CT Application(s) Summary Report

- **Protocol title:** A Phase III, Multicenter, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Induction Therapy with RO7790121 in Patients with Moderately to Severely Active Crohn's Disease
- **Protocol code number: GA45332**
- ***Public Registry Number:*** EU CT Number: 2024-513054-30-00
- **Version:** 1
- **Date:** 22 August 2024

- **Investigational Medicinal Product being tested:**

Biological ■ **Pharmaceutical** ☐ **Innovative** ☐

Herbal medicine ☐ **Medical device** ☐

- **Sponsor: F. Hoffmann-La Roche Ltd**
- **Indication:** Induction Therapy with RO7790121 in Patients with Moderately to Severely Active Crohn's Disease
- **Investigator's brochure (IB)**

Version: 7
Date: Feb 2025

- **Name of all Sites:**

CRC, Faculty of Medicine, Alexandria University

- **Name of PI(s):**

Dr. Ezzat Ali

- **EDA approval date:** 21 October 2025

- **Summary of pre-clinical studies:**

A) Nonclinical Pharmacology

- **In in-vitro assessments**

RO7790121 bound to endogenous cynomolgus monkey and New Zealand White rabbit TL1A with high affinity and modulated the TL1A/DR3 pathway. Although binding was also demonstrated in the mouse, functional activity in the mouse assays was not seen, as was demonstrated with humans, cynomolgus monkeys, and New Zealand White rabbits. DcR3 acts as a decoy receptor for TL1A in humans, so the absence of mouse DcR3 suggests that pathways regulating TL1A function and signaling are not fully recapitulated in this species (mice).

➢ **Primary Pharmacodynamics**

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- **Binding Affinity of RO7790121 to Recombinant Mouse, Rat, Rabbit, Cynomolgus Monkey, and Human sTL1A:**

RO7790121 bound to recombinant mouse, rat, rabbit, and cynomolgus monkey sTL1A (Biacore binding dissociation constant [Kd] values: mouse 1059 ± 336 pM; rat 4858 ± 249 pM; rabbit 361±31 pM; cynomolgus monkey 81 ± 23 pM; KinExA Kd values: mouse 95.3 pM; cynomolgus monkey 3.5 pM; RO7790121 bound to recombinant human sTL1A with high affinity (Biacore Kd values ≤100 pM; KinExA Kd values=1.38, 3.6 pM).

- **Binding to Endogenous TL1A**

RO7790121 binds both forms of endogenous TL1A, represented by the full-length monocyte membrane protein, as shown by flow cytometry on immune complex (IC)-activated human monocytes, and the soluble cleaved form, as measured by the reduction in unbound endogenous sTL1A with an assay that measures TL1A only if it is unbound by the antibody. RO7790121 binding to endogenous sTL1A was demonstrated by the reduction of unbound sTL1A in the mouse splenocyte assay, cynomolgus monkey , and human whole blood assays.

-Ex Vivo Primary Cell Functional Assays Measuring Binding to Endogenous sTL1A and Neutralization of Membrane TL1A and sTL1A

- **Production of IFN-γ in Human and Cynomolgus Monkey Whole Blood Activated by Immune Complex and Interleukin- 12/Interleukin-18**

-RO7790121 acts by neutralizing pro-inflammatory signaling mediated through the **TL1A/DR3 pathway**, which is involved in pathogenic T-helper cell (Th1, Th2, Th17) responses as well as NK and NKT cell activation. Under inflammatory conditions, TL1A is induced on antigen-presenting cells (monocytes, macrophages, dendritic cells), while DR3 is upregulated on effector cells (T cells, NK, NKT cells). Because baseline TL1A and DR3 expressions are minimal in healthy blood, pathway activation in the assay was achieved using immune complexes to induce TL1A expression on monocytes and IL-12/IL-18 to induce DR3 expression on NK/NKT cells.

The ex vivo whole-blood assay demonstrated that TL1A-dependent IFN-γ production is mediated by both **membrane-bound and soluble TL1A**. RO7790121 effectively inhibited IFN-γ secretion by neutralizing both forms of TL1A, with maximal inhibition observed at the highest concentrations tested, confirming its functional activity in human and cynomolgus monkey whole blood.

