16 September 2021
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Simponi

golimumab

Procedure no: EMEA/H/C/000992/P46/037

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 15 June 2021, the MAH submitted a final clinical study report of a phase 1b study (CNTO148DML1001) for Simponi (golimumab), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Type 1 diabetes (T1D) is an autoimmune disorder with severe sequelae. Children and young adults are those that most frequently develop T1D.

The MAH submitted a final clinical study report (CSR) for:

Study CNTO148DML1001: A phase 1b study to evaluate Simponi (golimumab) therapy in children, adolescents, and young adults with pre-symptomatic type 1 diabetes.

The MAH stated that the study CNTO148DML1001 was a standalone clinical trial which included participants in the pediatric population and was not part of the Marketing Authorization for Simponi or any Follow-up Measures or part of the Risk Minimization Plan.

2.2. Information on the pharmaceutical formulation used in the study

The study agent (golimumab or matched placebo) was administered subcutaneous (SC) every 2 weeks (q2W) for 26 weeks (see study design below).

2.3. Clinical aspects

2.3.1. Clinical study

CNTO148DML1001: A phase 1b study to evaluate Simponi (golimumab) therapy in children, adolescents, and young adults with pre-symptomatic type 1 diabetes (study name: T1GER PAWS; protocol No.: CNTO148DML1001).

Description

The study CNTO148DML1001 was a phase 1b, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to determine the safety and tolerability, PK, and immunogenicity of golimumab administered SC in children, adolescents, and young adult participants with Stage 2 T1D (see below "Diagnosis and Main Criteria for Inclusion").

Methods

Objectives

The **primary objective** was to determine the safety and tolerability of golimumab in children, adolescents, and young adults with pre-symptomatic Stage 2 Type 1 diabetes (T1D).

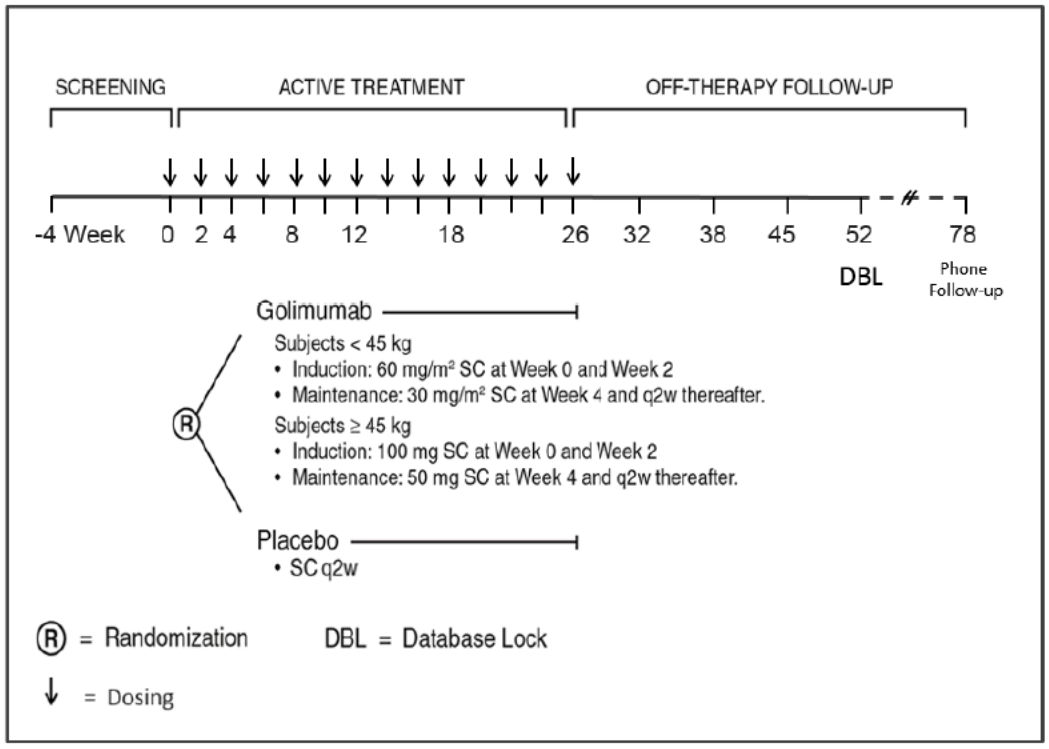
The **secondary objective** was to assess the pharmacokinetics (PK) and immunogenicity of golimumab in children, adolescents, and young adults with pre-symptomatic Stage 2 T1D.

