱ			X ^o	X ^o	X
Antibodies to golimumab ⁱ			X ^o	X ^o	X
a. Participants who discontinue the study and are not continuing golimumab treatment after exiting the study must return for final safety visit (ie, 16 weeks after last administration) for this study. Participants who are planning to continue golimumab treatment after exiting the study should have all final safety visit assessments done during the last study visit while on study golimumab. b. All assessments are to be completed prior to study intervention administration, unless otherwise specified. Visit window should be ±14 days for each visit up to and including the final visit c. Participants who discontinue study intervention but do not terminate study participation should return for the final safety visit. d. Prior to withdrawal of consent, participants who terminate study participation should complete assessments indicated at final safety visit. e. Participants' study intervention administrations will be based on the participants' weight and height at the current visit or the last recorded data for those performing AHA and for those at the study site. Weight and height need to be checked at least every 12 weeks during the study extension phase of the study. f. Participants should be evaluated for vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) before and approximately 30 minutes following study intervention administration by qualified site personnel. g. See Section 8.3.6 for TB evaluations. If TB is suspected at any time, a chest x-ray and QuantiFERON-TB or T-Spot test, or tuberculin skin test should be performed. h. Girls of childbearing potential. i. Blood samples should be collected prior to study intervention administration. The same blood draw can be used to collect serum samples for measuring study intervention concentration and antibodies to study intervention. j. All participants electing AHA of study interventions, will document the details of the study intervention, dosing day, time, anatomic site and if there were any complications of the injection, as well as adverse event (including injection-site reaction), concomitant medications and TB exposure information in an AHA diary, that is to be returned to the site at the upcoming visit, reviewed by the site staff (approximately every 12 weeks), and entered by site staff into the eCRF. k. After Week 54, only include concomitant medications in eCRF that are associated with AE and SAEs (ie, used to treat event or suspected in causing event) and/or with the treatment of UC. l. At Week 58, all participants are eligible for AHA of study intervention. Participants who are <12 years of age are eligible for AHA of study intervention by parent(s)/caregivers; participants >12 years of age are eligible for AHA by self or parent(s)/caregivers. m. Every 12 weeks (within the visit window), the participants must come to the study site for collection of the indicated efficacy assessments, to return AHA diary, and to obtain golimumab supplies for self- or caregiver- administration. If the visit is 7 days or less from their regular q4w dosing schedule, participants should self- or caregiver-administer at home after the study site visit. If outside of 7 days participants should self- or caregiver-administer on their q4w schedule at home. All other q4w administration should be performed at home. n. A diary will be provided for the participant to record AEs, TB evaluation, and concomitant medication review. o. Samples should be collected every 6 months during Year 1 of the study extension and, starting at Week 114, annually thereafter. p. PUCAI will be collected until each participant completes a Week 90 visit.					

Source: Applicant's submission, Clinical Protocol Study UCO3003 Amendment 6, pg. 18-25/209, Table 2

Abbreviations: AE, adverse event; AHA, at home administration; ANA, antinuclear antibody; dsDNA, double-stranded DNA; eCRF, electronic case report form; PUCAI, Pediatric Ulcerative Colitis Activity Index; q4w, every 4 weeks; SAE, serious adverse event; TB, tuberculosis; UC, ulcerative colitis

Table 62. Schedule of Activities for AHA and the Usability Assessment Substudy, Study UCO3003

Events	AHA and Usability Assessment Substudy Activities			
	First Training/self or caregiver administration visit ^b	Second self or caregiver administration visit ^b	Third self or caregiver administration visit ^b	Subsequent study interventions to end of study
Informed consent/assent for Substudy ^a	X			
Inclusion/exclusion criteria	X			
Training session conducted by site personnel	X			
Observation of self or caregiver training/administration by site personnel and completion of observer checklist (Appendix 10 [Section 10.10])	X			
Administration of golimumab by self or caregiver; or continued administration at the site, if desired	X	X	X	X
Completion of the Injection Device Assessment Questionnaire after completion of the second and third self- or caregiver administration visits by Substudy participants (Appendix 11 [Section 10.11])		X	X	
AHA diary	X	X	X	X
Device complaints/device-related AEs captured/investigated	X	X	X	X
a. Approximately 10-20 participants entering the study extension who elect to administer the study intervention at home will have the option to be enrolled in an Usability Assessment Substudy at Week 58. b. The training and self- or caregiver administration visits will occur at Weeks 58, 62, and 66 visits for those participating in the Usability Assessment Substudy				

Source: Applicant's submission, Clinical Protocol Study UCO3003 Amendment 6, pg. 18-25/209, Table 3

Abbreviations: AE, adverse event; AHA, at home administration

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Regulatory Project Manager	Andrew Chi	OND/ORO/DROI	Sections: 3	Select one: ☒ Authored ☐ Approved
	Signature: ANDREW P. CHI -S Digitally signed by ANDREW P. CHI -S Date: 2025.09.25 10:53:22 -04'00'			
Nonclinical Reviewer	Blessy George	OND/OII/DPTII	Sections: 5	Select one: ☒ Authored ☐ Approved
	Signature: BLESSY GEORGE -S Digitally signed by BLESSY GEORGE -S Date: 2025.09.25 11:32:57 -04'00'			
Nonclinical Team Leader	Sushanta Chakder	OND/OII/DPTII	Sections: 5	Select one: ☐ Authored ☒ Approved
	Signature: Sushanta K. Chakder -S Digitally signed by Sushanta K. Chakder -S Date: 2025.09.25 11:39:30 -04'00'			
DMEPA Human Factors Reviewer	Lisa Huang	OSE/OMEPRM/DMEPAI	Sections: 4.4	Select one: ☒ Authored ☐ Approved
	Signature: Lisa Huang -S Digitally signed by Lisa Huang -S Date: 2025.09.29 09:14:59 -04'00'			
DMEPA Human Factors Team Leader	Oluwamurewa Oguntimein	OSE/OMEPRM/DMEPAI	Sections: 4.4	Select one: ☐ Authored ☒ Approved
	Signature: Oluwamurewa Oguntimein -S Digitally signed by Oluwamurewa Oguntimein -S Date: 2025.09.30 09:52:02 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Product Quality Reviewer	Sarah Johnson	OPQ/OPQAIII/DPQAXIV	Sections: 4.2	Select one: ☒ Authored ☐ Approved
	Signature: SARAH JOHNSON -S Digitally signed by SARAH JOHNSON -S Date: 2025.09.25 12:02:06 -04'00'			
Product Quality Team Leader	Shadia Zaman	OPQ/OPQAIII/DPQAXIV	Sections: 4.2	Select one: ☐ Authored ☒ Approved
	Signature: SHADIA ZAMAN -S Digitally signed by SHADIA ZAMAN -S Date: 2025.09.25 12:52:36 -04'00'			
Microbiology Reviewer	Maria Gutierrez-Hoffman	OPQ/OPMA/DPMABI	Sections: 4.3	Select one: ☒ Authored ☐ Approved
	Signature: Maria G. Gutierrez-hoffmann -S Digitally signed by Maria G. Gutierrez-hoffmann -S Date: 2025.09.25 13:42:22 -04'00'			
Microbiology Team Leader	Madushini Dharmasena	OPQ/OPMA/DPMABI	Sections: 4.3	Select one: ☐ Authored ☒ Approved
	Signature: Madushini N. Dharmasena -S Digitally signed by Madushini N. Dharmasena -S Date: 2025.09.25 14:27:03 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Anand Balakrishnan	OTS/OCP/DIIP	Section: 6, 15.3	Select one: ☒ Authored ☐ Approved
	Signature: Anand Balakrishnan -S Digitally signed by Anand Balakrishnan -S Date: 2025.09.25 15:02:40 -04'00'			
Clinical Pharmacology Team Leader	Shen Li	OTS/OCP/DIIP	Section: 6, 15.3	Select one: ☐ Authored ☒ Approved
	Signature: Shen Li -S Digitally signed by Shen Li -S Date: 2025.09.25 15:25:28 -04'00'			
Pharmacometrics Reviewer	Robyn Konicki	OTS/OCP/DPM	Sections: 6, 15.3	Select one: ☒ Authored ☐ Approved
	Signature: Robyn E. Konicki -S Digitally signed by Robyn E. Konicki -S Date: 2025.09.25 17:35:44 -04'00'			
Pharmacometrics Team Leader	Vishnu Sharma	OTS/OCP/DPM	Section: 6, 15.3	Select one: ☐ Authored ☒ Approved
	Signature: Vishnu D. Sharma -S Digitally signed by Vishnu D. Sharma -S Date: 2025.09.26 09:15:15 -04'00'			
Associate Director for Labeling	Joette Meyer	OND/OII/DG	Section: 11	Select one: ☒ Authored ☐ Approved
	Signature: JOETTE M. MEYER -S Digitally signed by JOETTE M. MEYER -S Date: 2025.09.26 10:57:24 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Lesley Hanes	OND/OII/DG	Sections: 1, 2, 4.1, 7, 8.2, 8.3, 9, 10, 11, 12, 13, 15.1, 15.2, 15.4	Select one: ☒ Authored ☐ Approved
	Signature: LESLEY A. HANES -S Digitally signed by LESLEY A. HANES -S Date: 2025.09.26 12:23:40 -04'00'			
Statistical Reviewer	Haiwen Shi	OTS/OB/DBIII	Sections: 8.1	Select one: ☒ Authored ☐ Approved
	Signature: Haiwen Shi -S Digitally signed by Haiwen Shi -S Date: 2025.09.26 11:53:39 -04'00'			
Statistical Team Leader	Paul Imbriano	OTS/OB/DBIII	Sections: 1.2, 1.3, 8.1, 8.3	Select one: ☐ Authored ☒ Approved
	Signature: PAUL M. IMBRIANO -S Digitally signed by PAUL M. IMBRIANO -S Date: 2025.09.30 10:47:54 -04'00'			
Clinical Team Leader / Associate Director of Therapeutic Review (Division Signatory)	Tara Altepeter	OND/OII/DG	Sections: 14 (authored) All: Approved	Select one: ☒ Authored (14) ☒ Approved (All)
	Signature: TARA ALTEPETER -S Digitally signed by TARA ALTEPETER -S Date: 2025.09.30 12:12:14 -04'00'			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TARA A ALTEPETER
10/07/2025 09:35:27 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125289Orig1s157