- **Assessment of TL1A Neutralizing Activity by the Anti-TL1A Antibody in Human and Cynomolgus Monkey T Cells and New Zealand White Rabbit Peripheral Blood Mononuclear Cells**

- To increase the prevalence of DR3 on the cell surface and subsequently enhance the expression of IFN-γ, human or cynomolgus monkey T cells were stimulated with IL-12 and IL-18 and New Zealand White

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rabbit PBMCs were stimulated with immunocomplex and phytohemagglutinin. Species-matched recombinant TL1A was added to the stimulated cells to induce expression of IFN-γ, and IFN-γ mRNA was measured as the primary endpoint by quantitative real-time polymerase chain reaction.

- RO7790121 inhibited TL1A-induced IFN-γ in human T cells, cynomolgus monkey T cells, and New Zealand White rabbit PBMCs. Similar assays were conducted utilizing CD-1 mouse T cells, but were unsuccessful in demonstrating functional activity.

- **Reduction of Unbound Endogenous sTL1A in Mouse Splenocyte Preparations Activated by Immune Complexes and Anti-CD3**

- Attempts to develop a whole blood assay in mice, like that used in human and monkey whole blood, were not successful. Therefore, an alternative assay was developed. The potency and ability of RO7790121 to bind to endogenous mouse TL1A were measured in an assay in splenocyte preparations stimulated with IC (to induce expression of TL1A) and suboptimal anti-CD3 stimulation (to induce expression of DR3 on T cells and facilitate co-stimulation).

-The IFN-γ response in this assay was too low for proper evaluation of the inhibitory potency of RO7790121. However, in response to the IC stimulation of mouse splenocytes, endogenous sTL1A was elevated to a mean value of 1406 ± 206 pg/mL. This value was comparable to the values in human and cynomolgus monkey blood. A binding IC50 of 6.3 ± 3 pM was calculated from the reduction of unbound sTL1A.

- **In Vitro Cell-Based Functional Assays Measuring Neutralization of Recombinant Human sTL1A**

-To evaluate the functional potency and ability of RO7790121 to inhibit intracellular signaling of TL1A through DR3, the antibody was evaluated in TF-1 cells, which constitutively express DR3. RO7790121 inhibition of NFκB pathway activation was evaluated in TF-1 cells transduced with a luciferase gene under the control of the NFκB promoter.

-RO7790121 inhibited recombinant human sTL1A activation of DR3-mediated activation of the pro-inflammatory NFκB pathway in TF-1 cells. TL1A activated the apoptotic pathway mediated by caspase activation. RO7790121 was shown to inhibit recombinant human sTL1A caspase activation in TF-1 cells.

- **In Vivo Studies**

Studies with TL1A or DR3 gene-deficient mice as well as anti-TL1A efficacy studies in mouse disease models have shown the relevance of the TL1A pathway in several immune-mediated diseases including inflammatory bowel. Unfortunately, none of these models, or other in vivo mechanistic or pharmacology models relevant to the TL1A pathway, provide a clear translational relationship to predict the pharmacodynamic effects of RO7790121 in humans. Therefore, in vivo PK/PD or efficacy studies were not conducted with RO7790121.

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- **Secondary Pharmacodynamics**

Secondary pharmacodynamics with RO7790121 have not been conducted. The goal of secondary PD studies is to find the mode of action or effects that are not related to the desired therapeutic target.

- **Pharmacodynamic Drug Interactions**

In vitro or **in vivo** nonclinical pharmacokinetic drug interaction studies have not been conducted with RO7790121.

B) Pharmacokinetics and Drug Metabolism in Animals

-The PK of RO7790121 in cynomolgus monkeys was characterized by a low CL and a low Vss, resulting in mean $t_{½}$ values ranging from approximately 9 to 14 days, as the dose increased from 10 to 100 mg/kg, respectively. There was no evidence of target-mediated drug disposition at these doses.

-Following weekly IV or SC administration of RO7790121 to CD-1 mice or cynomolgus monkeys as part of GLP repeat-dose toxicity studies, systemic exposure increased with increasing dose. ADA was observed following repeat IV and SC dosing.

