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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/P46/038

Note

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

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1. Introduction

On the 15th of June, the MAH submitted the final Clinical Study Reports (CSRs) in relation to the clinical study Simponi to Arrest β cell Loss in Type 1 Diabetes (T1GER) – CNTO148DML2001, in accordance with Article 46 of Regulation (EC) No 1901/2006 (The 'Pediatric Regulation') as amended.

A short clinical overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH states that the Clinical Study-CNTO148DML2001 was a standalone clinical trial which included participants in the pediatric population and was not part of the Marketing Authorization for Simponi (golimumab) or any Follow-up Measures or part of the Risk Minimization Plan.

2.2. Information on the pharmaceutical formulation used in the study

Simponi (golimumab) is a fully human monoclonal antibody which binds to human tumor necrosis factor alpha (TNFα) with high affinity and specificity and neutralizes TNFα bioactivity. Golimumab is currently approved in adults with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and ulcerative colitis (UC). Additionally, golimumab has been evaluated in studies conducted under an Investigational New Drug (IND) for the treatment of polyarticular juvenile idiopathic arthritis (pJIA; 2 up to 18years of age), and pediatric UC (2 up to 18 years of age). Golimumab is administrated subcutaneously.

The recommended dose of golimumab for adults is 50-100 mg (depending on body weight and indication) once a month, on the same date each month.

For children with polyarticular juvenile idiopathic arthritis the recommended maintenance dose is 50 mg once a month, on the same date each month if body weight is ≥ 40kg. The recommended dose of golimumab for children with a body weight less than 40 kg is 30 mg/m^2 body surface area up to maximum single dose of 40 mg administered once a month, on the same date each month. The prescribed volume of injection should be selected according to patient's height and weight.

The posology used in the T1GER study was not entirely consistent with the approved posology in EU, see below.

2.3. Clinical aspects

2.3.1. Introduction

This submission includes 3 clinical study reports (CSRs) for the golimumab Phase 2a study CNTO148DML2001 (T1GER) which covered the following phases: Weeks 0 to 52 (double-blind treatment phase), Weeks 52 to 104 (off-therapy follow-up phase), and the Open-Label Extension (OLE) phase (62 weeks). This study evaluated whether golimumab administered subcutaneously (SC) in participants 6 to 21 years of age with newly diagnosed Type 1 Diabetes (T1D) has the potential to maintain residual β-cell function and improve metabolic control. T1D is an autoimmune disorder with severe sequelae with no approved disease modifying therapies. Children and young adults are those that most frequently develop T1D and, according to the MAH, have the most urgent need for a disease modifying therapy to reduce associated short- and long-term morbidity and mortality.

According to the MAH, both preclinical and clinical studies demonstrate that tumor necrosis factor alpha (TNFα) has a critical role in T1D development and progression.

2.3.2. Clinical study

Clinical study number and title

A Phase 2a, randomized, double-blind, placebo-controlled, parallel-group, study conducted at multiple sites in the United States that evaluated golimumab in participants with new-onset T1D.

Protocol No:	CNTO148DML2001
Title of Study:	SIMPONI to Arrest β cell Loss in Type 1 Diabetes
Study Name:	T1GER
Phase of Development:	2a

Description

Study CNTO148DML2001 (T1GER) is a completed Phase 2a, Proof of Concept (POC), multicenter, randomized, double-blind, placebo-controlled study of the efficacy, safety, pharmacokinetics (PK) and immunogenicity of golimumab compared with placebo in 84 participants 6 through 21 years of age who have been recently diagnosed with T1D. The study took place in the USA. The objective of the study was to determine if golimumab can preserve β-cell function in children and young adults with newly diagnosed T1D. The primary efficacy endpoint was Mixed-Meal Tolerance Test (MMTT) stimulated 4-hour C-peptide AUC at Week 52. Major secondary efficacy endpoints include change from baseline in insulin use in units per kilogram body weight per day at Week 52, change from baseline in hemoglobin A1c (HbA1c) at Week 52, and hypoglycemic event rates through Week 52.