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	BLA 125289
Supplement #:	Supplement-157 (Efficacy)
Related IND #:	IND 100181
Product Name:	Simponi (golimumab) supplied as a sterile liquid for SC injection in single use of prefilled syring (b) (4) (b) (4) contains either 100 mg (1 mL liquid) or 50 mg (0.5 mL liquid) of golimumab, with each 0.1 mL of liquid containing 10 mg of golimumab. (b) (4) (b) (4)
Indication(s):	(b) (4)
Applicant:	Janssen Biotech, Inc.
Dates:	Received Date: December 12, 2024, Filling Goal Date: February 10, 2025, PDUFA Goal Date: October 12, 2025.
Review Priority:	Standard (10-month review)
Biometrics Division:	DB III
Statistical Reviewer:	Haiwen Shi
Concurring Reviewers:	Paul Imbriano
Medical Division:	Division of Gastroenterology
Clinical Team:	Sara Jimenez, Reviewer; Tara Altepeter, Team leader
Project Manager:	Andrew Chi

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Simponi (golimumab) was approved for the treatment of adults with moderately to severely active UC on May 15, 2013. The Applicant is now seeking approval for (b) (4). Table 1 below includes a brief summary of the trials proposed by the Applicant to support the efficacy of golimumab in pediatric UC subjects.

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
UCO3003	MC, R, OL trial (Induction period: 6 weeks; Maintenance period: 48 weeks)	Golimumab/ 69 Infliximab/ 15	Primary Endpoint: clinical remission at Week 6 based on the Mayo score, defined as a score ≤2 points, with no individual subscore >1, based on Mayo endoscopy subscore assigned by the local endoscopist. The remission rate of golimumab in pediatric participants was compared with a historical placebo remission rate. Major Secondary Endpoints: See Appendix 1.	Primary Endpoint: At Week 6, 22 (31.9%; [90% CI: 22.7%, 41.1%]) golimumab treated participants achieved clinical remission as assessed by the Mayo score; The 22.7% lower limit of the 2-sided 90% CI is greater than the upper limit of the 95% CI for the historical adult placebo control (10.0%), estimated with a fixed-effects meta-analysis using inverse variance weighting method. Major Secondary Endpoints: See Appendix 1.
UCO1001	Phase 1b, MC, OL (14 weeks) ¹	Golimumab ² / 35	Primary Endpoint: There is no primary efficacy endpoint in this study. Clinical Efficacy Endpoints: See Appendix 2.	See Appendix 2.

* MC: multi-center, R: randomized, OL: open-label.

¹ The PK portion was through Week 14 and the efficacy evaluation was through Week 6.

² In participants with body weight <45 kg the induction doses were approximately 25% lower in UCO1001 than in UCO3003.

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes.

Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes.
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	No interim analysis was planned for this study.
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	Yes, the Applicant conducted a Bayesian logistic model as a supportive analysis. The details of the analysis were provided in SAP. The Applicant submitted a SAS program for this analysis. However, the Applicant did not submit the data from adult studies used in the analysis. The data may be requested from the Applicant to verify the analysis results.
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Yes.

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\BLA125289\0534
Were analysis datasets provided?	Yes.
Dataset structure (e.g., SDTM or ADaM)	SDTM and ADaM
Are the define files sufficiently detailed?	Yes.
List the dataset(s) that contains the primary endpoint(s)	ADaM: ADEFF for UCO3003
Are the <i>analysis datasets</i> sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes.
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No, removing one site does not have a big impact on the efficacy results for the primary and major secondary endpoints.
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes.

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc..	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.).	X			
Safety and efficacy were investigated for gender, racial, ethnic, and geriatric subgroups.	X			No efficacy was investigated for ethnic subgroups. The ethnicity data are available, and an IR will be sent asking for these subgroup analyses.
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application appears to be free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements.	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

There are no refuse-to-file issues.

5.2. Information Requests/Review Issues

1. An IR was sent to the Applicant on 31 January 2025 containing three statistical items (Question #1, 4, and 5). The first one (Question #1) regarding the derivation procedure used to calculate the stool frequency and rectal bleeding subscores in the Mayo score from daily diary data. The response from the Applicant on this item was received on 3 February 2025. The second statistical item (Question #4) requested the Applicant to 1) conduct a similar comparison with adult placebo rates estimated from meta-analyses for each major

secondary endpoint as was performed for the primary endpoint and 2) provide a comparison of the response rates in pediatric subjects treated with golimumab to the response rates of adult subjects treated with golimumab for all endpoints with available data in both the pediatric and adult studies. The third statistical item (Question #5) was to request the Applicant to clarify the reason for a discrepancy between the endpoint analysis (39 responders) and the FGAS2 analysis set (41 subjects) regarding the number of subjects in clinical response at Week 6. The expected date to receive a response from the Applicant for these items is 11 February 2025.

The review team plans to include the following IRs in the filing communication letter (Day 74: 2/24/2025)

2. Conduct subgroup analyses based on ethnicity for the primary endpoint, clinical remission at Week 6. In addition, to support long-term efficacy, conduct subgroup analyses based on sex, race, ethnicity, and age for the endpoint of clinical remission at Week 54.
3. Submit the details (i.e., data and program codes) for the systematic review and meta-analyses you performed to establish the efficacy criteria, the upper bound of the 95% CI for the historical placebo control (i.e., 10%) estimated with a fixed-effects meta-analysis using inverse-variance weighting method. In addition, submit the details (i.e., data and program codes) for the alternative meta-analysis methods including random-effects and sample size weighting method.
4. Submit the data from the adult studies used to conduct the Bayesian logistic regression model specified in supportive analysis 2.
5. Using the QS and SUPPQS SDTM datasets and ADSL ADaM dataset, we found that 25 subjects among the 69 subjects at Week 6 and 5 subjects among the 41 subjects at Week 54 did not use the most recent 3 consecutive days of diary data from the 7-day collection period for the calculation of the stool frequency and rectal bleeding subscores, including 2 subjects at Week 6 who used 3 nonconsecutive days (Subject (b) (6) used diary data on Day 4, 5, and 7 and Subject (b) (6) used diary data on Day 4, 6, and 7). When known, provide the specific reasons for each of these subjects why certain day(s) were excluded from the most recent 3 consecutive days in the subscore calculation (e.g., day of colonoscopy). In addition, the SAP states that “[s]ites are instructed to check the boxes next to the 3 days which are used to calculate stool frequency and rectal bleeding subscores.” Submit a detailed description of the instructions provided to sites for determining which days to include in the 7-day window and which 3 days to include in the subscore calculation.

The following review issues have been identified:

In the response to the 31 January 2025 IR received on 3 February 2025, the Applicant provided information regarding the calculation of the stool frequency and rectal bleeding subscores from daily diary data. While the submitted data

specifies the days included in the stool frequency and rectal bleeding subscores, information regarding the specific reasons why certain days were excluded from the calculation of subscores was not provided by the Applicant in their IR responses. The primary method used to derive stool frequency and rectal bleeding subscores and the ability of the data to support the appropriateness of the selected diary days will be examined by the review team.

6. Advisory Committee

	Response/Comments
If the Advisory Committee Decision Aid (ACDA) is required for this application, do you have any comments relevant to the completion of this document?	NA
Has the review division determined that an Advisory Committee (AC) meeting is needed?	☐ Yes ☒ No ☐ To be Determined
If an AC meeting may be held for this application, are there any areas of expertise that may be important for AC statistician(s) to have?	NA

Appendix 1: Major Secondary Efficacy Endpoint Results for Study UCO3003

Table 5: Summary of Major Secondary Week 6 Efficacy Endpoint Results; Full Golimumab 1 Analysis Set^a (UCO3003)

Major Secondary Week 6 Endpoints	Preliminary Findings n/N (Response Rate) (90% CI) ^b
Clinical remission assessed by the PUCAI score, defined as PUCAI score <10	23/69 (33.3%) (24.0%, 42.7%)
Clinical response assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist), defined as Mayo score decrease from baseline score of ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1	39/69 (56.5%) (46.7%, 66.3%)
Endoscopic healing (based on Mayo endoscopy subscore assigned by the local endoscopist), defined as an endoscopy subscore of the Mayo score of 0 or 1	28/69 (40.6%) (30.9%, 50.3%)

Source: Review team's analyses using SAS 9.4 on the Applicant submitted data ADSL.xpt and ADEFF.xpt and adapted from Table 4 in the Applicant submitted Summary of Clinical Efficacy.

^a The **Full Golimumab Analysis Set 1** (FGAS1) includes all enrolled participants who received at least 1 dose (complete or partial) of golimumab during the Short-Term (Induction) Phase (Weeks 0-6).

^b n = number of responders; N = number of participants in the FGAS1; CI = confidence interval (the confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution)

Table 6: Summary of Major Secondary Week 54 Efficacy Endpoint Results; Full Golimumab 2 Analysis Set^a (UCO3003)

Major Secondary Week 54 Endpoints	Preliminary Findings n/N (Response Rate) (90% CI) ^b
Symptomatic remission assessed by Mayo Score, defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0	16/41 (39.0%) (26.5%, 51.6%)
Clinical remission assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist), defined as a Mayo score ≤2 points, with no individual subscore >1	13/41 (31.7%) (19.8%, 43.7%)
Clinical remission assessed by the PUCAI score, defined as a PUCAI score <10	14/41 (34.1%) (22.0%, 46.3%)
Endoscopic healing (based on Mayo endoscopy subscore assigned by the local endoscopist), defined as an endoscopy subscore of the Mayo score of 0 or 1	15/41 (36.6%) (24.2%, 49.0%)

Major Secondary Week 54 Endpoints	Preliminary Findings n/N (Response Rate) (90% CI) ^b
Clinical remission assessed by the Mayo score (based on Mayo endoscopy subscore assigned by the local endoscopist), defined as a Mayo score ≤ 2 points, with no individual subscore >1 , and not received corticosteroids for at least 12 Weeks	13/41 (31.7%) (19.8%, 43.7%)
Clinical remission assessed by the Mayo score, for participants who are in clinical remission at Week 6 (based on Mayo endoscopy subscore assigned by the local endoscopist), defined as a Mayo score ≤ 2 points, with no individual subscore >1 .	12/22 (54.5) (37.1%, 72.0%)

Source: Review team's analyses using SAS 9.4 on the Applicant submitted data AD5L.xpt and ADEFF.xpt and adapted from Table 5 in the Applicant submitted Summary of Clinical Efficacy.

