CT Application(s) Summary Report

- **Protocol title:** A Phase III, Multicenter, Double-Blind, Placebo-Controlled, Treat-Through Study to Assess the Efficacy and Safety of Induction and Maintenance Therapy with Ro7790121 in Patients with Moderately to Severely Active Crohn's Disease
- **Protocol code number: GA45331**
- ***Public Registry Number:*** EU CT Number: 2024-513053-69-00
- **Version:** 1
- **Date:** 1 August 2024

- **Investigational Medicinal Product being tested:**

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

Herbal medicine ☐ **Medical device** ☐

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

Version: 6
Date: Feb 2025

- **Name of all Sites:**
  1. Air force specialized Hospital
  2. Faculty of Medicine, Alexandria University
  3. National Liver Institute, Menoufia University
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- **EDA approval date:** 01 June 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

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absence of mouse DcR3 suggests that pathways regulating TL1A function and signaling are not fully recapitulated in this species (mice).

- **Primary Pharmacodynamics**
- **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 expression is 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.

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- **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 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 in 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**

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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.

- **Secondary Pharmacodynamics**

Secondary pharmacodynamics with RO7790121 have not been conducted. as 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 were characterized by a low CL and a low Vss, resulting in mean $t_{½}$ values ranging from approximately 9 to 14 days, as 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 were 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**

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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 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 human.

➢ **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

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study indicated RO7790121 concentrations that were typical of human IgG1 antibodies following administration to mice.

• **In Cynomolgus Monkeys,** 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 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 are not applicable for 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**

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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.

- **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 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 immune-histochemical 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.I t was observed tha a large number of tissues had staining in all species. Tissue staining in the human tissue panel were generally similar to those stained 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 administration of RO7790121 included effects on clinical pathology parameters and cytokine release in the human CRA in vitro.

- **Summary of previous clinical studies:**

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RO7790121 has been explored in the following studies:

B7541001 study	a Phase **Ia double-blind** placebo-controlled SAD/MAD study in **healthy** participants to evaluate the safety, tolerability, PK, and PD of single IV and multiple SC and IV doses of RO7790121
B7541002 study	a Phase **IIa** single-arm, **open-label**, two-stage study to evaluate the efficacy, safety, tolerability, and PK of RO7790121 in **participants with moderate to severe UC**
B7541007 study	a Phase **IIb**, multicenter, randomized, **double-blind** placebo controlled parallel group dose ranging study to evaluate the efficacy, safety, and PK of RO7790121 in adult **participants with moderate to severe UC**
GA45392 (RVT-3101-201)	an **ongoing Phase II**, multicenter, **double-blind**, two-arm study of SC RO7790121 for the treatment of **participants with moderate to severe active CD** to evaluate the efficacy, safety, tolerability, and PK of RO7790121 in adult participants with CD

1. Clinical Pharmacokinetics:

1.1. Absorption, Bioavailability, Distribution, Metabolism, and Elimination

1.1.1. Study B7541001

Following single IV infusion doses of RO7790121 (1–800 mg), peak serum concentrations occurred approximately 1.5–2 hours after the end of infusion, followed by a multiphasic decline. The terminal half-life ranged from 6 to 23 days, increasing with dose. Exposure (AUC) increased in a greater than dose-proportional manner, while Cmax increased approximately dose-proportionally. Clearance decreased with increasing dose, and the volume of distribution was low (3.4–5.5 L), indicating primary confinement to the vascular compartment.

After multiple SC administrations (30, 100, and 300 mg Q2W for three doses), absorption was slow and variable, with median Tmax ranging from ~48 to 335 hours depending on dose and dosing day. Dose-normalized exposure on Day 1 was dose-proportional, while exposure on Days 15 and 29 showed a trend toward greater than dose proportionality. Apparent clearance and volume of distribution were similar across SC doses, with half-lives of ~9–21 days and evidence of accumulation (Rac ~2.3–4.2). Estimated SC bioavailability was moderate (~42–47%).