-Following IV dosing of RO7790121 in pregnant CD-1 mice and New Zealand White rabbits, exposure was observed in maternal and pooled fetal serum samples, and it was increased with increasing dose. ADA were detected in maternal serum samples; however, ADA were not detected in pooled fetal serum.

- **Absorption/Pharmacokinetic/Toxicokinetic Parameters**
- **Single-Dose Pharmacokinetics**

Following a single 10 mg/kg IV dose, the mean AUC_{inf}, CL, Vss, and $t_{½}$ values were 34,600 µg•h/mL, 0.308 mL/h/kg, 77.4 mL/kg, and approximately 9 days, respectively. After a single 100 mg/kg IV dose, the mean AUC_{inf}, CL, Vss, and $t_{½}$ values were 543,000 µg•h/mL, 0.185 mL/h/kg, 87.1 mL/kg, and approximately 14 days, respectively. The bioavailability of a 10 mg/kg SC dose compared to a 10 mg/kg IV dose was 80%, based on the mean $AUC_{0\text{-}42d}$ from the first dose.

- **Repeat-Dose Toxicokinetic**

In the repeat-dose toxicity studies, there were no apparent sex-related differences in exposure. Serum exposures (as assessed by Cmax and AUCtau) were generally similar in ADA-positive animals compared to ADA-negative animals.

- **Distribution**

Protein binding and tissue distribution studies were not conducted for RO7790121 in nonclinical species. The mean Vss values of RO7790121 in cynomolgus monkeys following a single IV dose of 10 and 100 mg/kg were 77.4 and 87.1 mL/kg, respectively, suggesting distribution into the extracellular fluids.

- **Metabolism**

Metabolism studies were not conducted with RO7790121, as these are not considered necessary or relevant for biologics such as RO7790121. Similar to other therapeutic proteins with molecular weights above the

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glomerular filtration cut-off, RO7790121 is expected to be metabolized primarily by proteolytic catabolism.

➢ **Excretion**

Standard elimination studies routinely conducted for small-molecule drugs are not considered necessary or relevant to biotechnology-derived pharmaceuticals such as RO7790121. Therefore, an excretion study was not conducted in animal species for RO7790121.

C)Toxicology and Safety Pharmacology

- In the GLP repeat-dose toxicity studies, the NOAELs were 250 mg/kg/week in the 3-month study in mice (for both IV and SC routes of administration) and 300 mg/kg/week (IV) in the 6-month study in cynomolgus monkeys; both NOAELs were the highest dose tested. In mice, mean Day 85 Cmax values were 8690 and 3590 µg/mL, and mean AUCtau values were 771,000 and 538,000 µg•h/mL for IV and SC routes, respectively, at the NOAEL (250 mg/kg/week). In cynomolgus monkeys, mean Day 176 Cmax and AUCtau values were 13,600 µg/mL and 1,330,000 µg•h/mL, respectively, at the NOAEL (300 mg/kg/week IV). No target organs have been identified with RO7790121.
- A dose range finding was conducted in pregnant New Zealand White rabbits via IV injection to establish doses in rabbits. The maternal and developmental NOAEL was established at 500 mg/kg/dose, the highest dose tested.
- An in vitro study to evaluate the functional activity of RO7790121 with human and cynomolgus monkey T cells and New Zealand White rabbit PBMCs demonstrated that New Zealand White rabbits and cynomolgus monkeys represented pharmacologically relevant species to humans.

➢ **Single-Dose Toxicity**

No dedicated single-dose studies have been conducted with RO7790121**.**

➢ **Repeat-Dose Toxicity**

- **In <u>mice</u>,** the higher group mean total protein and serum globulin values in this study were related to the presence of the test article, which is a mAb. Because no test article-related changes were seen in B cell numbers or the spleens, the higher group mean B cell numbers and splenic changes were not considered test article related. Serum concentration-time curves following the first dose in the 30-day exploratory study indicated RO7790121 concentrations that were typical of human IgG1 antibodies following administration to mice.