^a The **Full Golimumab Analysis Set 2** (FGAS2) includes participants who are in clinical response at Week 6 to golimumab (determined by the IWRS) as assessed by the Mayo score (local reader) and who received at least 1 dose (complete or partial) of golimumab during the Long-Term (Maintenance) Phase (Week 6-54).

^b n = number of responders; N = number of participants in the FGAS2; CI = confidence interval (the confidence intervals use the asymptotic formula based on the normal approximation to the binomial distribution)

Appendix 2: Clinical Efficacy Endpoint Results for Study UCO1001

Table 7: Summary of Week 6 Clinical Efficacy Endpoint Results; Treated Participant (UCO1001)

Clinical Efficacy Endpoints at Week 6	Preliminary Findings n/N (Response Rate) ^a
Clinical remission assessed by the Mayo score, defined as a Mayo score ≤ 2 points, with no individual subscore > 1	15/35 (42.9%)
Clinical remission assessed by the PUCAI score, defined as PUCAI score < 10	12/35 (34.3%)
Clinical response assessed by the Mayo score, defined as Mayo score decrease from baseline score of $\geq 30\%$ and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1	21/35 (60.0%)
Mucosal healing, ^b defined as an endoscopy subscore of the Mayo score of 0 or 1	19/35 (54.3%)

Source: Review team's analyses using SAS 9.4 on the Applicant submitted data ADVISEF.xpt and adapted from Table 7 in the Applicant submitted Summary of Clinical Efficacy.

^a n = number of responders; N = number of treated participants

^b Note that the term "mucosal healing" used in UCO1001 (i.e., endoscopy subscore of 0 or 1) is defined identically to the more recent term "endoscopic healing" that was used in UCO3003

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/s/

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PAUL M IMBRIANO
02/07/2025 03:46:38 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125289Orig1s157

PRODUCT QUALITY REVIEW(S)

Memorandum of Assessment:

Submission Tracking Number (STN):	BLA 125289-Supplement 157 (SD 1902, 1904, 1932, 1944, and 1945)
Subject:	Efficacy PAS: For the introduction of a new indication - (b) (4) [REDACTED] [REDACTED].
Date Received:	12/12/2024
Assessment/Revision Date:	9/12/2025
Primary Assessor:	Sarah Johnson, PhD, CDER/OPQ/OPQAI/DPQA XIV
Secondary Assessor:	Shadia Zaman, PhD, CDER/OPQ/OPQAI/DPQA XIV
Tertiary Assessor:	Anjali Shukla, CDER/OPQ/OPQAI/DPQAXIV
RBPM:	Musse Olani CDER/OPQ/OPRO/DRBPMI
Consults:	CDRH ICCR Consults #01038883, #250082
Applicant:	Janssen Biotech Inc.
Product:	Simponi (golimumab)
Indication:	Adult indications: Rheumatoid Arthritis (RA): Moderately to severely active RA, used in combination with methotrexate. Psoriatic Arthritis (PsA): Active PsA, used alone or in combination with methotrexate. Ankylosing Spondylitis (AS): Active AS. Ulcerative Colitis (UC): Moderately to severely active UC in patients who are corticosteroid dependent or have failed or were intolerant to conventional therapies (b) (6) [REDACTED]
Filing Action Date:	2/10/2025
Action Due Date:	10/12/2025

1. Summary Basis of Recommendation:

a. Recommendation: I recommend Approval of this supplement.

Justification: The Applicant, Janssen Biotech, Inc., submitted this efficacy supplement to add the indication for the treatment of pediatric patients weighing at least 15 kg with moderately to severely active ulcerative colitis (UC). Simponi drug product will be administered subcutaneously with the currently approved 50 mg/0.5 mL single dose prefilled syringe (50 mg/0.5mL or 100 mg/mL) with Simponi (b) (4) drug product or 100 mg/mL single dose prefilled SmartJect autoinjector, which are currently approved for use in the Simponi adult indications (RA, AS, PsA and UC). No changes were made to Module 3 CMC information for the approved PFS-U DP or autoinjector for use in the pediatric UC patient population.

No changes were made to the CMC sections of the USPI labeling. The OPQAI/DPQA labeling assessor noted "No Action Indicated."

Immunogenicity analysis of samples from pediatric UC was performed using the validated immunogenicity assays used to assess anti-drug antibodies (ADA) and neutralizing antibodies (nAbs) and reviewed in assessment of the Simponi Aria (golimumab intravenous presentation) sBLA 125433-Supplement 20 and 21 and BLA 125433 Supplement 30 and 31 in the analysis of ADAs and nAbs in various adult and pediatric patients. The established drug tolerance limits based on adult sera is up to >12,500 and 50,000 ng/mL golimumab in 50 ng/mL and 250 ng/mL anti-drug controls, respectively, in the screening/confirmatory method. The median serum levels reported for pediatric UC patients was $\leq 7.61 \mu\text{g/mL}$ whereas the levels in adults did not go above $6.40 \mu\text{g/mL}$. As the serum concentrations of drug is comparable to adults, the established drug tolerance limits based on adult sera are adequate for the pediatric UC population to ensure detection of anti-drug antibodies. Pre-validation statistical analyses showed comparable false positive rates within acceptance criteria (11.4% and 15.9% in pediatric studies UCO1001 and UCO3003), comparable screening cut points between adult (1.07 normalized value) and pediatric UC populations (1.05 normalized value), and absence of expected serum matrix interference differences in the validated immunogenicity assays. Therefore, these assays are deemed adequate to support clinical immunogenicity assessment in the pediatric UC population.

2. Assessment:

Note: Assessor comments are indicated in italics. Figures and tables are adopted or copied directly from the applicant's submission unless noted otherwise.

1. Environmental Assessment:

- ☒ The sponsor requests categorical exclusion from the requirements of preparing an environmental assessment under 21 CFR 25.31 (c). This is acceptable from an OPQA III perspective.

2. Origin of Drug Product:

- ☒ The drug product lots used in the clinical studies to support the new indication were lots manufactured and controlled as described in the license (e.g., commercial lots).
- ☐ The drug product lots used in the clinical studies to support the new indication were not manufactured and controlled as described in the license (e.g., clinical lots). However, comparability between these drug product lots, and the commercial lots were/are demonstrated for the purpose of supporting the marketing of commercial materials as described in the license for the new indication.

(b) (4)

3. Immunogenicity Assay Evaluation:

- ☐ No additional immunogenicity assessment was performed to support the new indication. No further action is needed.
- ☐ Additional immunogenicity assessment was provided in Module 5 and used to support the new indication. A justification was provided to support the suitability and validation of immunogenicity assays to be used for the assessment in the new patient population.
- ☒ Additional immunogenicity assessment was provided in Module 5 and used to support the new indication. Information and data to support the suitability/validation of the immunogenicity assays for the assessment in the new patient population were provided and assessed below.

MODULE 5 CLINICAL STUDY REPORTS

Immunogenicity Assessment

To support the proposed pediatric ulcerative colitis (UC) indication, the Applicant conducted immunogenicity as part of the clinical studies CNT0148UCO1001 (hereafter referred to as Study UCO1001 [CSR CNT0148UCO1001 2023]) and Study CNT0148UCO3003 (hereafter referred to as Study UCO3003 [CSR CNT0148UCO3003 2024]). The Applicant used a previously validated drug-tolerant EIA method for anti-drug antibodies (ADA) assessment (Report CP2012V-037) and a competitive ligand binding assay for neutralizing antibody (NAb) assessment (Report CP2015V-001) for overall product immunogenicity for the pediatric UC patient population. In this submission, the Applicant provided minor updates to the CP2012V-037 and CP2015V-001, the ADA and NAb assay validation reports, respectively, to provide updated pre-validation statistical analyses of normal human and diseased serum samples from various adult populations (ulcerative colitis, psoriatic arthritis, ankylosing spondylitis treatment naïve, and axial spondylarthritis).

These statistical analyses did not include untreated pediatric UC patient samples for cut point determination. An information request (IR) was sent to the Applicant on 8/7/2025 to provide scientific justification to support the suitability of using the assays validated with the adult serum samples rather than using the untreated pediatric patient samples (treatment naïve pediatric patient samples) for the proposed UC indication. In their 8/15/2025 response (eCTD 0577), the Applicant acknowledged that both the ADA and NAb assays did not include untreated pediatric patient samples in the pre-study validation. This was due to the challenge of procuring serum samples commercially from pediatric subjects with respect to volumes and the large number of individual subjects required for assay cut point determinations. Therefore, the assay cut points for both ADA and NAb assays were validated in the same disease-state populations' serum matrix from adult subjects during

pre-study validations and applied to the same disease population in pediatric patients. The Applicant justified using adult serum samples instead of pediatric samples for assay validation based on:

- a. False Positive Rate (FPR) analysis: When the validated ADA assay was applied to the pediatric clinical studies (Study UCO1001: 11.4% FPR, Study UCO3003: 15.9% FPR), both rates fell well within the validation acceptance criteria established for the statistical analyses conducted to ensure the FPRs were suitable for different adult and pediatric indications (Population-Specific FPR Acceptance cp2012v-037 study-report-1).
- b. Screening Cut Point (SCP) comparability: Adult treatment-naïve UC patients (SCP: 1.07 normalized value during pre-study validation) and the Pediatric baseline samples (Study UCO1001: 1.05 NV in-study SCP) demonstrated minimal difference between 95th percentiles of adult and pediatric UC serum matrices.
- c. For the NAb assay, no serum matrix differences were identified between adult and pediatric UC participants in the ADA assay, and the NAb assay utilizes a similar ligand binding format, the Applicant concluded there was no reason to expect nonspecific serum matrix interference in the NAb assay.