A total of 84 participants were enrolled, randomized, and treated (56 to golimumab and 28 to placebo). The target population must have presented with a peak stimulated C-peptide level ≥0.2 pmol/mL following a 4-hour MMTT obtained at study screening and be positive for at least 1 out of the following diabetes-related autoantibodies: GAD-65, IA-2, ZnT8, ICA, or insulin. Participants were to be randomized within 100 days after diagnosis of T1D.

Eligible participants were randomized in a 2:1 ratio to golimumab or placebo using a permuted block randomization procedure stratified by baseline 4-hour C-peptide AUC (≤0.66 pmol/mL or >0.66 pmol/mL). The duration of study participation was 108 weeks, including a 4-week screening period, a 52-week treatment period, and a 52-week off-therapy follow-up period.

Weeks 0 through 52: This study evaluated whether SC administered golimumab can maintain residual-cell function and improve metabolic control in children and young adults with newly diagnosed T1D. The CSR covering Weeks 0 through 52 is provided.

Weeks 52 through 104: In the off-therapy follow-up period (Week 52 through Week 104), safety and durability of effect of golimumab on measures of diabetes control were evaluated. The CSR for this study period was also provided.

Open-Label Extension: Subsequent to the granting of a Single Patient Investigational New Drug (SPIND) for a participant who had shown a particularly good response profile during the double-blind phase (an increase in C-peptide at Week 52 and an insulin dose adjusted hemoglobin A1c [IDAA1c] score <9), the Data Monitoring Committee, in the spirit of equipoise, recommended to restart active

treatment for those participants who were still in the off-therapy follow-up phase and had also shown a similar response profile during the double-blind phase. Responders at Week 52 who were still in the off-therapy follow-up period (Week 52 to Week 104) and were on active drug during the double-blind period were offered the option to participate in the OLE if eligibility criteria were met. Participants who did not meet the response criteria at Week 52 were to continue the off-therapy period. Participants who met the response criteria but either declined to participate in the OLE, or were determined to be on placebo, continued the off-therapy period as planned. It is noteworthy that participants who had already completed the study were not invited to re-start treatment in the OLE. The CSR for this study period was also provided.

Methods

Objective(s)

The overall objective of the study was to determine if golimumab could preserve β-cell function in children and young adults with newly diagnosed type 1 diabetes (T1D).

See Table 1 below for secondary objectives and endpoints and for specific objectives and endpoints in each period, that is in the:

1) Double-blind period; Weeks 0 through 52
2) Off-therapy period; Weeks 52 through 104
3) Open-Label Extension

Table 1

A Objectives and Endpoints (Double-blind Period; Weeks 0 through 52)

Objectives	Endpoints
Primary Objective and Endpoints	
To determine if golimumab could preserve β-cell function in children and young adults with newly diagnosed type 1 diabetes (T1D).	The Mixed-Meal Tolerance Test (MMTT) -stimulated 4-hour C-peptide area under the concentration-time curve (AUC) at Week 52.
Secondary Objectives and Endpoints: Efficacy	
To evaluate the impact of golimumab on measures of diabetes control in this participant population.	Change from baseline in insulin use in units per kilogram body weight per day over time. Change from baseline in hemoglobin A1c (HbA1c) over time. Hypoglycemic event rates (defined as blood glucose (BG) levels of ≤70, 55, and 35 mg/dL or clinical sequelae in the absence of a BG reading) through Week 52. MMTT-stimulated 4-hour C-peptide AUC over time.
Secondary Objectives and Endpoints: Safety	

Objectives	Endpoints
To determine the safety and tolerability of golimumab in children and young adults with T1D.	Proportion of participants with treatment-emergent adverse events (AEs) and severe AEs through Weeks 52. Proportion of participants with severe infections through Weeks 52. Proportion of participants with study agent injection site reactions through Week 52.
Secondary Objectives and Endpoints: Pharmacokinetics (PK) and Immunogenicity	
To evaluate the PK and immunogenicity of golimumab in this specific participant population with T1D.	Summary of serum golimumab concentrations and the PK profile after induction and maintenance dosing. Incidence and titers of antibodies to golimumab.
Exploratory Objective and Endpoints: Immunologic and Metabolic	
To evaluate how golimumab impacted immunologic profiles and indicators of β-cell stress, and the correlation with efficacy and safety endpoints in this study.	Correlation of cellular and serologic immune profiles with clinical metabolic outcomes on-therapy (Weeks 12, 26, 38, and 52). Relationship of exploratory markers of β-cell stress and survival with clinical metabolic outcomes on-therapy (Weeks 12, 26, 38, and 52).