- **In <u>Cynomolgus Monkeys</u>,** Administration of RO7790121 did not result in any test article-related clinical signs, body weight, ophthalmic, or physical examination observations or any changes for vital signs (heart and respiration rates), body temperatures, electrocardiogram evaluations, cytokines, immunophenotyping, hematology, coagulation, or urinalysis. The NOAEL was the highest dose tested of 300 mg/kg/week IV or SC and was associated with mean Cmax concentrations and AUCtau values of

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17800 µg/mL and 1,970,000 µg•h/mL, respectively, at 300 mg/kg/week IV and 9060 µg/mL and 1,350,000 µg•h/mL, respectively, for 300 mg/kg/week SC for combined sexes.

- **Genotoxicity**

In accordance with the current International Council for Harmonization (ICH) guidance on the preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6(R1) 2011), genotoxicity studies have not been conducted with RO7790121. The type of genotoxicity studies routinely conducted for pharmaceuticals is not applicable to biotechnology-derived pharmaceuticals, as it is not expected that RO7790121 would interact directly with DNA or other chromosomal material.

- **Carcinogenicity**

No carcinogenicity studies have been conducted with RO7790121. Consistent with the current ICH guidance on the preclinical safety evaluation of biotechnology-derived pharmaceuticals (
ICH S6(R1) 2011), which states that standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals, no carcinogenicity studies are planned.

- **Reproductive and Developmental Toxicity**
- **Embryo-fetal Development**

There were no test article-related deaths or early deliveries. There were no test article-related maternal clinical signs, effects on body weights or food consumption, or macroscopic findings. There were no test article-related effects on ovarian or uterine parameters, fetal viability, or fetal body weights, fetal external or visceral abnormalities. Maternal serum concentrations increased with increasing dose. The maternal and developmental NOAEL in mice was 450 mg/kg/dose, the highest dose tested. The maternal and developmental NOAEL in rabbits was 500 mg/kg/dose.

- **Local Tolerance**

Separate local tolerance studies with RO7790121 have not been conducted. However, injection sites were examined in the general toxicity studies conducted with RO7790121 in mice and cynomolgus monkeys. No injection site findings were observed.

- **Antigenicity**

Antigenicity studies with RO7790121 have not been conducted. However, in the GLP studies, ADA was detected in some animals in the dosing phase of the 3- and 6-month repeat-dose toxicity studies. Immunogenicity in animals is not considered predictive of immunogenicity in humans.

- **Immunotoxicity**
- **In Vitro Complement Protein C1q and FcR Binding Assays**

The potential for RO7790121 (IgG1 mAb) to cause complement-dependent cytotoxicity and antibody-dependent cell cytotoxicity was investigated in an in vitro screening assay. RO7790121 was negative for C1q binding, and Fc binding was similar to, or lower than, the negative control antibodies.

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- **In Vitro Human Lymphocyte Activation Assay**

A human lymphocyte activation (HuLA) assay, which evaluates secondary immune responses specific to human peripheral blood mononuclear cells (PBMC), was conducted to screen for the immunosuppressive potential of RO7790121 in vitro. RO7790121 did not suppress flu-antigen-induced proliferation of human lymphocytes in vitro at concentrations of up to 1000 µg/mL.

- **In Vitro Human Cytokine Release Assay**

In the human CRA (1129812), in vitro soluble phase (blood) and solid phase (PBMC) were used to assess if RO7790121 induced the release of 3 human pro-inflammatory cytokines (TNF-α, IL-6, and IFN-γ). RO7790121 did not elicit test article-related cytokine release (TNF-α, IL-6, and/or IFN-γ) in the soluble phase assay at concentrations from 1 to 1000 µg/mL.

- **In Vitro Tissue Cross Reactivity**

A preliminary study was conducted to establish the conditions for the immunohistochemical reactivity of RO7790121 with normal human, cynomolgus monkey, and CD-1 mouse tissues. Immunohistochemical staining methods, positive and negative controls, and concentrations were established to determine the potential cross-reactivity of fluoresceinated RO7790121.It was observed that a large number of tissues had staining in all species. Tissue staining in the human tissue panel was generally similar to that in cynomolgus monkey and mouse tissue panels.