Assessor comment:

- 1) *BLA 125289 golimumab (Simponi) and BLA 125433 golimumab intravenous (Simponi Aria) use identical immunogenicity assessment methods and the validation reports for this method are submitted to both BLAs. This is acceptable as products contain the same monoclonal antibody, golimumab, with identical primary amino acid sequence, molecular weight, and three-dimensional structure. The immunogenic epitopes recognized by the human immune system remain unchanged between formulations, as they are determined by the protein structure rather than the delivery method justified based on their shared active pharmaceutical ingredient and similar immunogenic potential, despite different routes of administration.*

The submitted nAb validation reports are dated with updates made in 2015. No data has changed between review of these reports in the sBLA 125433-Supplement 20 and 21 review memo and the current review. The ADA screening/confirmatory updates are dated with dates between 2020 and 2022. They are reviewed here as this is the first submission of these updates to the ADA assays to BLA 125289. Previous discussion of these methods occurred upon review of BLA 125433-S30 and S-31 (see memo dated 5/29/2020).

- 2) *The Applicant submitted partial validation reports, CPV2015V-110 v3.0 and CP2012V-037-A8 for the nAb and ADA screening/confirmatory methods, respectively. Assessment of these updates did not occur because the partial validation was to re-validate the methods for the (b) (4) that was not used in the proposed pediatric UCO1001 or UCO3003 studies that were submitted to support this supplement.*
- 3) *The Applicant's justification for how the validated ADA and nAb assays are suitable for use in the pediatric UC population was found acceptable due to the following:*
 - a) *The provided FPRs demonstrated that the screening cut point (SCP) for serum matrices from pediatric UC subjects was comparable to the SCP for adult UC subjects used in the pre-study validation of the ADA assay. In addition, the SCP of treatment-naïve adult UC JNJ-54160301 (golimumab) patients was 1.07 NV during pre-study validation while the in-study SCP calculated from baseline samples of Study UCO1001 was 1.05 NV, thus demonstrating minimal difference between the 95th percentiles of adult and pediatric UC*

serum matrices.

- b) *The OCP assessor confirmed in email communication on 8/1/2025 that the drug concentrations in the pediatric studies were generally within the range of the adult studies (for drug tolerance) for the UCO1001 and UCO3003 studies. The established drug tolerance limits based on adult sera (up to >12,500 and 50,000 ng/mL golimumab in 50 ng/mL and 250 ng/mL anti-drug controls, respectively, in the screening/confirmatory method) and other indications are acceptable for the screening/confirmatory method considering median serum levels reported in Section 3.1 of 2.5 Clinical Overview for pediatric UC patients during the UCO1001 or UCO3003 studies did not go above 7.61µg/mL whereas the levels in adults did not go above 6.40 µg/mL.*
- c) *The assay validation reports (CP2015V-015 and CP2015V-001 for nAb assay) were previously submitted and reviewed by OBP assessors for BLA 125433 (supplement 20 and supplement 21). In these reports, the reported drug tolerance was 1.02-2.28 µg/mL. The previous assessors found the nAb assay drug tolerance of 1.02-2.28 µg/mL golimumab acceptable because it represents a significant improvement over the previously approved method (1.59-fold better drug tolerance) and provides clinically relevant detection capability at typical patient exposure levels. While there some potential drug interference risk remains at higher concentrations, the improved performance justifies acceptance of this limitation. Of the 69 pediatric subjects treated with golimumab in Study UCO3003, 15 (21.7%) were positive for antibodies to golimumab through the final safety visit. Of these 15 subjects, 3 (20%) tested positive for neutralizing antibodies. Antidrug antibody (ADA) incidence in the pediatric study was comparable to adults (21.3%, 254/1195).*

Therefore, based on these reasons, these methods are adequate for pediatric UC populations.

- 3. Assessment conclusions:** Based on the above, from the product quality perspective, I recommend approval of the ulcerative colitis pediatric indication using the currently approved Simponi DP presentations for subcutaneous injection proposed in this supplement.
- 4. Future Inspection Items: None**
- 5. Status of PMC/PMR: None**

(b) (4)

(1) Scope of Changes

Simponi (Golimumab) was first approved on April 24, 2009, for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). The indications were subsequently expanded to include moderately to active psoriatic arthritis (PsA) and ankylosing spondylitis (AS), non-radiographic axial spondylarthritis (nr-AxSpA) in adult patients. On May 15, 2013, Simponi was approved for adult patients with moderately to severely active ulcerative colitis (UC). The Simponi SC formulation is not currently approved for use in pediatric patients for the UC indication.

(b) (4) proposed for use in pediatric UC: the prefilled syringe (b) (4), which is currently approved for use in the Simponi adult indications (RA, AS, PsA and UC), (b) (4)

Information on the currently approved DP presentations can be found in 2.3.P.1 and 3.2.P.1 of 3.2.P [active][pfs][common] of BLA 125289.

The Applicant, Janssen Biotech, Inc., submitted this efficacy supplement to add the proposed indication in pediatric ulcerative colitis (UC) via subcutaneous (SC) administration. With this submission, the

(b) (4)

The Reviewer Guide submitted in Module 1.2 summarizes all proposed changes made to BLA 125289 to support the proposed pediatric ulcerative colitis indication.

Assessor's Comment:

(b) (4)

(2) Product Quality Review

The data, and subsequent assessment of these data, to support the proposed changes summarized in (1) above are presented in subsequent sections of the memo.

(2A) Description and Composition of the Drug Product and Control of Excipients: The Simponi (golimumab) drug product (DP) is supplied as a sterile solution in a single use, 1 mL pre-filled syringe (PFS) with a fixed needle stoppered with a plunger stopper. The needle is covered with a needle shield. The Simponi PFS is manufactured in two dosages, a 50 mg/syringe (0.5 mL) and a 100 mg/syringe (1.0 mL) (2.3.P.1 and 3.2.P.1 of 3.2.P [active][pfs][common] of BLA 125289). The PFS with 50 mg (0.5 mL) dose may be assembled into any of the following (b) (4): SmartJect (b) (4)

(b) (4)

The PFS with 100 mg (1.0 mL) dose may be assembled into the SmartJect autoinjector (b) (4). The product is intended for subcutaneous administration.

(b) (4)

Assessor comments

(b) (4)

(2B) Description of Manufacturing Process and Process Controls and Controls of Critical Steps and Intermediates

(b) (4)



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Johnson

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125289Orig1s157

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: August 26, 2025

To: Andrew Chi
Regulatory Project Manager
Division of Gastroenterology (DG)

Through: Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Mary Carroll, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): SIMPONI (golimumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 125289

Supplement Number: S-157

Applicant: Janssen Biotech, Inc.

1 INTRODUCTION

On December 12, 2024, Janssen Research & Development, LLC, on behalf of Janssen Biotech, Inc. submitted for the Agency's review an Efficacy Supplement to their approved Biologics License Application (BLA) 125289/S-157 SIMPONI (golimumab) injection, for subcutaneous use. Reference is made to the information request received from FDA on 18 August 2025 requesting the Instructions for Use (IFU) for the SmartJect Presentation. With this submission, Janssen is seeking approval of golimumab [REDACTED] (b) (4).

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Gastroenterology (DG) on April 16, 2025 for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for SIMPONI (golimumab) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- SIMPONI (golimumab) IFU received on August 19, 2025, and received by DMPP on August 25, 2025.
- Draft SIMPONI (golimumab) Prescribing Information (PI) received on December 12, 2024, revised by the Review Division throughout the review cycle, and received by DMPP on August 4, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the PI
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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MARCIA B WILLIAMS
08/26/2025 02:26:08 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: August 14, 2025

To: Andrew Chi, Regulatory Project Manager
Division of Gastroenterology (DG)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for SIMPONI® (golimumab) injection, for subcutaneous use

BLA: 125289, S-157

Background:

In response to DG's consult request dated December 13, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and Instructions for Use (IFU) for supplement 157 for SIMPONI® (golimumab) injection, for subcutaneous use. We note that although OPDP was initially consulted to review the carton and container labeling, DG later notified OPDP that there have been no proposed changes to them.

This supplement provides for the treatment of pediatric patients with ulcerative colitis (UC).

PI/Medication Guide/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 4, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide and IFU, and comments will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov.

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: August 14, 2025

To: Andrew Chi
Regulatory Project Manager
Division of Gastroenterology (DG)

Through: Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Mary Carroll, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Quynh-Nhu Capasso, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): SIMPONI (golimumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 125289

Supplement Number: S-157

Applicant: Janssen Biotech, Inc.

1 INTRODUCTION

On December 12, 2024, Janssen Research & Development, LLC, on behalf of Janssen Biotech, Inc. submitted for the Agency's review an Efficacy Supplement to their approved Biologics License Application (BLA) 125289/S-157 SIMPONI (golimumab) injection, for subcutaneous use. With this submission, Janssen is seeking approval of golimumab (b) (4).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology (DG) on April 16, 2025 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for SIMPONI (golimumab) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft SIMPONI (golimumab) MG received on December 12, 2024, and received by DMPP and OPDP on August 4, 2025.
- Draft SIMPONI (golimumab) IFU received on December 12, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 4, 2025.
- Draft SIMPONI (golimumab) Prescribing Information (PI) received on December 12, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 4, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the PI
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

MARY E CARROLL
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DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

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and Reproductive Medicine
Office of New Drugs
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Division of Pediatrics and Maternal Health Review

Date: 6/25/2025 **Date consulted:** 12/13/2024

From: Katherine Kratz, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Gastroenterology (DG)

Drug: Simponi (golimumab), solution for injection

BLA: 125289/S-157

Applicant: Janssen Biotech, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: (b) (4)

**Materials
Reviewed:**

- DPMH consult request dated 12/13/24. DARRTS Reference ID: 5495821
- Applicant's submitted background package and proposed labeling for BLA 125289, Sequence Number (SN) 0534, dated 12/12/24.
- Epidemiology, Maternal Health, Biostatistics and Pharmacovigilance Integrated Review: Simponi Nordic Registry Study Report and Labeling Supplements by Margie Goulding PhD, Katherine Kratz MD, Ya-Hui Hseuh PhD, Van Tran PharmD, dated 11/15/24. DARRTS Reference ID: 5478208

- Applicant's Amendment to Prior Approval Supplement for BLA 125289, SN 0554 dated 5/1/25.