With multiple IV dosing (500 mg Q2W for three doses), AUC increased over time while Cmax remained similar across doses. Moderate accumulation was observed, with a half-life of ~20 days, low clearance, and small volume of distribution.

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Overall, the pharmacokinetic profile of RO7790121 is consistent with that of a typical IgG1 monoclonal antibody, characterized by slow absorption after SC dosing, low clearance, small volume of distribution, and a long half-life.

1.1.2. Study B7541002

Participants with moderate to severe ulcerative colitis (UC) received RO7790121 at 500 mg intravenously every 2 weeks (Q2W) for a total of 7 doses. Peak serum concentrations (Cmax) ranged from 0.0993 to 1.24 mg/mL, with a geometric mean of 0.2634 mg/mL. Following Cmax, RO7790121 exhibited a biphasic decline, with a mean terminal half-life of 19.3 days. The geometric mean AUCtau at steady state was 57.61 mg·hr/mL, and the peak-to-trough ratio (PTR) was 3.0, indicating moderate fluctuation across the dosing interval. The geometric mean clearance (CL) was 0.00868 L/hr, and the volume of distribution at steady state (Vss) was low (4.69 L), consistent with predominant distribution within the plasma compartment.
Overall, the pharmacokinetic profile of RO7790121 in UC patients was comparable to that observed in healthy participants, supporting similar disposition characteristics across populations.

1.1.3. Study B7541007

During the induction phase of the Phase IIb study in participants with ulcerative colitis, median serum RO7790121 trough concentrations measured at Weeks 4, 8, 12, and 14 showed an approximately dose-proportional increase across the three induction dose groups. Trough concentrations increased progressively from Week 4 through Week 12, indicating accumulation during the induction period.
During the maintenance phase, dose sequences where the same dose was maintained across both phases, trough concentrations remained comparable from Week 14 through the end of treatment, consistent with the achievement of steady state.

1.2 Bioavailability

The subcutaneous bioavailability of RO7790121 was estimated from a population PK analysis (PMAR-EQDD-B754a-Proof of Concept-1272) using data from four studies in healthy participants (B7541001, B7541006) and UC patients (B7541002, B7541007), and was approximately 69%.

1.3 Pharmacokinetic Interactions

No drug-drug interaction study has been conducted for RO7790121.

2. Clinical Pharmacodynamics:

2.1.Study B7541001

Exploratory PD markers followed in healthy participants included sTL1A, hsCRP, IP-10, and leukocytes. RO7790121 did not affect the levels of hsCRP, IP-10, and leukocytes. Median serum total sTL1A levels generally peaked at Day 15 or Day 29 post-dose for the SAD cohort and at Day 30 or Day 43 (2 days or 15 days post last dose) for the MAD cohort in participants who were administered RO7790121. There

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were notable differences in median total sTL1A levels between participants who were administered RO7790121 and participants who were administered placebo, demonstrating target engagement.

2.2. Study B7541002

The biomarkers investigated in UC patients were serum total sTL1A, fecal calprotectin, and hsCRP. The considerable increase from baseline in total sTL1A profiles in UC participants indicated evidence of sustained peripheral sTL1A target engagement during treatment/induction. In the post-induction phase, the total sTL1A levels decreased slightly but were still higher as compared to baseline, which was suggestive of continued target engagement. The fecal calprotectin showed a significant reduction from baseline (51%-78%) following treatment with RO7790121 and the reduction was sustained through Week 26. The hsCRP concentrations showed a considerable decrease relative to baseline from Week 2 to Week 4, which was maintained through Week 26.

2.3. Study B7541007

The biomarkers investigated in UC patients were serum total sTL1A, fecal calprotectin, and hsCRP. There was no discernible change in the hsCRP across the 3 RO7790121 doses. Following treatment with RO7790121, a sharp increase in serum total sTL1A was observed starting at Week 4 and remained at those high level through Week 14 across all 3 RO7790121 doses, suggesting sTL1A target engagement over the induction phase the elevated serum total sTL1A levels, and thereby target engagement, was sustained throughout the maintenance phase. For participants that switched from placebo to RO7790121, an increase in serum total sTL1A was observed almost immediately following the switch.