B Objectives and Endpoints (Off-therapy Period; Weeks 52 through 104)

Objectives	Endpoints
Efficacy	
To evaluate the impact of golimumab on measures of diabetes control in this participant population. To evaluate the off-therapy durability of golimumab on measures of diabetes control in this participant population.	Change from baseline in insulin use in units per kilogram body weight per day over time. Change from baseline in HbA1c over time. Hypoglycemic event rates (defined as BG of ≤70, 55, and 35 mg/dL or clinical sequelae in the absence of a BG reading) through Week 52, after Week 52 through Week 104, and the entire study. MMTT-stimulated 4-hour C-peptide AUC over time.
Safety	
To determine the safety and tolerability of golimumab in children and young adults with T1D.	Proportion of participants with treatment-emergent AEs and severe AEs through Weeks 52 and 104. Proportion of participants with severe infections through Weeks 52 and 104.
Pharmacokinetics (PK) and Immunogenicity	
To evaluate the PK and immunogenicity of golimumab in this specific participant population with T1D.	Summary of serum golimumab concentrations and the PK profile after induction and maintenance dosing. Incidence and titers of antibodies to golimumab.

Objectives	Endpoints
Exploratory Objective and Endpoints: Immunologic and Metabolic	
To evaluate how golimumab impacts immunologic profiles and indicators of β-cell stress, and the correlation with efficacy and safety endpoints in this study.	Correlation of cellular and serologic immune profiles with clinical metabolic outcomes during off-therapy (Weeks 78 and 104) Relationship of exploratory markers of β-cell stress and survival with clinical metabolic outcomes during off-therapy (Weeks 78 and 104).

C Open-Label Extension

Objective	Endpoint
To evaluate additional one year of safety and exploratory efficacy endpoints in those participants that have shown a particular response in the double-blind period.	Continue to evaluate safety and exploratory efficacy endpoints as per the Time and Events Schedule (OLE) and no new efficacy hypotheses will be tested compared to the double-blind period.

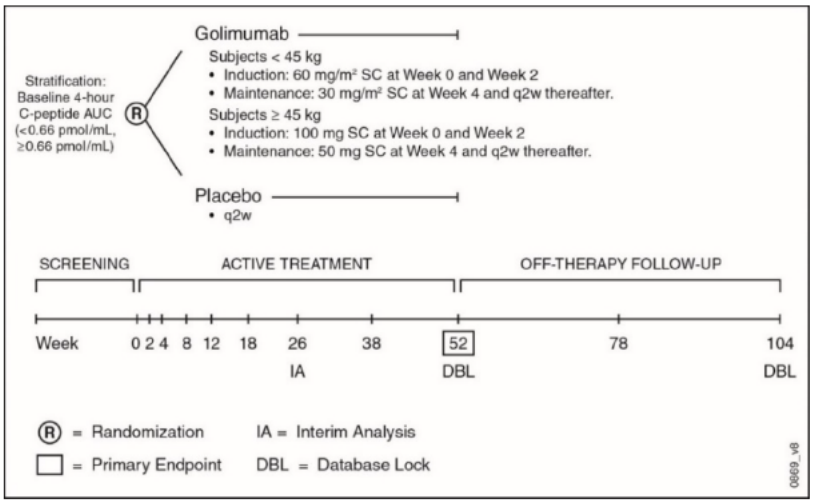
Study design

This is a Phase 2a randomized, double-blind, placebo-controlled, parallel-group, multicenter, study of golimumab in participants with new-onset T1D.

The planned duration of study participation was 108 weeks which included a 4-week screening and post-randomization period. Following screening, participants were randomized within 28 days. Post-randomization, there was a 52-week treatment period with study agent (Week 52 database lock [DBL]) followed by a 52-week off-therapy period (Week 104 DBL). The study protocol was amended to allow responders to restart their participation in the 52-week OLE after Week 52 (treatment period) study (this is included in the OLE CSR).