Consult Request: "DG is requesting assistance in reviewing the above efficacy supplement. We kindly request review of the submitted PI and the proposed changes to ensure appropriate compliance with the PLLR."

I. INTRODUCTION AND BACKGROUND

On December 12, 2024, the Applicant, Janssen Biotech, Inc., submitted an efficacy supplement (sBLA) for Simponi (golimumab) to support [REDACTED] (b) (4). The Applicant is submitting this sBLA to fulfill a postmarketing commitment (PMC #5) to conduct a clinical development program in pediatric participants ages 2 through <18 years with moderately to severely active UC issued with the May 2013 approval of Simponi for the treatment of adult UC. DG consulted the DPMH Maternal Health Team (MHT) December 13, 2024 to assist with the Pregnancy and Lactation subsections of labeling.

Notably, in November 2024, the DPMH MHT completed an integrated review of postmarketing pregnancy data for a consultation from the Division of Rheumatology and Transplant Medicine (DRTM).¹ The integrated review involved collaboration with the Divisions of Epidemiology-2 (DEPI-2), Pharmacovigilance-1 (DPV-1) and Biometrics VII (DB-7) to analyze the "Final Registry Report" for a Nordic study titled "Exposure to Golimumab During Pregnancy: A Review and Analysis of Birth Outcomes from the Swedish, Danish, and Finnish Medical Birth Registers: Final Report (CNT0148ART4001)." This study was conducted by the Applicant as post-authorization commitment with the European Medicine Agency. The study provided data on pregnancy and infant outcomes following in-utero exposure to golimumab from the national medical birth registers of Denmark, Finland and Sweden, with linkages to drug dispensing and health care data. Based on the integrated review of the Nordic study results, the review team concluded that the data from the Nordic study should be added to labeling with an explanation of the limitations of the data. After conducting a cumulative review of the Applicant's pharmacovigilance database for pregnancy data and a comprehensive literature search related to pregnancy, no other safety signals were identified; therefore, no additional information, beyond that from the Nordic study, was recommended for inclusion in labeling. On April 18, 2025, the labeling for Simponi was changed as a result of this integrated review.

On May 1, 2025, the Applicant submitted an amendment to this sBLA to update the proposed labeling submitted on December 12, 2024. The labeling submitted by the Applicant on May 1, 2025 reflects the labeling changes associated with the Nordic study that were approved on April 18, 2025.

¹ Epidemiology, Maternal Health, Biostatistics and Pharmacovigilance Integrated Review: Simponi Nordic Registry Study Report and Labeling Supplements by Margie Goulding PhD, Katherine Kratz MD, Ya-Hui Hseuh PhD, Van Tran PharmD, dated 11/15/24. DARRTS Reference ID: 5478208

Relevant Regulatory History

- 4/2009: Simponi (for subcutaneous injection) was approved in the United States (U.S.) for the treatment of moderate to severe rheumatoid arthritis (RA) in combination with methotrexate (MTX), active psoriatic arthritis (PsA), alone or in combination with MTX, and active ankylosing spondylitis (AS).
- 5/2013: Simponi was approved in the U.S. for the treatment of moderate to severe UC in adults with an inadequate response or intolerant to prior treatment or requiring continuous steroid therapy.
- 7/2013: Simponi ARIA (for IV injection) was approved in the U.S. for the treatment of moderate to severely active RA in adults in combination with MTX.
- 10/2017: Simponi ARIA was approved for the treatment of PsA and AS as well as polyarticular juvenile idiopathic arthritis (pJIA).

Drug Characteristics²

Drug class	Tumor necrosis factor alpha (TNF α) blocker
Mechanism of action	Golimumab is a human monoclonal antibody that binds to human TNF α . This interaction prevents the binding of TNF α to its receptors, thereby inhibiting the biological activity of TNF α .
Dosage forms	Solution for subcutaneous injection
Molecular weight	Not specified
Half-life	2 weeks
% protein bound	Not specified
Bioavailability	53%

Current State of the Labeling

- The current labeling is in the Pregnancy and Lactation Labeling Rule (PLLR) format.
- There is a boxed warning for serious infections and malignancy.
- There is no boxed warning or warning and precaution for embryo-fetal toxicity.
- There is no contraindication for pregnancy or lactation.
- Serious adverse reactions
 - Serious Infections
 - Invasive Fungal Infections
 - Hepatitis B Reactivation
 - Malignancies
 - Congestive Heart Failure
 - Demyelinating Disorders
 - Lupus-like Syndrome
 - Hypersensitivity Reactions
- 8.1, Pregnancy:
 - Human data “An observational, exposure-based, cohort study based on data from the Swedish, Danish, and Finnish Medical Birth Registers conducted between 2006-2020 (Sweden and Denmark) and 2006-2019 (Finland) compared the risk of major birth defects in 134 live-born infants exposed to golimumab (116 from women treated for

² United States Prescribing Information (USPI) for SIMPONI (golimumab) injection, for subcutaneous use, 4/2025.

- rheumatic conditions, 18 from women treated for ulcerative colitis) to no treatment or nonbiologic systemic therapy. The unadjusted rate of major birth defects in infants exposed in utero was similar across all groups. However, this study had important limitations such as a small number of pregnant women exposed to golimumab, a wide exposure ascertainment window, and incomplete risk adjustment for potential confounders.”
- Animal data: In an embryofetal developmental toxicology study and pre- and post-natal development study with exposures up to 360 times greater than the exposure at the MRHD (on an area under the curve (AUC) basis and 460 times greater than that found with the MRHD (on a maximum blood concentration (Cmax) basis, respectively, there was no evidence of fetal malformations, embryotoxicity, developmental defects in infants, or maternal toxicity. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. Golimumab was present in neonatal serum from the time of birth and for up to 6 months postpartum.
 - 8.2, Lactation:
 - Human data: None
 - Animal data: “In the pre- and postnatal development study in cynomolgus monkeys in which golimumab was administered subcutaneously during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 400-fold lower than the maternal serum concentrations.”
 - There are no pregnancy testing or contraception recommendations.
 - There is no known drug-drug interaction with hormonal contraceptives.

II. REVIEW

Pregnancy and UC

UC in pregnancy has been previously described by DPMH.^{3,4,5} Briefly, the risk of poor pregnancy outcomes in patients with UC is greatest in those with active disease at the time of conception. Poor pregnancy outcomes include antepartum hemorrhage, preterm delivery, and low birth weight infants. The risk of congenital abnormalities does not appear to be increased in patients with IBD.⁶

Pregnancy and Rheumatoid Arthritis (RA)

RA in pregnancy has been previously described by DPMH and there are Clinical Considerations for disease-associated maternal and/or embryo/fetal risk in labeling for other drugs approved to treat RA.^{7,8} Like UC, increased disease activity is associated with adverse pregnancy outcomes

³ DPMH Post-Marketing Requirement Memo for Zeposia (ozanimod), NDA 209899, by Wenjie Sun, MD, dated March 5, 2021. DARRTS Reference ID: 4757744.

⁴ DPMH Review of Omvoh (mirikizumab), BLA 761279, by Kristie Baisden, DO, dated 12/19/2022. DARRTS Reference ID: 5094480.

⁵ DPMH Review of ZYMFENTRA (infliximab-dyyb), BLA 761358, by Katherine Kratz, MD, dated 10/3/2023. DARRTS Reference ID: 5247747.

⁶ Peppercorn, M et al. Fertility, pregnancy, and nursing in inflammatory bowel disease. UpToDate. Topic 4083 Version 59.0. Accessed 1/15/2025.

⁷ Drugs@FDA. Olumiant (baricitinib). Accessed 6/17/2025.

⁸ Drugs@FDA. Xeljanz (tofacitinib). Accessed 6/17/2025.

including preterm delivery, antepartum hemorrhage,^{9,10} low birth weight and small for gestational age.

Pregnancy, Lactation, Fertility Cases from Clinical Trials

There were no events of pregnancy or lactation or cases related to human fertility in the pediatric studies conducted for this submission.

Literature Search

DPMH conducted a search of published human studies PubMed for 1) pregnancy cases, 2) lactation cases, and 3) fertility cases. The following search terms were used: “Simponi” OR “golimumab” AND 1) “pregnancy,” “pregnancy outcomes,” “birth defects,” “malformations,” “stillbirth,” and “spontaneous abortion.” 2) “lactation” and “breastfeeding.” 3) “fertility,” “contraception,” “oral contraceptives,” and “infertility.” No new data related to golimumab and pregnancy were identified since the FDA integrated review was conducted in November 2024. The following publications were found related to lactation:

- Matro et al.:¹¹ One woman treated with golimumab submitted breast milk samples up to 7 days after treatment. Golimumab was not detected in any of the samples.
- Saito et al.:¹² A lactating woman was receiving golimumab 50 mg subcutaneously every 4 weeks for inflammatory bowel disease. She collected milk samples at 3 and 5 days after the fourth dose and the levels of golimumab were just above the limit of quantification of <0.1 mcg/L.

There was one publication identified related to golimumab and fertility:

- Chatzimeletiou et al.¹³ Golimumab was administered subcutaneously to the patient once a month for 4 years. It is unclear why anti-TNF α treatment resulted in a higher incidence of morphologically abnormal spermatozoa, but these findings did not affect sperm concentration, motility or DNA fragmentation, which were all within normal limits.

⁹ Tsai YC, Chang HC, Chiou MJ, Luo SF, Kuo CF. Fetal-neonatal and maternal pregnancy outcomes in women with rheumatoid arthritis: a population-based cohort study. *BMJ Open*. 2022 Oct 26;12(10):e059203. doi: 10.1136/bmjopen-2021-059203. PMID: 36288841; PMCID: PMC9615975.