3. Clinical Efficacy:

3.1. Study B7541002

The primary efficacy endpoint was met. The study showed statistically significant results in the primary endpoint with an endoscopic improvement rate of 38.2% (95% CI: 23.8%, 53.7%) at Week 14 in the PP population. The null hypothesis of 6% was rejected with a p-value <0.001. Similar CIs were found in the FAS population. The proportions of participants achieving remission at Week 14 (defined as a total Mayo score < 2 with no individual subscore > 1) were 24.0% (95% CI: 13.1%, 38.2%) and 26.7% (95% CI: 14.6%, 41.9%) in FAS and PP populations, respectively. The proportion of participants achieving endoscopic remission at Week 14 in FAS population with non-responder imputation was 10.0% (95% CI: 3.3%, 21.8%). The proportions of participants achieving remission (defined as a Mayo endoscopic subscore of 0 or 1, without friability, with stool frequency subscore of 0, and rectal bleeding subscore of 0), symptomatic remission, deep remission, clinical response, and histologic remission at Week 14 were 18.0% (95% CI: 8.6%, 31.4%), 18.0% (95% CI: 8.6%, 31.4%), 8.0% (95% CI: 2.2%, 19.2%), 72.0% (95% CI: 57.5%, 83.8%), and 40.0% (95% CI: 26.4%, 54.8%), respectively. The decreases from baseline in mean partial and total Mayo scores and UC endoscopic index of severity score were observed at Week

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14 with the treatment of RO7790121.The proportion of participants achieving remission at Week 14 was 18.0% (95% CI: 8.6%, 31.4%) in FAS population with non-responder imputation using MLE method (maximum likelihood estimator).

3.2. Study B7541007

The primary efficacy endpoint of the proportion of participants achieving clinical remission at Week 14 was not met. None of the treatment doses were statistically significantly **superior** to placebo (1-sided p-values were above 0.05 for each treatment group). However, for each of the secondary efficacy endpoints of proportion of participants achieving CR2, MR2, and EI at Week 14, all treatment doses differentiated from placebo. In general, the efficacy improvements seen during induction appear to be maintained during maintenance. For example, between Week 14 and Week 56, the MR2 rates continued to improve numerically or remained similar across treatment sequences, except for the 150 mg → 50 mg, 450 mg → 50 mg, and 450 mg → 150 mg sequences (which slightly declined numerically). At Week 56, the proportion of sustained MR2 remitters ranged from 0 to 33.3% among participants who switched from placebo to RO7790121 at the start of maintenance, and ranged from 33.3% to 75% among participants administered RO7790121 during both induction and maintenance. At Week 56, the proportion of MR2 remitters among non-remitters at Week 14 ranged from 12.5% to 54.5% among the 9 treatment sequences.

4. Clinical Safety

4.1. Safety in Healthy Participants

4.1.1. Study B7541001

A total of 92 healthy participants received study treatment (60 in the SAD period and 32 in the MAD period), with single doses up to 800 mg and multiple doses up to 500 mg administered. Six participants discontinued the study (three each from SAD and MAD), including one placebo participant per period. No discontinuations were attributed to treatment-related adverse events (AEs). Two participants were lost to follow-up, two withdrew consent, and one placebo participant discontinued for non-AE reasons at the investigator's request. Overall, RO7790121 was well tolerated. There were no deaths, serious AEs, severe AEs, AEs related to ADA/NAbs, dose reductions, or temporary treatment interruptions due to AEs. No clinically significant findings were observed in laboratory parameters, vital signs, or ECGs across SAD and MAD cohorts. In the MAD period, one participant discontinued due to a treatment-unrelated AE (pyuria), which was mild and resolved within one day.