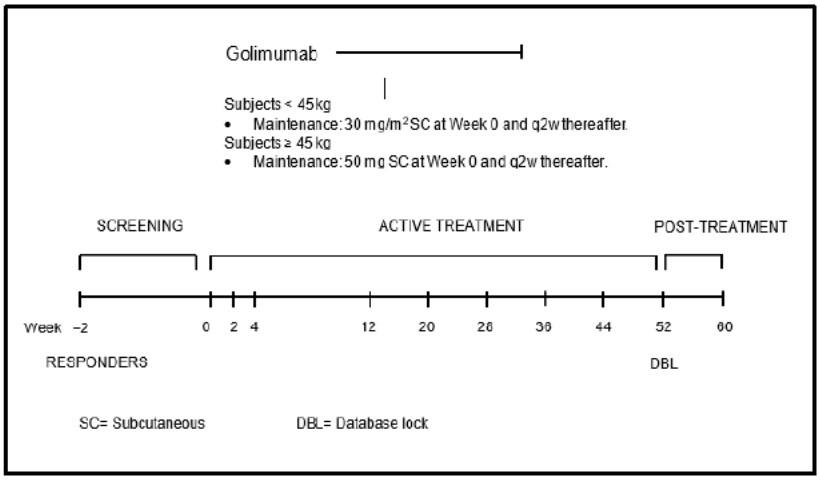
Schematic overviews of the double-blind and off-treatment study design and the OLE are provided in Figures 1 and 2, respectively.

Figure 1: Schematic Overview of the Study



AUC = Area under the curve; DBL = Database lock; IA = interim analysis; q2w = Every 2 weeks; ® = randomization; SC = subcutaneous.

Figure 2: Schematic Overview of Open-Label Extension



Study population /Sample size

The participants were between 6 and 21 years of age, had received a diagnosis of T1D according to American Diabetes Association (ADA) criteria, were able to undergo randomization within 100 days after diagnosis, and had a peak C-peptide level of at least 0.2 pmol per milliliter after a 4-hour mixed-meal tolerance test. In addition, all the participants had positive results on testing for at least one of the following antibodies associated with T1D: anti–glutamic acid decarboxylase 65, anti–islet antigen 2, anti–zinc transporter 8, anti–islet-cell antigen, or anti-insulin (if the anti-insulin antibody level was obtained within 10 days after the initiation of exogenous insulin therapy). The participants were required to be up to date with and agree to receive age-appropriate immunizations, except for live vaccines.

For the OLE, responders were defined as based on the Single Patient Investigational New Drug (SPIND) profile and had to meet a C-peptide and Remission score profile.

Patients with a history of other clinically significant diseases, including autoimmune diseases (except stable autoimmune thyroiditis), were excluded.

Treatments

All study agents (golimumab or placebo) were administered subcutaneously (SC). This was the prefilled syringe with a needle guard to deliver a single, fixed dose of 50 mg, or the prefilled syringe with a VarioJect injection device which delivered a single, variable dose of 10 to 45 mg in 5 mg increments. Identical devices containing placebo were used to deliver a volume equivalent to that of active treatment for participants randomized to the placebo arm, Table 2.

Table 2: Golimumab SC Dosing Regimens by Body Weight Cut-Off for participants Who Were Randomized to the Golimumab Treatment Group

Body weight*	Week 0 and 2	Week 4 through Week 52
<45 kg	60 mg/m^2	30 mg/m^2 q2w
≥45 kg	100 mg	50 mg q2w

*Body weight to be evaluated approximately every 3 months with dose adjustment if necessary.

Outcomes/endpoints

The primary endpoint was the Mixed-Meal Tolerance Test (MMTT) -stimulated 4-hour C-peptide area under the concentration-time curve (AUC) at Week 52.

See Table 1 above for for secondary endpoints and for specific endpoints in each period, that is in the:

1) Double-blind period; Weeks 0 through 52

2) Off-therapy period; Weeks 52 through 104

3) Open-Label Extension

Statistical Methods

This study was designed to enroll approximately *81* participants in order to have sufficient power to detect a difference between the golimumab and the placebo treatment groups for the primary efficacy endpoint. The rationale for the study sample size was based on the hypothesis tests for the primary efficacy endpoint.