Although staining with fluoresceinated RO7790121 was observed in numerous tissue elements, the reported expression of TL1A is limited primarily to endothelium in normal tissue, although mononuclear cell types are also reported to express TL1A in inflamed or injured tissues. No adverse findings were observed, indicating that the staining observed in the ex vivo tissue cross-reactivity studies does not translate to in vivo effects.

- **Toxicology Analysis**

No target organs have been identified with RO7790121. Findings related to the administration of RO7790121 included effects on clinical pathology parameters and cytokine release in the human CRA in vitro.

- **Summary of previous clinical studies:**

RO7790121 has been evaluated in several completed and ongoing clinical studies as part of its clinical development program. Completed studies include Study **B7541001, B7541002, B7541006, B7541007, and B7541013,** while ongoing studies include **GA45392, GA45329, and GA45330.** In addition, further clinical studies are planned, including **GA45331, GA45332, CS45570, and CC45687.** RO7790121 is currently being developed for the treatment of immune-mediated diseases, **including ulcerative colitis (UC), Crohn's disease (CD), atopic dermatitis (AD),** and **metabolic dysfunction-associated steatohepatitis (MASH).**

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Study B7541001

Study B7541001 was a **Phase Ia randomized, double-blind, placebo-controlled single- and multiple ascending dose study** conducted in healthy participants to evaluate the **safety, tolerability, pharmacokinetics (PK),** and **pharmacodynamics (PD)** of RO7790121 administered as single intravenous (IV) doses and multiple IV or subcutaneous (SC) doses.

A total of **92 healthy participants** received study treatment. RO7790121 demonstrated a **favorable safety and tolerability profile,** with no deaths, serious adverse events (SAEs), or severe adverse events reported. Most treatment-emergent adverse events (TEAEs) were mild in severity. The most frequently reported TEAE was **headache.** No clinically significant findings were observed in laboratory parameters, vital signs, or electrocardiograms.

Pharmacokinetic analyses showed that RO7790121 exhibited characteristics typical of **IgG1 monoclonal antibodies,** including **low clearance, small volume of distribution, and a relatively long terminal half-life** ranging from approximately **6 to 23 days following IV administration. Following SC administration, absorption was slow, and moderate accumulation was observed with repeated dosing.**

1. Study B7541002

Study B7541002 was a **Phase IIa single-arm, open-label study conducted in participants with moderate to severe ulcerative colitis** to evaluate the **efficacy, safety, tolerability,** and **pharmacokinetics** of RO7790121 administered intravenously.

Fifty participants received **500 mg IV every 2 weeks for a total of seven doses.** The study demonstrated **statistically significant improvement in the primary efficacy endpoint,** with **endoscopic improvement observed at Week 14.** Improvements were also observed in clinical remission and clinical response endpoints.

Overall, RO7790121 was **generally well tolerated.** Treatment-emergent adverse events were reported in **66% of participants,** with the most common events including **arthralgia, ulcerative colitis exacerbation, abdominal pain, alopecia, back pain, and nasopharyngitis.** Grade ≥3 laboratory abnormalities were observed in a small number of participants, including decreased lymphocyte counts and increased creatine phosphokinase. No deaths were reported.

2.Study B7541007 Study

B7541007 was a **Phase IIb multicenter, randomized, double-blind, placebo-controlled dose-ranging study** conducted in participants with **moderate to severe ulcerative colitis** to evaluate **the efficacy, safety, and pharmacokinetics** of RO7790121.

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A total of **245 participants** were randomized and received RO7790121 at doses of **50 mg, 150 mg, or 450 mg subcutaneously every 4 weeks,** or **placebo** during **the induction phase,** followed by active treatment during **the maintenance phase.**

During the **induction phase,** approximately **47.8% of participants experienced at least one TEAE,** with the most frequently reported events including anemia and headache. During the maintenance phase, TEAEs were reported in **58.9% of participants,** with the most commonly reported events including **ulcerative colitis exacerbation, SARS-CoV-2 infection, anaemia, pyrexia, and headache.**

Serious adverse events occurred infrequently and were generally assessed as unrelated to study treatment. Overall, RO7790121 demonstrated **a manageable safety profile** in participants with ulcerative colitis.