In the SAD period, 45 all-causality TEAEs were reported by 21/44 RO7790121-treated participants, with 15 events considered treatment related (13 participants). In the placebo group, 20 all-causality TEAEs were reported by 7/16 participants, with 9 treatment-related events (5 participants).
In the MAD period, 44 all-causality TEAEs were reported by 17/24 RO7790121-treated participants, with 21 treatment-related events (11 participants). In the placebo group, 17 all-causality TEAEs were reported by all 8 participants, with 6 treatment-related events (5 participants).Headache was the most frequently reported TEAE overall and the most common treatment-related TEAE. Abdominal pain was the second

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most common treatment-related TEAE. The majority of TEAEs were mild; moderate TEAEs were more frequent in MAD than SAD cohorts, with no severe TEAEs reported. Although treatment-related TEAEs were more common in MAD cohorts, their incidence did not increase with higher doses.
In conclusion, RO7790121 demonstrated a favorable safety and tolerability profile in healthy participants, supporting further clinical development.

4.2. Safety in Phase II/III Studies

4.2.1. Study B7541002

A total of 50 participants with moderate to severe ulcerative colitis were enrolled and treated with RO7790121 500 mg IV every 2 weeks for a total of 7 doses. Of these, 28 were male and 22 were female, with a mean age of 40 years.

Treatment-Emergent Adverse Events (TEAEs)

Among the 50 treated participants, 33 (66.0%) reported at least one all-causality TEAE. The most frequently reported TEAEs (≥3 participants) were arthralgia and ulcerative colitis (6 participants [12.0%] each), followed by abdominal pain, alopecia, back pain, nasopharyngitis, nausea, and pharyngitis (3 participants [6.0%] each).

Treatment-Related TEAEs

A total of 8 participants (16.0%) experienced treatment-related TEAEs, each reported in one participant (2.0%). These included abdominal pain, acrochordon, increased alanine aminotransferase, alopecia, arthralgia, increased aspartate aminotransferase, back pain, diastolic hypertension, hematoma, headache, hypertension, infusion site bruising, muscle spasms, nausea, peripheral oedema, oropharyngeal pain, pruritus, and vertigo.

Laboratory Abnormalities

Grade ≥ 3 laboratory abnormalities were observed in 7 participants. Hematology abnormalities included decreased lymphocyte counts in 3 participants, while chemistry abnormalities included increased creatine phosphokinase (CPK) in 3 participants and hyponatremia in 1 participant.
Overall, the safety findings in Study B7541002 were consistent with the known profile of RO7790121 and manageable within the study setting.

4.2.2. Study B7541007

It was conducted across four periods: screening, induction, maintenance, and follow-up. During the 12-week induction phase, participants received RO7790121 at 50 mg, 150 mg, or 450 mg, or matched placebo, administered subcutaneously every 4 weeks. This was followed by a 40-week maintenance phase, during which all participants received active treatment at 50 mg, 150 mg, or 450 mg SC every 4 weeks. A 12-week follow-up period was conducted to complete final safety assessments.
A total of 245 participants were randomized and received at least one dose of study drug. The mean age of participants was 40.7 years during the induction phase and 40.8 years during the maintenance phase.

Treatment-Emergent Adverse Events (TEAEs)

Induction Phase

Among the 245 participants treated during induction, 117 (47.8%) reported at least one all-causality

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TEAE. The most frequently reported TEAEs (≥5%) were anaemia and headache (13 participants [5.3%] each). Treatment-related TEAEs were reported by 32 participants (13.1%), with the most common being injection site reactions (7 participants [2.9%]), headache (5 participants [2.0%]), fatigue (4 participants [1.6%]), and ulcerative colitis (3 participants [1.2%]).

Maintenance Phase

During the maintenance phase, 224 participants received treatment, of whom 132 (58.9%) reported at least one all-causality TEAE. The most frequently reported TEAEs (≥5%) were ulcerative colitis (22 participants [9.8%]), SARS-CoV-2 test positive (18 participants [8.0%]), anaemia (17 participants [7.6%]), and pyrexia and headache (12 participants [5.4%] each).

Treatment-related TEAEs were reported by 30 participants (13.4%), most commonly injection site reactions (6 participants [2.7%]), alopecia (5 participants [2.2%]), ulcerative colitis and SARS-CoV-2 test positive (4 participants [1.8%] each), and rash (3 participants [1.3%]).