¹⁰ Kishore S, Mittal V, Majithia V. Obstetric outcomes in women with rheumatoid arthritis: Results from Nationwide Inpatient Sample Database 2003-2011☆. *Semin Arthritis Rheum*. 2019 Oct;49(2):236-240. doi: 10.1016/j.semarthrit.2019.03.011. Epub 2019 Mar 23. PMID: 30992155.

¹¹ Matro R, Martin CF, Wolf D, Shah SA, Mahadevan U. Exposure Concentrations of Infants Breastfed by Women Receiving Biologic Therapies for Inflammatory Bowel Diseases and Effects of Breastfeeding on Infections and Development. *Gastroenterology*. 2018 Sep;155(3):696-704. doi: 10.1053/j.gastro.2018.05.040. Epub 2018 May 30. PMID: 29857090.

¹² Saito J, Yakuwa N, Hosokawa Y, Hamada H, Suzuki T, Sago H, Kaneko K, Yamatani A, Murashima A. Establishment of a measurement system to evaluate breast milk transfer of biological agents using dry filter paper: A multi-institutional study. *Br J Clin Pharmacol*. 2024 Jan;90(1):146-157. doi: 10.1111/bcp.15876. Epub 2023 Aug 21. PMID: 37548054.

¹³ Chatzimeletiou K, Fleva A, Sioga A, Georgiou I, Nikolopoulos TT, Markopoulou M, Petrogiannis N, Anifandis G, Patrikiou A, Kolibianakis E, Giannakou A, Grimbizis G. Effects of Different Drug Therapies and COVID-19 mRNA Vaccination on Semen Quality in a Man with Ankylosing Spondylitis: A Case Report. *Medicina (Kaunas)*. 2022 Jan 24;58(2):173. doi: 10.3390/medicina58020173. PMID: 35208497; PMCID: PMC8875133.

Reviewer comment:

DPMH did not find new publications related to pregnancy since the integrated review of golimumab was conducted in November 2024. The published data related to lactation and fertility are limited and insufficient to inform labeling as they pertain to three patients.

III. DISCUSSION AND CONCLUSIONS

Pregnancy

The Applicant updated the Risk Summary and Human Data sections under subsection 8.1 of labeling based on the Nordic study and the November 2024 FDA integrated review. DPMH does not recommend any further updates to the Risk Summary or Human Data sections at this time. DPMH notes that Simponi labeling does not include a Clinical Considerations (CC) section for UC or RA and recommends adding this to labeling. DPMH notes that the CC section for other approved biologic products indicated to treat UC and RA includes associations with preterm delivery, low birth weight infants and small for gestational age but does not include the association with antepartum hemorrhage. As labelings for these other approved products do not include information about antepartum hemorrhage in the CC, DPMH discussed adding it to the labeling for Simponi with the DG team. DG stated that they favor not including antepartum hemorrhage in the CC at this time, as it would not align with other labelings. The addition of antepartum hemorrhage to the CC for products indicated to treat RA and UC may be considered in the future. See the labeling recommendations below.

DPMH does not recommend issuing postmarketing requirements for pregnancy safety studies, as no new safety signal has been identified.

Lactation

DPMH does not recommend updates to the lactation labeling, as no new information is available.

Females and Males of Reproductive Potential

DPMH does not recommend including subsection 8.3 of labeling, as no new information is available.

LABELING RECOMMENDATIONS

DPMH revised subsection 8.1 of labeling. The revisions appear in blue below. DPMH recommendations are below and reflect the discussions with DG. DPMH refers to the final BLA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

7.X Live Vaccines/Therapeutic Infectious Agents

Live vaccines should not be given concurrently with SIMPONI [see *Warnings and Precautions (5.X)*]. Therapeutic infectious agents should not be given concurrently with SIMPONI [see *Warnings and Precautions (5.X)*]. Infants born to women treated with SIMPONI during their

pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to SIMPONI in utero is not recommended for 6 months following the mother's last SIMPONI injection during pregnancy [see *Use in Specific Populations* (8.1)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from postmarketing case reports with golimumab use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. An observational study of northern European births observed similar unadjusted rates of major birth defects in infants exposed in utero to golimumab compared to no treatment or nonbiologic systemic therapy. However, this study had important limitations (*see Data*).

There are risks to the mother and the fetus associated with rheumatoid arthritis and ulcerative colitis in pregnancy (*see Clinical Considerations*). Monoclonal antibodies, such as golimumab, are transported across the placenta during the third trimester of pregnancy and may affect immune response in the in utero exposed infant (*see Clinical Considerations*).

In an animal reproductive study, golimumab administered by the subcutaneous route to pregnant monkeys, during the period of organogenesis, at doses that produced exposures approximately 360 times the maximum recommended human dose (MRHD) had no adverse fetal effects (*see Data*). In a pre- and post-natal development study with pregnant monkeys, subcutaneous administration of golimumab, during the later gestational and lactation periods, at doses producing maximal maternal blood concentrations approximately 460 times those found with the MRHD had no adverse developmental effects on infants (*see Data*).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and of miscarriage is 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

Golimumab crosses the placenta during pregnancy. Another TNF-blocking monoclonal antibody administered during pregnancy was detected for up to 6 months in the serum of infants. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to SIMPONI in utero is not recommended for 6 months following the mother's last SIMPONI injection during pregnancy [see *Warnings and Precautions* (5.10) and *Drug Interactions* (7.3)].

Data

Human Data

An observational, exposure-based, cohort study based on data from the Swedish, Danish, and Finnish Medical Birth Registers conducted between 2006-2020 (Sweden and Denmark) and 2006-2019 (Finland) compared the risk of major birth defects in 134 live-born infants exposed to golimumab (116 from women treated for rheumatic conditions, 18 from women treated for ulcerative colitis) to no treatment or nonbiologic systemic therapy. The unadjusted rate of major birth defects in infants exposed in utero was similar across all groups. However, this study had important limitations such as a small number of pregnant women exposed to golimumab, a wide exposure ascertainment window, and incomplete risk adjustment for potential confounders.

Animal Data

In an embryofetal developmental toxicology study in which pregnant cynomolgus monkeys were treated with golimumab during the period organogenesis from gestation days (GD) 20 to 51, exposures up to 360 times greater than the exposure at the MRHD (on an area under the curve (AUC) basis with maternal subcutaneous doses up to 50 mg/kg twice weekly) produced no evidence of fetal malformations or embryotoxicity. There was no evidence of maternal toxicity. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. In a pre- and postnatal developmental study in which pregnant cynomolgus monkeys were treated with golimumab from gestation day 50 to postpartum day 33, maximal drug concentrations approximately 460 times greater than that found with the MRHD (on a maximum blood concentration (C_{max}) basis at steady-state with maternal subcutaneous doses up to 50 mg/kg twice weekly) were not associated with any evidence of developmental defects in infants. There was no evidence of maternal toxicity. Golimumab was present in fetal serum at the end of the second trimester and in neonatal serum from the time of birth and for up to 6 months postpartum.

8.2 Lactation

Risk Summary

There is no information regarding the presence of SIMPONI in human milk, the effects on breastfed infants, or the effects on milk production. Maternal IgG is known to be present in human milk. Golimumab is present in the milk of lactating cynomolgus monkeys (*see Data*). If golimumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to golimumab are unknown. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for SIMPONI and any potential adverse effects on the breast-fed infants from SIMPONI, or from the underlying maternal condition.

Data

In the pre- and postnatal development study in cynomolgus monkeys in which golimumab was administered subcutaneously during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 400--fold lower than the maternal serum concentrations.

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/s/

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LYNNE P YAO
06/25/2025 11:43:38 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 11, 2025
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 125289/S-157
Product Name, Dosage Form, and Strength:	Simponi (golimumab) injection, 50 mg/0.5 mL, 100 mg/mL, (b) (4)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Janssen Biotech, Inc.
FDA Received Date:	December 12, 2024
TTT ID #:	2024-12229
1MEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP
DMEPA 1 Associate Director for Nomenclature and Labeling:	Idalia E. Rychlik, PharmD

1 INTRODUCTION

Janssen Biotech, Inc. submitted an Efficacy Supplement for Simponi (golimumab) (b) (4)

. Subsequently, the Division of Gastroenterology (DG) requested that we review the proposed Simponi Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review of BLA 125289/S-157.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

We evaluated the proposed Simponi Medication Guide (MG) and determined that it is acceptable from a medication error perspective.

However, the proposed Simponi Prescribing Information (PI), Instructions for Use (IFU), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Gastroenterology (DG) in Section 4 and for Janssen Biotech, Inc. in Section 5.