3. Study GA45392

Study GA45392 (RVT-3101-201; TAHOE) is an **ongoing Phase II study** evaluating RO7790121 in participants with **moderately to severely active Crohn's disease.**

Based on evaluation of the clinical development program, the Sponsor decided to **accelerate development of RO7790121 into Phase III clinical trials in Crohn's disease,** and screening and further enrollment into this study were discontinued in January 2024. Participants were allowed to enter an **open-label extension phase,** where RO7790121 is administered at **450 mg SC every 4 weeks.**

As of the clinical cut-off date, a limited number of serious adverse events have been reported, including **worsening Crohn's disease, anaphylaxis reaction, lung cancer, and hemifacial paresthesia.** Two events were considered related to the study drug by the investigator. One participant experienced an **anaphylactic reaction during the first dose,** which resolved after appropriate medical management.

- RO7790121 continues to be evaluated in several ongoing and planned clinical studies as part of its global clinical development program. Ongoing studies include:
  - **GA45329 (AMETRINE-1) –** a Phase III multicenter, double-blind, placebo-controlled treat through study evaluating induction and maintenance therapy with RO7790121 in patients with moderately to severely active ulcerative colitis.
  - **GA45330 (AMETRINE-2) –** a Phase III multicenter, double-blind, placebo-controlled study evaluating induction therapy with RO7790121 in patients with moderately to severely active ulcerative colitis.

Planned studies include:

- **GA45331 (SIBERITE-1) –** a Phase III treat-through study evaluating induction and maintenance therapy with RO7790121 in patients with Crohn's disease.
- **GA45332 (SIBERITE-2) –** a Phase III study evaluating induction therapy with RO7790121 in patients with Crohn's disease.

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• **CS45570** – a Phase IIb study evaluating RO7790121 in patients with moderate to severe atopic dermatitis.
• **CC45687** – a Phase Ib study evaluating the safety, pharmacokinetics, and activity of RO7790121 in patients with advanced MASH liver fibrosis.

Overall, the available clinical data suggest that RO7790121 demonstrates **favorable pharmacokinetic characteristics, evidence of target engagement, and a generally acceptable safety profile,** supporting its continued clinical development across multiple immune-mediated diseases.

- **Protocol:** A Phase III, Multicenter, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Induction Therapy with RO7790121 In Patients with Moderately to Severely Active Crohn's Disease

Phase: III

CD is a chronic, progressive inflammatory disease of the gastrointestinal tract, characterized by periods of relapse and remission, which can ultimately lead to bowel damage and disability. Most patients present with an inflammatory phenotype, but over time, uncontrolled inflammation can lead to complications such as fibrotic strictures, fistula formation, or intestinal neoplasia. Half of all patients with CD develop intestinal complications within 20 years of diagnosis leading to surgical intervention. -The current goals of CD treatment are to induce and maintain clinical and endoscopic remission, halt the progressive course of disease, and prevent long-term complications. Current available therapies such as corticosteroids, immunosuppressants, and advanced therapies, including biological agents, are effective in many patients; however, the long-term efficacy rates remain unsatisfactory, with up to 30% of patients not exhibiting an initial response to treatment, and up to 50% of patients losing response over time. Furthermore, currently available advanced therapies are associated with various risks or adverse drug reactions such as serious infections, cardiovascular events, thrombosis, and malignancies. Despite available treatments, disease progression and complications result in an estimated 50%-80% of CD patients requiring surgery in their lifetime. While timely surgery is appropriate to avoid complications, surgery is not curative and carries risks of postoperative complications with associated risks of mortality. Furthermore, postoperative recurrence is common, depending on patient risk factors, such that approximately 50% of patients have endoscopic recurrence within one year of ileocolic resection. Repeated surgical procedures can result in short bowel syndrome with chronic malabsorption and potential dependence on total parenteral nutrition. Therefore, an unmet need exists for more safe and effective treatments for CD. -RO7790121 is a fully human IgG1 mAb against TL1A. TL1A is a member of the TNF superfamily of proteins (TNFSF) that is encoded by the TNFSF15 gene. TL1A plays a central role in the regulation of gut mucosal immunity and participates in immunological and fibrosis pathways involved in IBD pathogenesis. Detailed information on RO7790121 is provided in the RO7790121 Investigator's Brochure.