The **exploratory objectives** were:

- to evaluate the metabolic course of participants with pre-symptomatic Stage 2 T1D.
- to assess immunologic profiles and indicators of β-cell stress in this study population.

Study design

Schematic Overview of the Study



Note: Week 52 was the last study visit to the study site for participants; Week 78 was an additional safety follow-up contact with each participant and was done by means of investigator telephone interview (no clinical site visit required).

Study population /Sample size

Following screening, approximately 10 to 15 eligible participants (see "Diagnosis and Main Criteria for Inclusion") were to be randomized to receive golimumab or placebo, administered SC every 2 weeks (q2w) for 26 weeks (active treatment) and monitored for an additional 26 weeks (off-therapy follow-up). An additional safety follow-up contact with each participant was performed at Week 78 (26 weeks after the off-therapy follow-up period) by means of investigator telephone interview. The initial randomization ratio of 2:1 to active: placebo was applied up to protocol Amendment 1. A randomization ratio of 6:1 was applied from protocol Amendment 2 onwards.

In this study, no formal sample size and power calculation were performed. The placebo-controlled design, randomization ratio, and number of participants were customary for Phase 1 safety studies and were deemed adequate to assess study objectives.

Number of Subjects (planned and analyzed):

Approximately 10 to 15 eligible participants were planned to be randomized to receive golimumab or placebo.

A total of 8 participants with Stage 2 T1D were enrolled and randomized from 4 centers (6 participants from 2 centers in the USA and 2 participants from 2 centers in Finland).

Diagnosis and Main Criteria for Inclusion:

Male and female participants aged 6 through 21 years (inclusive) with Stage 2 T1D. Participants were required to be positive for at least 2 of the following diabetes-related autoantibodies obtained at study screening:

- Glutamic acid decarboxylase (GAD-65) Autoantibodies
- Insulinoma-associated 2 Autoantibodies (IA-2A)
- Zinc transporter-8 (ZnT8)
- Islet Cell Cytoplasmic Autoantibodies (ICA)
- Insulin Autoantibodies (IAA)

Participants were required to be medically stable on the basis of physical examination, medical history, laboratory results, and vital signs performed at screening and to have a plasma glucose of 7.8 to 11.0 mmol/L (140 to 199 mg/dL) at the 120-minute timepoint of a 2-hour OGTT, OR have a plasma glucose of >200 mg/dL (>11.1 mmol/L) at the 30, 60, or 90-minute timepoint of a 2-hour OGTT OR have a HbA1c ≥5.7% but <6.5% (≥39 to <48 mmol/mol) evaluated at screening.

Duration of Treatment: The planned duration of study participation was approximately 82 weeks, including a 4-week screening, 26-week treatment period followed by a 26-week off-therapy follow-up period, and an additional safety follow-up contact with each participant which was performed 26 weeks after the off-therapy follow-up period (at Week 78) by means of investigator telephone interview.

Treatments

A total of 14 doses of the study agent (golimumab or matched placebo), were to be administered SC q2w. Study participants weighing <45 kg who were randomized to active treatment received an induction dose of golimumab 60 mg/m^2 SC at Weeks 0 and 2 followed by a maintenance dose of 30 mg/m^2 SC at Week 4 and q2w through Week 26. Study participants weighing ≥45 kg who were randomized to the active treatment group received an induction dose of golimumab 100 mg SC at Weeks 0 and 2 followed by a maintenance dose of golimumab 50 mg SC at Week 4 and q2w through Week 26. Participants randomized to the placebo treatment group received a SC placebo injection q2w through Week 26 to match the active arm.