Note that DMEPA 1 is evaluating the HF validation study results under separate cover and, based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR THE DIVISION OF GASTROENTEROLOGY (DG)

A. Prescribing Information

1. Highlights of Prescribing Information

- As currently presented, the pediatric dosage information contains the symbols (e.g., $\geq$). We recommend replacing the symbols with their intended meaning (e.g., greater than or equal to). See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

2. Section 2 Dosage and Administration

- a. As currently presented, the pediatric dosage information contains the symbols (e.g., $\geq$). We recommend replacing the symbols with their intended meaning (e.g., greater than or equal to). See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

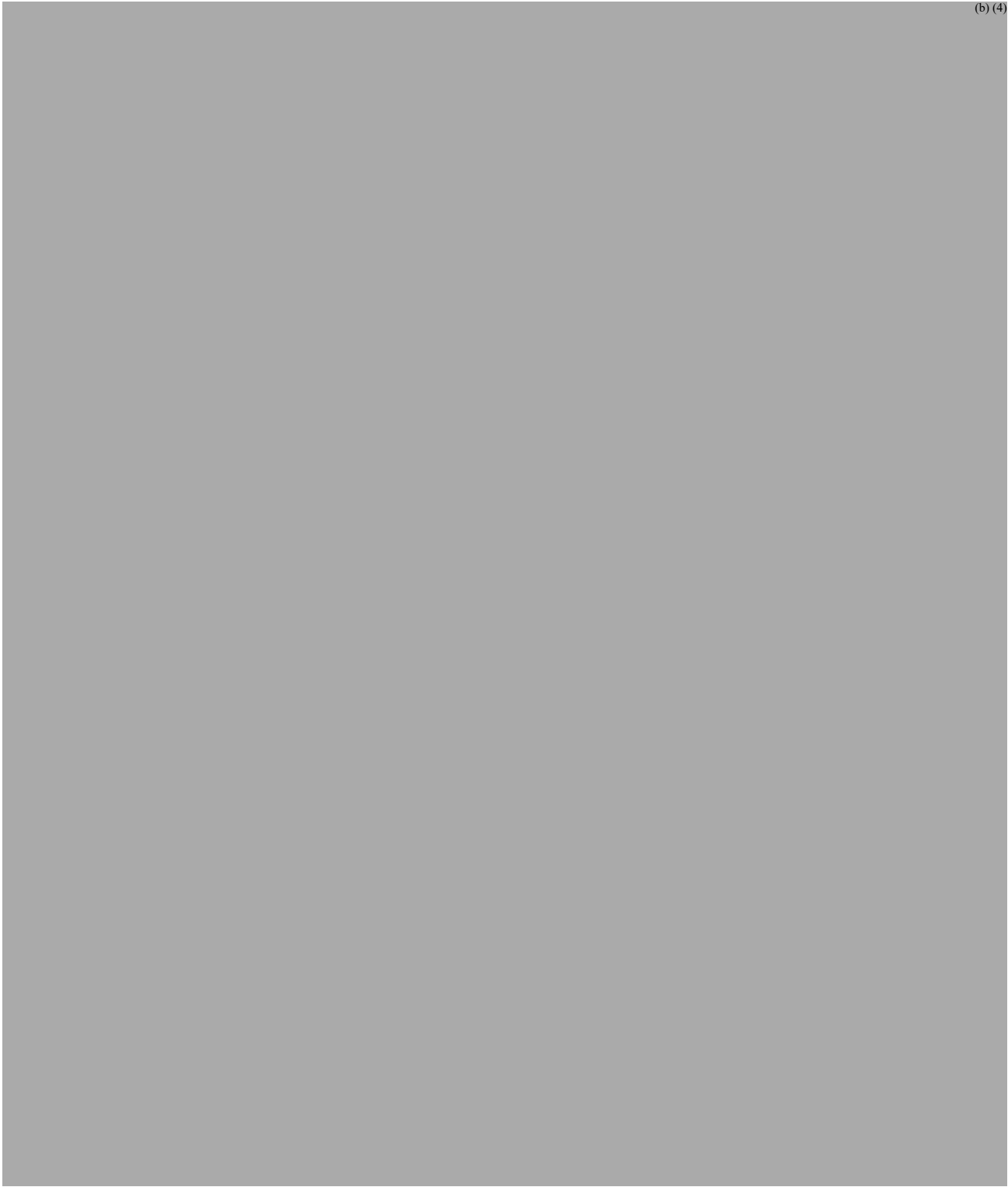
B. Instructions for Use (IFU)

1. Each numeric value presented in the storage statement is not immediately followed by its intended unit of measurement (i.e., °C or °F). The presentation of the storage statement should be clearly stated to avoid storage errors. Revise “Store SIMPONI in the refrigerator between 36° to 46°F (2° to 8°C)” to “Store SIMPONI in the refrigerator between 36°F to 46°F (2°C to 8°C)”.

5 RECOMMENDATIONS FOR JANSSEN BIOTECH, INC.



^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2022. Available from: <https://www.fda.gov/media/158522/download>.



APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Simponi received on December 12, 2024 from Janssen Biotech, Inc.

Table 2. Relevant Product Information for Simponi																		
Initial Approval Date	April 24, 2009																	
Proper Name	golimumab																	
Indication	- Adult patients with moderately to severely active <u>rheumatoid arthritis</u> in combination with methotrexate - Adult patients with active <u>psoriatic arthritis</u> alone or in combination with methotrexate - Adult patients with active <u>ankylosing spondylitis</u> - Adult (b) (4) with moderately to severely active <u>ulcerative colitis</u>																	
Dosage Form	injection																	
Strength	50 mg/0.5 mL, 100 mg/mL, (b) (4)																	
Route of Administration	subcutaneous																	
Dose and Frequency	Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis 50 mg subcutaneously once monthly Ulcerative Colitis - Adults 200 mg subcutaneous injection at Week 0, followed by 100 mg at Week 2, and then maintenance therapy with 100 mg every 4 weeks. - Pediatrics (proposed) <table><tr><th rowspan="2">Pediatric Weight</th><th colspan="3">Recommended Dosage</th></tr><tr><th>Week 0</th><th>Week 2</th><th>Week 6 and every 4 weeks thereafter</th></tr><tr><td>≥40 kg*</td><td>200 mg</td><td>100 mg</td><td>100 mg</td></tr><tr><td>15 – <40 kg*</td><td>100 mg</td><td>50 mg</td><td>50 mg</td></tr></table> (b) (4) * For pediatric patients weighing 15 kg or greater, administer the appropriate dose using the pre-filled syringe (50 mg/0.5 mL or 100 mg/mL) (b) (4)			Pediatric Weight	Recommended Dosage			Week 0	Week 2	Week 6 and every 4 weeks thereafter	≥40 kg*	200 mg	100 mg	100 mg	15 – <40 kg*	100 mg	50 mg	50 mg
Pediatric Weight	Recommended Dosage																	
	Week 0	Week 2	Week 6 and every 4 weeks thereafter															
≥40 kg*	200 mg	100 mg	100 mg															
15 – <40 kg*	100 mg	50 mg	50 mg															

Table 2. Relevant Product Information for Simponi

How Supplied	SIMPONI® (golimumab) Injection is a preservative-free, sterile, clear to slightly opalescent, colorless to light yellow solution for subcutaneous use in a single-dose prefilled autoinjector (contains a prefilled glass syringe), a single-dose prefilled glass syringe (b) (4). The Type 1 glass syringe has a coated stopper. The fixed stainless steel needle (5 bevel, 27G, ½ inch) is covered with a needle shield to prevent leakage of the solution through the needle and to protect the needle during handling prior to subcutaneous administration. The needle shield is made of a dry natural rubber containing latex. (b) (4) <table><tr><td>50 mg/0.5 mL single-dose prefilled syringe</td><td>1 pack</td><td>NDC 57894-070-01</td></tr><tr><td>100 mg/mL single-dose prefilled syringe</td><td>1 pack</td><td>NDC 57894-071-01</td></tr><tr><td>50 mg/0.5 mL single-dose prefilled SmartJect® autoinjector</td><td>1 pack</td><td>NDC 57894-070-02</td></tr><tr><td>100 mg/mL single-dose prefilled SmartJect® autoinjector</td><td>1 pack</td><td>NDC 57894-071-02</td></tr></table>			50 mg/0.5 mL single-dose prefilled syringe	1 pack	NDC 57894-070-01	100 mg/mL single-dose prefilled syringe	1 pack	NDC 57894-071-01	50 mg/0.5 mL single-dose prefilled SmartJect® autoinjector	1 pack	NDC 57894-070-02	100 mg/mL single-dose prefilled SmartJect® autoinjector	1 pack	NDC 57894-071-02
50 mg/0.5 mL single-dose prefilled syringe	1 pack	NDC 57894-070-01													
100 mg/mL single-dose prefilled syringe	1 pack	NDC 57894-071-01													
50 mg/0.5 mL single-dose prefilled SmartJect® autoinjector	1 pack	NDC 57894-070-02													
100 mg/mL single-dose prefilled SmartJect® autoinjector	1 pack	NDC 57894-071-02													
Storage	Refrigerate SIMPONI between 36°F to 46°F (2°C to 8°C) in the original carton to protect from light until the time of use. Do not freeze. Do not shake. Do not use SIMPONI beyond the expiration date (EXP) on the carton or the expiration date on the prefilled syringe (observed through the viewing window), the prefilled SmartJect autoinjector or the prefilled pen. If needed, SIMPONI may be stored at room temperature up to 77°F (25°C) for a maximum single period of 30 days in the original carton to protect from light. Once a syringe, autoinjector or prefilled pen has been stored at room temperature, do not return the product to the refrigerator. If not used within 30 days at room temperature, discard SIMPONI.														
Container Closure	(b) (4) prefilled syringe, prefilled SmartJect autoinjector														

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Simponi labels and labeling submitted by Janssen Biotech, Inc.