The sample size calculation was based on the primary endpoint, an MMTT 4-hour C-peptide AUC at Week 52. Due to skewed C-peptide AUC data, normalizing transformation of $\log_{(AUC+1)}$ was applied for sample size assessment. According to MAH, the method has been well accepted and used in numerous clinical studies. Based on published data, a common standard deviation (SD) of $\log_{(AUC+1)}$ of 0.215 was assumed, and the back-transformed means for 4-hour C-peptide AUC were assumed to be 0.385 and 0.635 for the placebo and golimumab treatment groups, respectively, i.e., the expected treatment difference (back-transformed) was 0.25. Based on these assumptions, with 81 participants (54 on golimumab and 27 on placebo), there was 90% power to detect a treatment difference with a 2-sided significance level of 0.05 through a 2-sample t-test.

There was no formal statistical hypothesis testing for the Week 104 DBL nor was there any sample size calculation for the off-therapy period. No hypothesis testing will be performed for the OLE, and data generated will be summarized descriptively.

Results

Recruitment/ Number analysed

A total of 84 participants with newly diagnosed T1D were enrolled and randomized. Of these, 56 participants were randomized to the golimumab treatment arm and 28 participants were randomized to the placebo treatment arm. The first participant was randomized on 28 Oct 2016 and the last participant on 24 May 2018. The last patient last visit for the open-label extension phase was the 05 Jan 2021.

Of the 84 participants, 11 (13.1%) participants discontinued the study agent prior to Week 52 of which 9 (10.7%) participants terminated participation in the study (golimumab: 6 [10.7%] participants; placebo: 3 [10.7%] participants). The most common reason for study agent discontinuation and termination from participating in the study was withdrawal of consent (7 [8.3%] participants and 6 [7.1%] participants, respectively). Two (3.6%) participants in the golimumab treatment arm discontinued the study agent due to AEs.

All 74 participants who completed the 52-week treatment period continued into the off-therapy period (golimumab: 49; placebo: 25). Of these, 5 participants terminated study participation early; 3 participants were lost to follow-up while 2 participants were terminated early for other reasons (1

participant was unblinded on Study Day 365 [Week 52 visit]) by the site to assess possibility for continued treatment through Single Patient Investigational New Drug (SPIND), data for the participant has not been included in this CSR, while 1 participant was non-compliant with blood sugar/study diary entry and had discontinued the study at Week 52.

During the pen-label extension (OLE), of the 5 eligible participants, 4 had an OLE screening visit as well as a Mixed-Meal Tolerance Test (MMTT) assessment; however, for 1 participant the Week 78 visit was used as the screening visit as it was <6 months prior to the initiation of the OLE. Of the 5 participants, 1 participant completed the OLE but had no MMTT data, while 4 participants terminated study participation due to the following reasons: met Insulin dose adjusted HbA1c (IDAA1C) stopping rules, met withdrawal criteria, sponsor's discretion due to C+R and R responder's criteria, physician's decision due to safety concerns pertaining to Coronavirus Disease-19 pandemic.

Baseline data

A summary of demographics and baseline disease characteristics of all randomized participants are presented in Table 3.

Table 3: Summary of Demographics and Baseline Disease Characteristics; All Randomized Subjects Analysis Set (Study CNTO148DML2001)

	Placebo	Golimumab	Total
All Randomized Subjects	28	56	84
Age* (years)			
N	28	56	84
Mean (SD)	13.97 (4.022)	13.86 (3.724)	13.89 (3.802)
Median	13.96	14.27	14.10
Range	(6.7; 21.2)	(6.6; 20.1)	(6.6; 21.2)
Age			
N	28	56	84
<12	8 (28.6%)	20 (35.7%)	28 (33.3%)
>=12- ≤18	13 (46.4%)	27 (48.2%)	40 (47.6%)
>18	7 (25.0%)	9 (16.1%)	16 (19.0%)
Sex			
N	28	56	84
Male	18 (64.3%)	31 (55.4%)	49 (58.3%)
Female	10 (35.7%)	25 (44.6%)	35 (41.7%)
Race			
N	28	56	84
American Indian / Alaskan native	0	0	0