Overall, RO7790121 demonstrated a manageable safety profile across both induction and maintenance phases, with a low and comparable incidence of treatment-related TEAEs between study periods.

4.2.3. Study RVT-3101-201

This is an ongoing blinded study. As of the data cutoff 08 December 2023 date, the available safety data did not reveal any new safety concerns.

4.3. Deaths and Serious Adverse Events

4.3.1. Study B7541001

There were no SAEs or deaths reported in the completed Phase I (Study B7541001).

4.3.2. Study B7541002

Within the B7541002 study, there were 4 SAEs reported. Three of these SAEs resulted from worsening underlying disease activity. The fourth SAE was a case of alopecia/baldness, which was considered treatment related by the investigator but not treatment related per the Sponsor. There were no deaths reported in the study.

4.3.3. Study B7541007

A total of 28 SAEs were reported in 25 patients during the study. Two patients experienced SAEs in both the induction and maintenance phases: one patient had COVID-19 pneumonia during induction and a tibia fracture during maintenance, while another patient experienced three events of cholecystitis (one during induction and two during maintenance).Two SAEs of anemia occurred during the screening phase prior to first dose and were therefore not considered TEAEs. The remaining 26 SAEs in 23 patients were classified as treatment-emergent SAEs (TE-SAEs).

Induction Phase:

Ten participants (4.1%) experienced 10 SAEs. These included events across placebo and active treatment groups. Most SAEs were assessed as unrelated to study drug. Two events—ulcerative colitis

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(placebo) and embolism (450 mg group)—were considered related by investigators but were assessed as unrelated by the Sponsor.

Post-Induction / Pre-Maintenance (No Maintenance Dosing):

Two participants experienced SAEs after completing induction but did not receive maintenance dosing. One case of ulcerative colitis was considered unrelated. One case of appendiceal neoplasm (low-grade appendicular mucinous neoplasm, pTis) was considered related by the investigator and possibly related by the Sponsor, based on temporal association and confounding by underlying ulcerative colitis.

Maintenance Phase:

Twelve participants (5.4%) experienced 13 SAEs across treatment sequences. The majority were assessed as unrelated to study drug. One event—lower gastrointestinal haemorrhage in the 450 mg→450 mg group—was considered related by the investigator but assessed as unrelated by the Sponsor.

Overall, SAEs occurred at a low frequency, with no consistent pattern suggesting a treatment-related safety signal. Most events were assessed as unrelated to RO7790121, and differences between investigator and Sponsor causality assessments were limited and addressed on a case-by-case basis.

5. Immunogenicity:

5.1.Study B7541001

The incidence of anti-drug antibodies (ADA) ranged from 50% to 100% across the SAD and MAD cohorts. Among participants receiving RO7790121, 56 of 68 participants were ADA positive, corresponding to an overall confirmed treatment-induced ADA incidence of 82.4%. Interpretation of immunogenicity data was limited for 11 participants whose RO7790121 serum concentrations remained above the assay tolerance level throughout the study. ADA positivity was first detected at 336 hours (Day 14) post-dose in the SAD cohorts and on Day 29 in the MAD cohorts.The incidence of neutralizing antibodies (NAb) ranged from 0% in two SAD and two MAD cohorts to 100% in the 3 mg IV cohort. Overall, 24 of 68 participants receiving RO7790121 were NAb positive, resulting in a confirmed NAb incidence of 35.3%. Assessment was limited in 43 participants due to RO7790121 concentrations exceeding assay tolerance. NAb positivity was first detected at 672 hours (Day 28) post-dose in the SAD cohorts and at 1680 hours (Day 70) post-dose in the MAD cohorts.Where evaluable, mean serum RO7790121 concentrations were lower in ADA-positive participants compared with ADA-negative participants, and were further reduced in participants with NAb log titers ≥ 0.70. Differences in PK exposure between ADA-positive and ADA-negative participants, as well as between participants with NAb log titers < 0.70 versus ≥ 0.70, were more pronounced in the MAD cohorts; however, no definitive conclusions regarding clinical impact could be drawn from the available data.