Weight, and if necessary, body surface area, was calculated at Week 0 and Week 12 for the dose of golimumab (Table 1 below).

Table 1: Golimumab SC Dosing Regimens by Body Weight Cut-off for Participants Who Are Randomized to the Golimumab Treatment Group		
Body weight*	**Week 0 and 2**	**Week 4 through Week 26**
<45 kg	60 mg/m^2	30 mg/m^2 q2w
≥45 kg	100 mg	50 mg q2w
Number of injections	1 or 2**	1**

*Body weight to be evaluated at Week 12 with dose adjustment if necessary (below and see Schedule of Activities table).
**Refer to Appendix 6 of the study Protocol.
SC = subcutaneous; q2w = every 2 weeks

Outcomes/endpoints

Criteria for Evaluation:

SAFETY EVALUATIONS

Safety evaluation included regular monitoring for clinically-related adverse events (AEs) including injection-site reactions, clinical laboratory changes, and active monitoring of early detection of active tuberculosis (TB). Monitoring of cytomegalovirus (CMV) and Epstein-Barr virus (EBV) viral load was done to detect if there is any study treatment effect on primary immune response to these infections that often take place during childhood and adolescence or could impact reactivation of these viruses in those who have been infected previously.

PHARMACOKINETIC EVALUATIONS

Serum samples for the measurement of golimumab concentrations were collected at Weeks 0, 2, 4, 8, 12, and 26. Samples at Week 0, 2, and 4 were associated with the induction doses administered at Weeks 0 and 2. Serum samples were analyzed to determine concentrations of golimumab using a validated, specific, and sensitive immunoassay method by or under the supervision of the sponsor.

IMMUNOGENICITY EVALUATIONS

Samples for antibodies to golimumab assessment were collected at baseline (Week 0), Week 2, Week 4, Week 8, Week 12, and Week 26 and were analyzed using a drug-tolerant enzyme immunoassay. The detection and characterization of antibodies were performed using a validated highly-sensitive, drug-tolerant assay method by or under the supervision of the sponsor. Serum samples were screened for antibodies binding to golimumab and the titer of confirmed positive samples were reported. Participants who were positive for antibodies to golimumab were further tested for neutralizing antibodies.

METABOLIC ASSESSMENTS

Metabolic assessments included blood glucose, C-peptide, insulin, pro-insulin, and pro-insulin/C-peptide ratios from the OGTT, HbA1c, and continuous glucose monitoring (CGM).

Statistical Methods

No formal hypothesis testing was conducted. Study data were summarized using descriptive statistics. Continuous variables were summarized using the number of observations, mean, standard deviation (SD), coefficient of variation, median, and range as appropriate. Categorical values were summarized using the number of observations and percentages as appropriate. Graphic data displays were also be used to summarize the data. No formal sample size and power calculation were performed.

Safety assessments included the examination of the incidence rates of AEs, vital signs, clinical laboratory parameters, and physical examinations. Safety analyses were conducted on the Safety Analysis Set, which was defined as all participants who had received at least 1 dose of study agent.

Serum golimumab concentrations were summarized over time. For each treatment group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum were calculated for the golimumab serum concentrations at each sampling time of golimumab.

The incidence of antibodies to golimumab was summarized over time for all participants who received at least 1 dose of golimumab and had appropriate samples for detection of antibodies to golimumab. The maximum titers of antibodies to golimumab were summarized for participants who were positive for antibodies to golimumab.

Metabolic endpoint analysis included the 2-hour C-peptide area under the concentration-time curve (AUC) in response to an OGTT, the HbA1c data, and the conversion rates from Stage 2 to Stage 3 T1D.