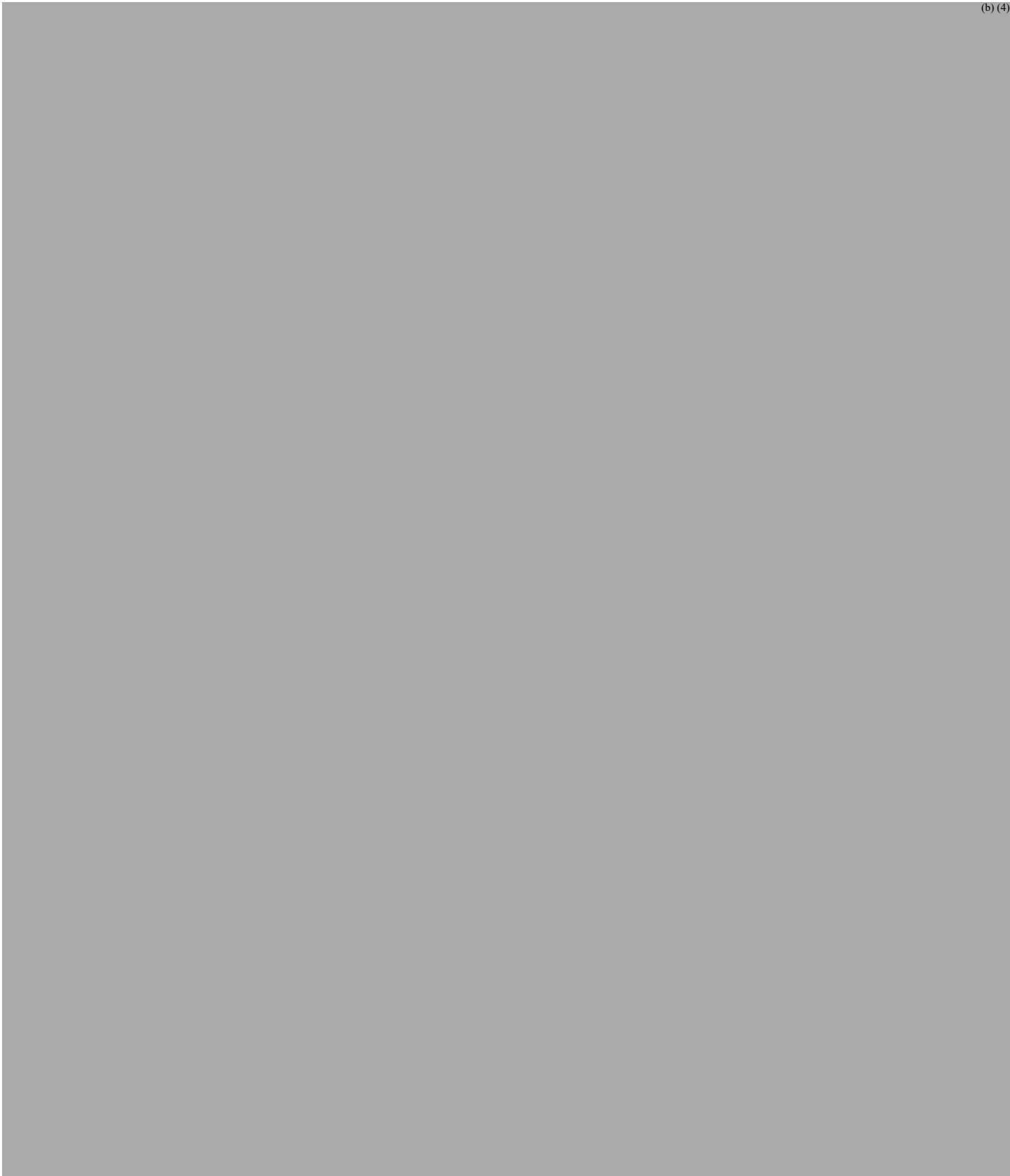
- Prescribing Information received on December 12, 2024, available from <\\CDSESUB1\EVSPROD\bla125289\0534\m1\us\114-labeling\draft\labeling\uspi-pediatric-uc-tracked-changes-pdf.pdf>.
- Medication Guide received on December 12, 2024, available from <\\CDSESUB1\EVSPROD\bla125289\0534\m1\us\114-labeling\draft\labeling\medication-guide-pediatric-uc-tracked-changes-pdf.pdf>.
- Instructions for Use for the prefilled syringe received on December 12, 2024, available from <\\CDSESUB1\EVSPROD\bla125289\0534\m1\us\114-labeling\draft\labeling\ifu-prefilled-syringe-tracked-changes-pdf.pdf>.
- Instructions for Use for the vario-dose prefilled pen (proposed) received on December 12, 2024, available from <\\CDSESUB1\EVSPROD\bla125289\0534\m1\us\114-labeling\draft\labeling\ifu-45mg045ml-prefilled-pen-pdf.pdf>.
- Container labels received on December 12, 2024
- Carton labeling received on December 12, 2024
- Professional Sample Carton Labeling received on December 12, 2024

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B.2 Container Labels and Carton Labeling Images

(b) (4)





APPENDIX C. PREVIOUS DMEPA REVIEWS

On March 14, 2025, we searched for previous DMEPA reviews relevant to this current review using the term “BLA 125289”. Our search identified zero previous reviews since the date of our last search on October 4, 2024.^c

^c Vee S. Label and Labeling Review for Simponi (BLA 125289/S-156). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 OCT 30. TTT ID No.: 2024-10680.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125289Orig1s157

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 24, 2025
Application Type and Number:	BLA 125289/S-157
Product Name, Dosage Form, and Strength:	Simponi (golimumab) injection, (b) (4)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Janssen Biotech, Inc (Janssen)
PNR ID #:	2025-1044726238
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Associate Director for Nomenclature and Labeling:	Idalia E. Rychlik, PharmD

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Simponi, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the Reference section and Appendix A, respectively. Janssen did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

Simponi is approved for adult patients (see Table 1 below) and is available in 50 mg/0.5 mL and 100 mg/mL strengths. Janssen is proposing to add an indication (b) (4)

Thus, Janssen submitted the proposed proprietary name, Simponi, for review on January 17, 2025 under BLA 125289/S-157.

1.2 PRODUCT INFORMATION

The following product information is provided in the prescribing information received as part of the original supplement submission on December 12, 2024.

Table 1. Relevant Product Information for Simponi		
Intended pronunciation:	SIM-po-nee	
Proper Name:	golimumab	
Indication:	(b) (4)	Adult patients with: • Moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate • Active psoriatic arthritis (PsA) alone, or in combination with methotrexate • Active ankylosing spondylitis (AS) • Moderate to severe Ulcerative colitis (UC) with an inadequate response or intolerant to prior treatment or requiring continuous steroid therapy
Dosage Form:	injection	

Table 1. Relevant Product Information for Simponi					
Strength:	(b) (4)			50 mg/0.5 mL; 100 mg/mL	
Route of administration:	Subcutaneous injection				
Dose and frequency:	Pediatric Weight	Recommended Dosage			- RA, PsA, and AS: 50 mg administered by subcutaneous injection once a month - UC: 200 mg initially administered by subcutaneous injection at Week 0, followed by 100 mg at Week 2 and then 100 mg every 4 weeks
		Week 0	Week 2	Week 6 and every 4 weeks thereafter	
	Greater than or equal to 40 kg*	200 mg	100 mg	100 mg	
	15 kg to less than 40 kg*	100 mg	50 mg	50 mg	
	(b) (4)				
	* For pediatric patients weighing 15 kg or greater, administer the appropriate dose using the pre-filled syringe (50 mg/0.5 mL or 100 mg/mL)				
	(b) (4)				
How Supplied:	(b) (4)			50 mg/0.5 mL single-dose prefilled syringe – 1 pack 100 mg/mL single-dose prefilled syringe – 1 pack 50 mg/0.5 mL single-dose prefilled SmartJect autoinjector – 1 pack 100 mg/mL single-dose prefilled SmartJect autoinjector – 1 pack	

Table 1. Relevant Product Information for Simponi

Storage:	Refrigerate SIMPONI between 36°F to 46°F (2°C to 8°C) in the original carton to protect from light until the time of use. Do not freeze. Do not shake. Do not use SIMPONI beyond the expiration date (EXP) on the carton or the expiration date on the prefilled syringe (observed through the viewing window), the prefilled SmartJect autoinjector or the prefilled pen. If needed, SIMPONI may be stored at room temperature up to 77°F (25°C) for a maximum single period of 30 days in the original carton to protect from light. Once a syringe, autoinjector or prefilled pen has been stored at room temperature, do not return the product to the refrigerator. If not used within 30 days at room temperature, discard SIMPONI.
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2 DISCUSSION

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Simponi.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Simponi would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) concurred with the findings of OPDP's assessment for Simponi. The Division of Rheumatology and Transplant Medicine (DRTM) concurred with the findings of OPDP's assessment for Simponi.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Simponi.

2.2.1 UNITED STATES ADOPTED NAMES (USAN) SEARCH

There is no USAN stem present in the proposed proprietary name.^a

2.2.2 COMPONENTS OF THE PROPOSED PROPRIETARY NAME

Janssen did not provide a derivation or intended meaning for the proposed proprietary name, Simponi, in their submission. This proprietary name is comprised of a single word that does not contain any components (i.e., a modifier, route of administration, dosage form, etc.) that can contribute to medication errors.

^a USAN stem search conducted on March 19, 2025.

2.2.3 COMMENTS FROM OTHER REVIEW DISCIPLINES AT INITIAL REVIEW

The Division of Rheumatology and Transplant Medicine (DRTM) did not forward any comments or concerns relating to Simponi at the initial phase of the review.

2.2.4 SAFETY ASSESSMENT OF THE PROPOSED NAME, SIMPONI

(b) (4)

[REDACTED]

. Additionally, our routine postmarketing surveillance has not identified any signals attributed to name confusion involving Simponi. We further acknowledge that, when marketing under the same proprietary name, the differences such as the different strengths can be communicated and differentiated by labels and labeling.

Therefore, given the aforementioned considerations, we do not object to the Applicant's proposal to market the proposed product with the proprietary name, Simponi.

2.2.5 COMMUNICATION OF DMEPA'S DETERMINATION

On March 24, 2025, DMEPA 1 communicated our determination to the Division of Rheumatology and Transplant Medicine (DRTM).

3 CONCLUSION

The proposed proprietary name, Simponi, is conditionally acceptable.

3.1 COMMENTS TO JANSSEN BIOTECH, INC

We have completed our review of the proposed proprietary name, Simponi, and have concluded that this proprietary name is conditionally acceptable.

If any of the proposed product characteristics as stated in your submission, received on January 17, 2025 are altered prior to approval of the marketing application, the proprietary name must be resubmitted for review.

4 REFERENCES

1. *United States Adopted Names (USAN) Stems*

USAN Stems List contains all the recognized USAN stems, available at <https://www.ama-assn.org/about/united-states-adopted-names/united-states-adopted-names-approved-stems>.

5 APPENDICES

APPENDIX A. FDA'S PROPRIETARY NAME RISK ASSESSMENT EVALUATES PROPOSED PROPRIETARY NAMES FOR MISBRANDING AND SAFETY CONCERNS

1. **Misbranding Assessment:** For prescription drug products, the Office of Prescription Drug Promotion (OPDP) assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by the Office of Non-Prescription Drugs (ONPD). OPDP or ONPD evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or ONPD provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment:** The safety assessment is conducted by DMEPA, and includes the following:
 - a. **Preliminary Assessment:** We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 3. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.^b

^b National Coordinating Council for Medication Error Reporting and Prevention. <https://www.nccmerp.org/about-medication-errors>. Last accessed 10/05/2020.

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