5.2. Study B7541002

The incidence of ADA as analyzed by the ADA assay with acid pretreatment was 82% with log10 titer values ranging from 1.31 to 4.42 and 1 value above the assay range (> 4.64). Five (5) participants (10%) tested NAb positive with the cell-based NAb assay and had relatively low log10 titer values ranging from 0.809 to 1.38. Following RO7790121 administration, the median time to first detection of ADA and NAb were 140 and 114 days, respectively.The similarity of the PK profiles in ADA positive and negative

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subjects, and NAb positive and negative subjects suggested a small overall immunogenic potential on PK. Trends of lower total sTL1A target engagement starting from Week 8 were observed for ADA and NAb positive participants compared to the ADA and NAb negative participants. There were no apparent effects of ADA and NAb status on endoscopic and remission endpoints at Week 14 (based on Fisher's Exact Test nominal p-values). However, the small sample size and the high incidence of ADA did not provide sufficient information to make a definitive conclusion on the impact of ADA/NAb on the efficacy.

5.3.Study B7541007

At Week 14, a total of 91.1%, 64.8%, and 39.8% of participants were ADA positive in the RO7790121 50 mg, 150 mg, and 450 mg groups, respectively. At Week 14, a total of 33.3%, 17.9%, and 7.9% of participants were NAb positive in the RO7790121 50 mg, 150 mg, and 450 mg groups, respectively. During the induction phase, there appeared to be minimal to no impact of ADA or NAb status on PK in the RO7790121 50 mg group, while numerically lower RO7790121 concentrations were observed in the ADA-positive or NAb positive participants in the 150 mg and 450 mg groups.

Despite lower PK in ADA-positive and NAb positive participants, there was heterogeneity in clinical efficacy endpoint outcomes by ADA and NAb status. There was heterogeneity in partial Mayo score by ADA and NAb status. ADA and NAb did not appear to have any impact on trough fecal calprotectin or hs-CRP during the induction phase. Participants with ADA or NAb generally had lower mean serum total sTL1A than those without ADA or NAb.

Overall, in the Phase IIb study, potential immunogenic adverse events were low in frequency, and an adjudication of immunogenicity-related adverse events did not reveal any events of clinical concern.

--Potential Clinical Impact of Immunogenicity

Treatment of participants with monoclonal antibodies may result in inappropriate immune responses and range from mild events with no apparent clinical manifestations to life-threatening reactions. Safety concerns associated with immunogenicity of monoclonal antibodies are acute reactions as an anaphylaxis, anaphylactoid reactions, serum sickness, tumor lysis syndrome, cytokine release syndrome, and non-acute reactions such as delayed hypersensitivity. Signs and symptoms of these events may develop during or shortly after administration of the IP.

The Sponsor will continue to monitor immunogenicity and the impact on safety and efficacy will be evaluated.

- **Protocol:** A Phase III, Multicenter, Double-Blind, Placebo-Controlled, Treat-Through Study to Assess the Efficacy and Safety of Induction and Maintenance Therapy with Ro7790121 in Patients with Moderately to Severely Active Crohn's Disease

  Phase: III

  Objective(s):

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Primary Objective	Corresponding Endpoints
• To evaluate the efficacy of RO7790121 compared with placebo in maintaining remission	• Clinical remission, defined as CDAI < 150, at Week 52 • Endoscopic response, defined as decrease in SES-CD from baseline ≥ 50%, at Week 52

Key Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of RO7790121 compared with placebo in inducing response	• Clinical remission, as defined above, at Week 12 • Endoscopic response, as defined above, at Week 12 • 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

Key Secondary Objectives (cont.)	Corresponding Endpoints (cont.)
To evaluate the efficacy of RO7790121 compared with placebo in maintaining response	• Endoscopic remission, as defined above, at Week 52 • Symptomatic remission, as defined above, at Week 52 • Corticosteroid-free clinical remission, defined as clinical remission at Week 52 and no use of corticosteroids for CD at least 8 weeks prior to Week 52 • Maintenance of clinical remission, defined as clinical remission at both Weeks 12 and 52 • Maintenance of endoscopic response, defined as endoscopic response at both Weeks 12 and 52 • Clinical remission and endoscopic remission at Week 52 • Ulcer-free endoscopy, as defined above, at Week 52
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 through Week 12 and Week 52 • Fatigue, as measured by FACIT-F, from baseline to Week 12 and Week 52 • IBDQ score, from baseline to Week 12 and Week 52
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 • Clinical remission at Week 52 • Endoscopic response at Week 12 • Endoscopic response at Week 52