Table 3: Summary of Demographics and Baseline Disease Characteristics; All Randomized Subjects Analysis Set (Study CNTO148DML2001)

	Placebo	Golimumab	Total
Asian	1 (3.6%)	0	1 (1.2%)
Black / African American	0	5 (8.9%)	5 (6.0%)
Multiple	1 (3.6%)	4 (7.1%)	5 (6.0%)
Native Hawaiian / Other Pacific Islander	0	0	0
Not reported	0	1 (1.8%)	1 (1.2%)
Other	0	0	0
Unknown	0	0	0
White	26 (92.9%)	46 (82.1%)	72 (85.7%)
Baseline Weight (kg)			
N	28	56	84
Mean (SD)	58.07 (23.594)	55.81 (19.792)	56.57 (21.019)
Median	57.00	52.50	55.90
Range	(21.9; 114.9)	(23.6; 98.5)	(21.9; 114.9)
Baseline Weight (kg)			
N	28	56	84
<45	7 (25.0%)	19 (33.9%)	26 (31.0%)
>=45	21 (75.0%)	37 (66.1%)	58 (69.0%)
Baseline Height (cm)			
N	28	56	84
Mean (SD)	159.12 (19.164)	158.89 (18.152)	158.97 (18.380)
Median	161.55	158.10	160.00
Range	(118.0; 187.5)	(121.3; 190.0)	(118.0; 190.0)
BMI (kg/m^2)			
N	28	56	84
Mean (SD)	22.20 (7.042)	21.41 (4.462)	21.68 (5.428)
Median	20.98	20.62	20.70
Range	(14.9; 46.0)	(14.1; 33.2)	(14.1; 46.0)
Number of days since diagnosis			
N	28	56	84
Mean (SD)	75.5 (19.01)	73.6 (19.64)	74.2 (19.34)

Table 3: Summary of Demographics and Baseline Disease Characteristics; All Randomized Subjects Analysis Set (Study CNTO148DML2001)

	Placebo	Golimumab	Total
Median	83.5	75.5	77.5
Range	(35; 100)	(19; 101)	(19; 101)
Number of days since diagnosis			
N	28	56	84
<60	8 (28.6%)	12 (21.4%)	20 (23.8%)
>=60	20 (71.4%)	44 (78.6%)	64 (76.2%)
Fasting blood glucose prior to MMTT (mg/dL)			
N	28	56	84
Mean (SD)	124.6 (37.53)	119.1 (36.19)	120.9 (36.51)
Median	117.5	113.0	114.5
Range	(78; 270)	(51; 257)	(51; 270)
4-h peak C-peptide (nmol/L)			
N	28	56	84
Mean (SD)	1.1696 (0.86079)	1.0724 (0.61842)	1.1048 (0.70469)
Median	0.9042	0.9307	0.9257
Range	(0.258; 3.739)	(0.268; 3.494)	(0.258; 3.739)
4-h C-peptide AUC (nmol/L)			
N	28	56	84
Mean (SD)	0.878 (0.6340)	0.780 (0.3958)	0.813 (0.4865)
Median	0.698	0.700	0.700
Range	(0.20; 2.64)	(0.15; 2.21)	(0.15; 2.64)
4-h C-peptide AUC (nmol/L)			
N	28	56	84
<0.66	12 (42.9%)	26 (46.4%)	38 (45.2%)
>=0.66	16 (57.1%)	30 (53.6%)	46 (54.8%)
2-h C-peptide AUC (nmol/L)			
N	28	56	84
Mean (SD)	0.879 (0.6534)	0.798 (0.4355)	0.825 (0.5158)
Median	0.651	0.695	0.685
Range	(0.21; 2.76)	(0.08; 2.50)	(0.08; 2.76)

Table 3: Summary of Demographics and Baseline Disease Characteristics; All Randomized Subjects Analysis Set (Study CNTO148DML2001)