Results

Recruitment/ Number analysed

Study Disposition; Randomized Subjects (Study CNTO148DML1001)

	Placebo	Golimumab	Total
Analysis Set: All Randomized Subjects	3	5	8
Subjects randomized	3 (100%)	5 (100%)	8 (100%)
Subjects treated with study agent	3 (100%)	5 (100%)	8 (100%)
Completed study participation	3 (100%)	5 (100%)	8 (100%)
Terminated study participation prematurely	0	0	0
Reason for termination			
Discontinued the study agent	1	0	1
Reason for discontinuation			
Adverse event	1 (33.3%)	0	1 (12.5%)

A total of 21 participants were screened of which 8 participants with Stage 2 T1D were enrolled and randomized from 4 centers (6 from 2 centers in the US and 2 from 2 centers in Finland). Of these, 5 participants were randomized to the golimumab treatment arm and 3 participants were randomized to the placebo treatment arm. There were no incorrect randomizations in this study and all participants received the assigned treatment.

Of 8 participants, 1 participant in the placebo group discontinued the study treatment after Week 20 due to an AE. No participants from the golimumab treatment group reported discontinuation of study treatment. Two participants had skipped the Week 45 follow-up visit due to COVID-19 hospital restrictions.

CHMP comment:

According to the MAH, one participant in the placebo group experienced an AE of serum sickness (3 days after the Week 20 dose received). This event was assessed by the investigator as reasonably related to the study treatment that led to discontinuation of study treatment (placebo).

Major protocol deviations

One participant in the golimumab treatment group reported 2 major protocol deviations during the study. For one participant in the golimumab treatment group, on Study Day 1 (Screening phase) the protocol was not adhered to for a laboratory test. With sponsor approval, this participant had CBC

checked locally with an inclusionary white blood cell count of 4.0×10^9/L before randomization. Between Study Days 30 and 170, the participant developed 7 episodes of neutropenia (lowest value recorded on Study Day 96: 0.7×10^9/L). The participant should have been withdrawn permanently from receiving study drug as he met the criteria of a severe AE and AE probably related to study drug; this was not done and recorded as a major protocol deviation.

These events were assessed by the investigator as Grades 2 or 3, moderate to severe in intensity and probably related to the study drug. The site investigator closely monitored this participant for safety, with additional local safety laboratory hematology testing. Per protocol guidelines, for an AE that was assessed as severe and related to study treatment, this deviation should have qualified the participant for permanent discontinuation from study treatment. The first severe neutropenia occurred on Study Day 30. The medical monitor was consulted regarding the clinical treatment plan of continued neutrophil monitoring and criteria for withholding study drug and agreed to the plan of continuing study drug if absolute neutrophil count exceeded 1.0×10^9/L given the fact that reduced neutrophils have been described in children who are at increased risk for the development of T1D (Salami 2018). Study treatment was withheld in all cases of severe neutropenia; however, the participant was not permanently discontinued to receive study treatment. This resulted in this being flagged as a major protocol deviation.

Baseline data

The majority of participants were white (7 [87.5%]) and male (7 [87.5%]). The mean (SD) age of the study population was 10.69 (2.396) years (range: 7.5 to 14.8 years) with a higher proportion of the participants aged <12 years (5 [62.5%]). The mean (SD) baseline 2-hour (120-minute) glucose value, 2-hour peak C-peptide, and 2-hour C peptide AUC were higher in the golimumab treatment group compared with the placebo group. At baseline, all 8 participants were positive for diabetes related autoantibodies (GAD-65 [100%], IA-2 [75%], insulin and ZnT8 [50% each], and ICA [25%]).

The mean (SD) duration of treatment exposure was 26.26 (0.19) weeks for golimumab and 24.29 (3.59) weeks for placebo. During this period, the mean (SD) number of study agent administrations were also comparable: 13.2 (1.79) doses of golimumab and 13 (1.73) doses of placebo.

Efficacy results

According to the MAH, there were no efficacy analyses planned for this study. Exploratory metabolic assessments were summarized descriptively. Due to low sample size, no firm conclusions could be drawn for the metabolic assessments data.

Three participants from the golimumab treatment group progressed to Stage 3 T1D on Study Days 186, 378, and 401; indicating the progression occurred after the last dose of study drug i.e., during the follow-up phase.

Pharmacokinetics and Immunogenicity results

Pharmacokinetics:

The PK Analysis Set included 5 participants who received at least 1 golimumab injection and had sufficient PK samples for analysis.