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Objective(s):

Primary Objective	Endpoints
To evaluate the efficacy of RO7790121 compared with placebo in inducing response	• Clinical remission, defined as CDAI < 150, at Week 12 • Endoscopic response, defined as decrease in SES-CD from baseline ≥ 50%, at Week 12
CDAI = Crohn's disease activity index; SES-CD = Simple Endoscopic Score for Crohn's disease.	
Key Secondary Objectives	**Corresponding Endpoints**
To evaluate the efficacy of RO7790121 compared with placebo in inducing response	• Symptomatic remission, defined as SF ≤ 2.8 and APS ≤ 1 with neither score greater than baseline, at Week 12 • Endoscopic remission, defined as SES-CD = 0 to 4 with decrease from baseline ≥ 2 and no subscore > 1, at Week 12 • Ulcer-free endoscopy, defined as SES-CD ulcerated surface • subscore of 0, at Week 12 • SF, from baseline through Week 12 • APS, from baseline through Week 12
To evaluate the efficacy of RO7790121 compared with placebo in terms of CD-related symptoms and health-related quality of life	• Bowel urgency, from baseline to Week 12 • Fatigue, as measured by FACIT-F, from baseline to Week 12 • IBDQ score, from baseline to Week 12
To evaluate the efficacy of RO7790121 compared with placebo in TL1A biomarker defined subgroups	Among TL1A biomarker-defined subgroups of participants: • Clinical remission at Week 12 • Endoscopic response at Week 12
APS = average of daily abdominal pain scores in the past week; CD = Crohn's disease; CDAI = Crohn's disease activity index; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; IBDQ = Inflammatory Bowel Disease Questionnaire; SES-CD = Simple Endoscopic Score for Crohn's disease; SF = average of daily number of liquid or very soft stools in the past week	
Other Secondary Objectives	**Endpoints**
To evaluate the efficacy of RO7790121 compared with placebo in inducing response	• Clinical response, defined as a decrease in CDAI from baseline ≥ 100, at Week 12

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	• Symptomatic response, defined as decrease in SF and APS ≥ 30% with neither greater than baseline, at Week 12
To evaluate the efficacy of RO7790121 compared with placebo in terms of the participant's global impressions and general well-being	• Overall change in CD symptoms, as measured by PGIC, from baseline to Weeks 2, 6, and 12 • Overall severity in CD symptoms, as measured by PGIS, from baseline to Weeks 2, 6, and 12 • General well-being, from baseline through Week 12
To evaluate the safety of RO7790121 compared with placebo	Incidence and severity of the following: • Adverse events • Serious adverse events • Adverse events leading to study treatment discontinuation • Adverse events of special interest
To evaluate the persistence of fistulas of participants treated with RO7790121 compared to placebo	Presence of draining fistulas from baseline through Week 12
APS = average of daily abdominal pain scores in the past week; CD = Crohn's disease; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; SF = average of daily number of liquid or very soft stools in the past week.	

Rationale:

The purpose of this study is to assess the efficacy and safety of RO7790121 (formerly PF-06480605 and RVT-3101) in patients with moderately to severely active Crohn's disease (CD). RO7790121 is a fully human neutralizing immunoglobulin G1 (IgG1) monoclonal antibody (mAb) against tumor necrosis factor-like ligand 1A (TL1A). TL1A plays a central role in the regulation of gut mucosal immunity and participates in immunological and fibrosis pathways involved in inflammatory bowel disease (IBD) pathogenesis by binding its receptor, death receptor 3 (DR3). Therapeutic options have expanded substantially over the past decade, with biologics (e.g., anti-tumor necrosis factor [TNF], anti-IL-12/IL 23, and anti-integrin molecule mAbs) and small-molecule treatments (e.g., Janus kinase [JAK] inhibitor upadacitinib) now available in addition to conventional therapies. However, a high unmet medical need remains for treatments with better benefit risk profiles that attenuate inflammation and clinical sequelae and provide sustained control to improve the long-term prognosis of patients with CD.