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Other Secondary Objectives	Corresponding Endpoints
To evaluate the efficacy of RO7790121 compared with placebo in inducing and/or maintaining response	• Clinical response, defined as a decrease in CDAI from baseline ≥100, at Week 12 • 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, 12, and 52 • Overall severity in CD symptoms, as measured by PGIS, from baseline to Weeks 2, 6, 12, and 52 • General well-being, from baseline through Week 52
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

Other Secondary Objectives (cont.)	Corresponding Endpoints (cont.)
To evaluate the persistence of fistulas of participants treated with RO7790121 compared to placebo	Presence of draining fistulas from baseline through Week 12 and Week 52

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 Phase III, multicenter, double-blind, placebo-controlled, treat-through study will evaluate the efficacy and safety of RO7790121 compared with placebo in patients with moderately to severely active CD. Several key aspects of the study design and study population are summarized below.

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:	Three arms	**Number of Participants to Be Enrolled:**	Approximately 600

Study Treatment

RO7790121 (500 mg) or placebo will be administered IV at Weeks 0, 2, 6, and 10 (induction phase). RO7790121 (450 mg or 150 mg) or placebo will then be administered SC every 4 weeks (Q4W) from Week 12 through Week 52 (maintenance phase). In the open-label extension phase, RO7790121 will be administered either 450 mg SC 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 70 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:**
  - **AUC:** area under the concentration-time curve
  - **AUCinf:** area under the concentration-time curve from time 0 to infinity
  - **AUCtau:** area under the concentration-time curve during the dosing interval
  - **CD:** Crohn's disease
  - **CDAI:** Crohn's disease Activity Index
  - **CI:** Confidence interval
  - **CL/F:** apparent clearance
  - **CL:** systemic clearance
  - **Cmax:** maximum observed concentration
  - **CPK:** Creatine phosphokinase
  - **CR2:** clinical remission 2
  - **CRA:** cytokine release assay
  - **CT:** clinical trials
  - **CYP:** cytochrome P450
  - **DDDI** disease–related drug-drug interactions
  - **DR3:** Death receptor 3
  - **EDA:** Egyptian Drug Authority
  - **EI:** endoscopic improvement
  - **GLP:** Good Laboratory Practice
  - **IBD:** inflammatory bowel disease
  - **IC:** immune complex
  - **IC50:** 50% inhibitory concentration
  - **ICH:** International Council for Harmonization
  - **IFN-γ:** interferon gamma
  - **IgG:** immunoglobulin G
  - **IgG1:** immunoglobulin G1
  - **IL:** interleukin
  - **IV:** Intravenous
  - **JAK:** Janus kinase
  - **Kd:** binding dissociation constant
  - **MAbs:** monoclonal antibody
  - **mg:** milligram
  - **Nab:** neutralizing antibody
  - **NFκB:** nuclear factor kappa-light-chain-enhancer of activated B cells
  - **NK:** natural killer
  - **NOAEL:** no observed adverse effect level
  - **OLE:** Open Label Extension
  - **PBMC:** peripheral blood mononuclear cell

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- **PD:** pharmacodynamics
- **PK:** pharmacokinetics
- **SC:** Subcutaneous
- **t½:** terminal elimination half-life
- **TK** toxicokinetic
- **TL1A:** tumor necrosis factor-like ligand 1A
- **TNF:** anti-tumor necrosis factor
- **TNF:** Tissue Necrosis Factor
- **Vss:** volume of distribution at steady state
- **Vz/F:** apparent volume of distribution
- **ADA:** anti-drug antibody/antibodies
- **BIOINN:** Central administration of Biological and Innovative products and clinical studies

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