Following SC administration of 60 mg/m^2 induction doses at Weeks 0 and 2, median trough serum golimumab concentrations at Week 2 and Week 4 were 5.54 µg/mL (mean ± SD: 5.09±1.351) and 8.19 µg/mL (mean ± SD: 9.01±2.78), respectively. Trough serum golimumab concentrations started to decline once the lower maintenance dose of 30 mg/m^2 was started at Week 4 and every 2 weeks

thereafter. At Week 12, the median trough serum golimumab concentration was 4.85 µg/mL (mean ± SD: 4.52±2.40). At Week 26, the median trough serum golimumab concentration was 4.24 µg/mL (mean ± SD: 3.95±2.85). According to the MAH, it is indicated that steady-state trough golimumab levels in T1D participants were maintained through Week 26.

Immunogenicity:

Antibodies to golimumab were detected in 2 of 5 golimumab-treated participants with appropriate samples through Week 26. The highest titer was 1:1536.

One of these two anti-drug antibody (ADA) positive participants were positive for neutralizing antibodies.

Safety results

Summary of All Adverse Events

All 8 participants experienced at least 1 TEAE through Week 52 (Table below).

Overall Summary of Treatment-Emergent Adverse Events through Week 52
Safety Analysis Set (CNTO148DML1001)

	Week 0-26		Week 26-52		Week 0-52	
	Placebo	Golimumab	Placebo	Golimumab	Placebo	Golimumab
Analysis Set: Safety	3	5	3	5	3	5
Avg duration of follow-up (weeks)					50.76	53.57
Subjects with 1 or more:						
AEs	3 (100%)	5 (100%)	3 (100%)	5 (100%)	3 (100%)	5 (100%)
Related AEs[a]	1 (33.3%)	1 (20%)	0	0	1 (33.3%)	1 (20%)

	Week 0-26		Week 26-52		Week 0-52	
	Placebo	Golimumab	Placebo	Golimumab	Placebo	Golimumab
AEs leading to death[b]	0	0	0	0	0	0
Serious AEs	0	0	0	0	0	0
Related serious AEs	0	0	0	0	0	0
AEs leading to discontinuation	1 (33.3%)	0	0	0	1 (33.3%)	0

Key: AE = adverse event, Avg = average
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study intervention.
[b] AEs leading to death are based on AE outcome of Fatal.
Note: AEs for week 0-26 was to summarize AEs onset through week 26 including the last day of the treatment period while AEs of week 26-52 for AEs onset after week 26 through week 52.
AEs for week 0- 52 was to summarize AEs onset through week 52 including week 52 visit day.
Duration of follow up was derived by the duration until week 52 visit day.

During the study, no deaths, SAEs, severe infections including TB, or malignancies were reported, according to the MAH.

One participant in the placebo group experienced an AE of serum sickness on Day 144 (3 days after the Week 20 dose received). This event was assessed by the investigator as reasonably related to the study treatment and led to discontinuation of study treatment (placebo). The event of serum sickness resolved in 7 days. One participant in the golimumab treatment group developed TEAEs (including neutropenia and injection-site urticaria) that were assessed by the investigator as reasonably related to the study drug.

TSFAE04: Number of Subjects With Reasonably Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term through Week 52; Safety Analysis Set (CNTO148DML1001)

	Week 0-26		Week 26-52		Week 0-52	
	Placebo	Golimumab	Placebo	Golimumab	Placebo	Golimumab
Analysis Set: Safety	3	5	3	5	3	5
Avg duration of follow-up (weeks)					50.76	53.57
Subjects with 1 or more related AEs	1 (33.3%)	1 (20%)	0	0	1 (33.3%)	1 (20%)
System-organ class/Preferred term						
Blood and lymphatic system disorders	0	1 (20%)	0	0	0	1 (20%)
Neutropenia	0	1 (20%)	0	0	0	1 (20%)
General disorders and administration site conditions	0	1 (20%)	0	0	0	1 (20%)
Injection Site Urticaria	0	1 (20%)	0	0	0	1 (20%)
Immune system disorders	1 (33.3%)	0	0	0	1 (33.3%)	0
Serum Sickness	1 (33.3%)	0	0	0	1 (33.3%)	0

Key: AE = adverse event, Avg = average
Note: An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 23.0.
Note: AEs for week 0-26 was to summarize AEs onset through week 26 including the last day of the treatment period while AEs of week 26-52 for AEs onset after week 26 through week 52.
AEs for week 0- 52 was to summarize AEs onset through week 52 including week 52 visit day.
Duration of follow up was derived by the duration until week 52 visit day.