Design:

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This is a Phase III, multicentre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of induction therapy with RO7790121 in patients with moderately to severely active CD. The induction-only study will serve as a replication of the induction endpoint of the treat-through study (Study GA45331) **to support registration of RO7790121 for the treatment of adults with moderately to severely active CD.**

Phase:	Phase III	**Population Type:**	Adult patients and patients aged 16 to < 18 years where locally permissible
Control Method:	Placebo	**Population Diagnosis or Condition:**	Moderately to severely active Crohn's disease
Interventional Model:	Parallel groups	**Population Age:**	Age ≥ 18 to ≤ 80 years and patients aged 16 to < 18 years where locally permissible
Test Product:	RO7790121	**Site Distribution:**	Multi-site
Active Comparator:	Not applicable	**Study Treatment Assignment Method:**	Randomization
Number of Arms:	Two arms	**Number of Participants to Be Enrolled:**	Approximately 425

Study Treatment

RO7790121 (500 mg) or placebo will be administered IV at Weeks 0, 2, 6, and 10 (induction phase). In the open-label extension phase, RO7790121 will be administered either 450 mg SC every 4 weeks (Q4W) or 450 mg SC every 2 weeks (Q2W). Modification of the study drug dose is not permitted during the double-blind phases of the study. However, dose intensification or de-escalation (either from Q4W to Q2W or from Q2W to Q4W, respectively) may be permitted during the OLE phase. Any other dosing frequencies (e.g., weekly dosing) are not permitted.

Duration of Participation

The total maximum duration of study participation for an individual is expected to be approximately 30 weeks without OLE participation. With OLE participation, treatment will continue until RO7790121 is commercially available in that region or until the Sponsor decides to terminate the study, whichever is earlier.

- ***Recommendation &/ or*** **Questions & Answers: NA**

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- **Abbreviation:**

AD – Atopic Dermatitis
ADA – Anti-Drug Antibody
ADCC – Antibody-Dependent Cellular Cytotoxicity
AE – Adverse Event
APS – Average of Daily Abdominal Pain Scores
AUC – Area Under the Curve
AUCinf – Area Under the Curve from Time Zero to Infinity
AUCτ (AUCtau) – Area Under the Curve Over a Dosing Interval
CD – Crohn's Disease
CDAI – Crohn's Disease Activity Index
CL – Clearance
CRA – Cytokine Release Assay
ECG – Electrocardiogram
FACIT-F – Functional Assessment of Chronic Illness Therapy – Fatigue
GLP – Good Laboratory Practice
IB – Investigator's Brochure
IBD – Inflammatory Bowel Disease
IBDQ – Inflammatory Bowel Disease Questionnaire
IC – Immune Complex
IFN-γ – Interferon Gamma
IgG1 – Immunoglobulin G1
IL – Interleukin
IV – Intravenous
JAK – Janus Kinase
mAb – Monoclonal Antibody
MASH – Metabolic Dysfunction-Associated Steatohepatitis
mg – Milligram
mg/kg – Milligram per Kilogram
µg/mL – Microgram per Milliliter
mL/h/kg – Milliliter per Hour per Kilogram
pM – Picomolar
NF-κB – Nuclear Factor Kappa B
NK – Natural Killer Cell
NOAEL – No-Observed-Adverse-Effect Level
PBMC – Peripheral Blood Mononuclear Cell
PD – Pharmacodynamics
PGIC – Patient Global Impression of Change
PGIS – Patient Global Impression of Severity

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PK – Pharmacokinetics
R3 – Death Receptor 3
SAE – Serious Adverse Event
SC – Subcutaneous
SES-CD – Simple Endoscopic Score for Crohn's Disease
SF – Average Number of Liquid or Very Soft Stools
TEAE – Treatment-Emergent Adverse Event
TL1A – Tumor Necrosis Factor-Like Ligand 1A
TNF – Tumor Necrosis Factor
UC – Ulcerative Colitis
Vss – Volume of Distribution at Steady State

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