	Placebo	Golimumab	Total
HbA1c (%)			
N	28	56	84
Mean (SD)	7.13 (1.229)	6.98 (1.147)	7.03 (1.169)
Median	6.90	6.80	6.80
Range	(5.6; 11.1)	(5.1; 11.3)	(5.1; 11.3)
HbA1c (%)			
N	28	56	84
≤6.5%	12 (42.9%)	21 (37.5%)	33 (39.3%)
>6.5%	16 (57.1%)	35 (62.5%)	51 (60.7%)
Insulin use units per day			
N	25	55	80
Mean (SD)	0.44 (0.195)	0.42 (0.263)	0.43 (0.243)
Median	0.47	0.42	0.42
Range	(0.1; 0.8)	(0.0; 1.0)	(0.0; 1.0)
Number of positive diabetes-related autoantibodies			
N	28	55	83
1	0	1 (1.8%)	1 (1.2%)
>1- ≤3	12 (42.9%)	18 (32.7%)	30 (36.1%)
>3	16 (57.1%)	36 (65.5%)	52 (62.7%)
Number of subjects with positive diabetes-related autoantibody			
N	28	55	83
GAD-65	20 (71.4%)	46 (83.6%)	66 (79.5%)
IA-2	13 (46.4%)	31 (56.4%)	44 (53.0%)
ZnT8	22 (78.6%)	41 (74.5%)	63 (75.9%)
ICA	22 (78.6%)	45 (81.8%)	67 (80.7%)
Insulin	24 (85.7%)	49 (89.1%)	73 (88.0%)

* Age is calculated based on randomization date away from birth date.

CHMP comment:

In total 84 patients were randomized, 56 patients to the golimumab arm and 28 patients to the placebo arm. The baseline characteristics were substantially similar in the two groups. In the report the MAH however points out that the 4 h C peptide AUC (nmol/L) at baseline is imbalanced between the groups with a somewhat higher proportion with higher 4 h C peptide AUC (nmol/L) in the placebo group as compared to the golimumab group. This imbalance is small.

Efficacy results

Weeks 0 through 52

All 84 randomized participants were included in the full analysis set for efficacy analyses and safety population (treated participants). The study met its primary and partly its secondary endpoints, see below.

Primary efficacy endpoint

The primary endpoint is the Mixed-Meal Tolerance Test (MMTT)-stimulated 4-hour C-peptide AUC (pmol/mL) at Week 52. The MAH states that due to the skewed distribution of C-peptide AUC data, a normalization transformation of log $_{(AUC+1)}$ was applied. A Mixed Model Repeated Measure (MMRM) model was utilized to assess the primary efficacy endpoint, in which post-baseline $\log_{(AUC+1)}$ was the response variable. The model was adjusted for baseline AUC, age, gender, time, baseline-by-time interaction, and treatment-by-time interaction.

Golimumab significantly slowed disease progression as measured by C-peptide AUC decline. The least squared (LS)Mean (95% CI) of the treatment difference in $\log_{(AUC+1)}$ scale was 0.17 (0.08, 0.26) with a p-value of 0.0004, thereby meeting the primary objective of the study. The baseline mean (SD) C-peptide AUC was 0.88 (0.634) in the placebo group and 0.78 (0.396) in the golimumab group. According to the MAH among those who completed the Week 52 visit, the mean (SD) decrease in C-peptide AUC was -0.49 (0.437) for the placebo group, compared with -0.13 (0.352) for the golimumab group; and mean percent decreases from baseline were 56% and 12% for the placebo and golimumab groups, respectively.

For change from baseline in C-peptide AUC ($\log_{[AUC+1]}$ scale) through Week 52, clear separation was according to the MAH, observed as early as Week 12. The MAH states that the treatment benefit reached a plateau at Week 26.

According to the MAH, six sensitivity analyses were performed and confirmed the statistically significant treatment benefit of golimumab on C-peptide AUC. Subgroup analyses by demographic and baseline disease characteristics were performed for C-peptide AUC at Week 52 to evaluate the consistency of the treatment effect. Heterogeneity was observed in subgroups defined by age. The MAH states that for participants aged >18 years, no treatment difference was observed but that it should be noted that this subgroup analysis was based on a small sample size (7 participants in the placebo group and 9 in the golimumab group).