Except for 5 non-serious but severe TEAEs (golimumab: 4 events of neutropenia in 1 participant; placebo: 1 event of serum sickness in 1 participant), all other TEAEs were assessed as mild or moderate in intensity, according to the MAH.

Between the Week 52 last visit and the Week 78 telephone contact period, there was one participant from the golimumab treatment group that experienced multiple AEs of hypoglycemia after progressing to Stage 3 T1D on Day 378. All these AEs of hypoglycemia were moderate in intensity, and possibly related to study treatment, according to the MAH.

The MAH has also summarized the safety results (short critical expert overview) as follows:

- The most commonly reported treatment-emergent adverse events (TEAEs) from Week 0 to Week 52 were headache, nasopharyngitis, upper respiratory tract infection, influenza, and neutropenia. There were no deaths, SAEs, severe infections including tuberculosis, or malignancies.
- One participant in the placebo group developed an AE of serum sickness that led to discontinuation of study treatment.
- Two events of injection-site reaction were reported in 2 participants (one in each participant) receiving golimumab, both were mild and of short duration.
- One participant experienced multiple episodes of Level 2 hypoglycemia after progressing to Stage 3 T1D during the safety follow-up period.
- Three participants each from both treatment groups developed mild, non-serious infections which included nasopharyngitis, influenza, upper respiratory tract infection, otitis externa, rhinitis, and gastroenteritis.
- One participant in the golimumab treatment group developed TEAEs (including neutropenia and injection-site urticaria) that were assessed by the investigator as reasonably related to the study drug. Reduced neutrophils have been described in children who are at increased risk for the development of T1D.
- There were no clinically significant findings in clinical chemistry, Epstein-Barr virus/cytomegalovirus serology, vital signs, or physical examination.

CHMP comment:

No deaths, SAEs, severe infections including TB, or malignancies were reported, according to the MAH.

Overall, the adverse events noted in the study participants with Stage 2 T1D are consistent with the known safety profiles of golimumab (e.g. according to the current SmPC approved for the pJIA indication section 4.8, Very common: upper respiratory tract infection including nasopharyngitis; Common: viral infections such as influenza, leukopenia including neutropenia, headache, injection site reactions such as urticaria).

There is one participant from the golimumab treatment group experienced multiple AEs of hypoglycemia after progressing to Stage 3 T1D during the safety follow-up period. All these AEs of hypoglycemia were moderate in intensity, according to the MAH.

Only 8 participants with Stage 2 T1D (5 in the golimumab group and 3 in the placebo group) were enrolled in the study (treatment with golimumab for 26 weeks followed by a 26-week off-therapy period), no conclusion could be drawn for safety of golimumab for treatment in children/adolescent with Stage 2 T1D.

No update to the product information has been proposed by the MAH as part of this Article 46 submission, which is endorsed.

Conclusions as provided by the MAH

In children and adolescents, with Stage 2 T1D, treatment with golimumab for 26 weeks followed by a 26-week off-therapy period resulted following:

- No new safety signals were detected compared with the known AE profile of golimumab.
- After SC administration, the steady-state levels of golimumab were maintained though Week 26 and were similar across different age groups.
- Due to low sample size, no firm conclusions could be drawn for the metabolic assessments data.

Overall, golimumab was well tolerated in the small group of children/adolescents with Stage 2 T1D evaluated in this CNTO148DML1001 study.

The MAH has, in their benefits and risks conclusions, further concluded "Based on the data from Study CNTO148DML1001, there is no need to update the product information or risk management plan. The overall benefit-risk balance of golimumab remains positive."

2.3.2. Discussion on clinical aspects

Golimumab is a human monoclonal antibody belonging to the class of tumor necrosis factor alpha (TNFα) inhibitors, which are biologic immune modulators used to treat a variety of adult and pediatric autoimmune diseases.

The MAH submitted a final study report of a phase 1b study (CNTO148DML1001) for Simponi (golimumab), in accordance with Article 46 of Regulation (EC) No1901/2006. Study CNTO148DML1001 was a phase 1b study to evaluate SIMPONI®(golimumab) therapy in children, adolescents, and young adults with pre-symptomatic type 1 diabetes.

According to the MAH, the study CNTO148DML1001 was a standalone clinical trial which included participants in the pediatric population and was not part of the Marketing Authorization for Simponi or any Follow-up Measures or part of the Risk Minimization Plan.

Study CNTO148DML1001 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Participants were randomly assigned to receive golimumab or placebo, administered SC every 2 weeks (q2w) for 26 weeks and monitored for an additional 26 weeks (treatment for 26 weeks followed by a 26-week off-therapy period). The primary objective was to determine the safety and tolerability of golimumab in children, adolescents, and young adults with pre-symptomatic Stage 2 Type 1 diabetes (T1D).

Results

A total of 8 participants with Stage 2 T1D were enrolled and randomized from 4 centers (6 from 2 centers in the US and 2 from 2 centers in Finland). Of these, 5 participants were randomized to the golimumab treatment arm and 3 participants were randomized to the placebo treatment arm. All participants received the assigned treatment. All participants completed the study treatment except 1 participant in the placebo group who developed an AE of serum sickness that led to discontinuation of the study treatment 3 days after the Week 20 dose received.

The mean age of the study population was 10.69 years (range: 7.5 to 14.8 years) with a higher proportion of the participants aged <12 years (5 [62.5%]).

The mean (SD) duration of treatment exposure was 26.26 (0.19) weeks for golimumab and 24.29 (3.59) weeks for placebo. During this period, the mean (SD) number of study agent administrations were also comparable: 13.2 (1.79) doses of golimumab and 13 (1.73) doses of placebo.

Efficacy

According to the MAH, there were no efficacy analyses planned for this study. Exploratory metabolic assessments were summarized descriptively. Due to low sample size, no firm conclusions could be drawn for the metabolic assessments data.

Safety

Eight participants with Stage 2 T1D (5 in the golimumab group and 3 in the placebo group) included in the study CNTO148DML1001.

No deaths, SAEs, severe infections including TB, or malignancies were reported during the study. The most commonly reported treatment-emergent adverse events (TEAEs) from Week 0 to Week 52 were headache, nasopharyngitis, upper respiratory tract infection, influenza, and neutropenia. One participant from the golimumab treatment group developed 7 episodes of neutropenia between Study Days 30 and 170 (no events in placebo group). One participant in the golimumab treatment group developed TEAEs including neutropenia and injection-site urticaria and no injection-site events reported in the placebo group.

Overall, no new safety concerns have emerged in the children/adolescent with Stage 2 T1D who participated in the study CNTO148DML1001. The adverse events noted in the study participants with Stage 2 T1D, including infections, neutropenia and injection site reactions, are consistent with the known safety profiles of golimumab; and covered in the SmPCs for Simponi approved for treatment of several adult and pediatric autoimmune diseases.

Only 8 participants with Stage 2 T1D (5 in the golimumab group and 3 in the placebo group) were enrolled in the study (treatment with golimumab for 26 weeks followed by a 26-week off-therapy period), no conclusion could be drawn for safety of golimumab for treatment in children/adolescent with Stage 2 T1D.

No update to the product information has been proposed by the MAH as part of this Article 46 submission, which is endorsed.

3. CHMP overall conclusion and recommendation

A total of 8 children/adolescent subjects with Stage 2 T1D (5 in the golimumab group and 3 in the placebo group) were enrolled in the phase 1b study CNTO148DML1001. No new safety signals have emerged.

The benefit-risk balance of golimumab remains unchanged and no update of the SmPC is warranted.

☒ **Fulfilled**

No regulatory action required.