CHMP comment:

The primary endpoint of the study was the Mixed-Meal Tolerance Test (MMTT)-stimulated 4-hour C-peptide AUC (pmol/mL) at Week 52. The MAH states that due to the skewed distribution of C-peptide AUC data, a normalization transformation of log (AUC+1) was applied. A Mixed Model Repeated Measure (MMRM) model was utilized to assess the primary efficacy endpoint, in which post-baseline log(AUC+1) was the response variable. The model was adjusted for baseline AUC, age, gender, time, baseline-by-time interaction, and treatment-by-time interaction. This is accepted.

Overall golimumab significantly slowed disease progression as measured by Mixed-Meal Tolerance Test (MMTT)-stimulated 4-hour C-peptide AUC decline. The least square (LS)Mean (95% CI) of the treatment difference in log(AUC+1) scale was 0.17 (0.08, 0.26) with a p value of 0.0004. Thus, the primary endpoint of the study was reached.

According to the MAH subgroup analyses by demographic and baseline disease characteristics were performed for C peptide AUC at Week 52 to evaluate the consistency of the treatment effect. The MAH points out that for participants aged >18 years, no treatment difference was observed. This analysis was however based on very small sample size.

Secondary efficacy endpoints

Each continuous secondary endpoint (insulin use and HbA1c) was analyzed using an MMRM model. The model was adjusted for baseline, age, gender, time, baseline-by-time, and treatment-by-time interactions. The number of hypoglycemia events was analyzed using a Poisson regression model, accounting for the duration of study participation through Week 52. The model was adjusted for baseline HbA1c and age.

The summary of the secondary endpoints is presented in Table 4.

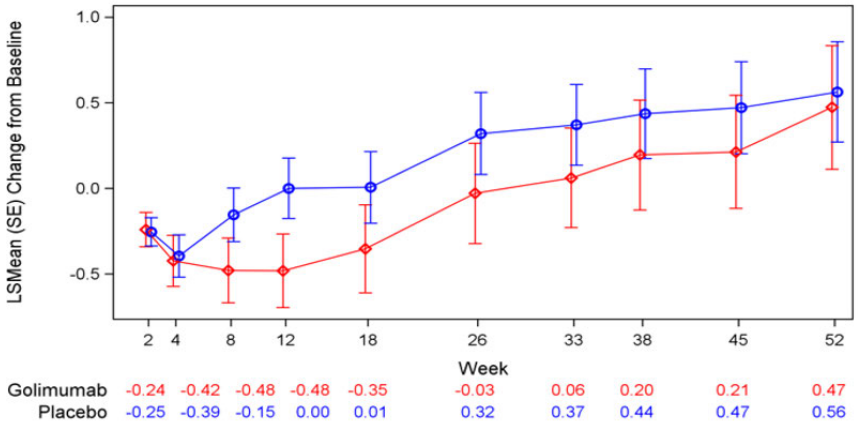
Table 4: Summary of Secondary Endpoints; Full Analysis Set (Study CNTO148DML2001)

	Placebo **N = 28**	**Golimumab** **N = 56**	**Treatment Difference**	**p-value**
Change from baseline in daily insulin use (units/kg/day) at Week 52	LSMean (SE): 0.243 (0.0419)	LSMean (SE): 0.066 (0.0267)	LSMean (95% CI): -0.178 (-0.28, -0.08)	0.0004*
Change from baseline in HbA1c (%) at Week 52	LSMean (SE): 0.56 (0.294)	LSMean (SE): 0.47 (0.210)	LSMean (95% CI): -0.09 (-0.81, 0.63)	0.8020
Hypoglycemic event rates through Week 52[#]	Event rate: 43.36	Event rate: 39.01	Rate Ratio 0.90 (0.629, 1.286)	0.5614*

CI: Confidence interval; LS: Least square; SE: standard error. #Actual number of events.
* indicates p-value is under multiplicity control.

The MAH states that for the change from baseline in HbA1c shown in Figure 3, a treatment separation was observed as early as Week 8 with golimumab showing a numerical treatment benefit of about 0.3% or more through Week 26 and at least 0.2% through Week 45. The separation appeared to trend closer over time. At Week 52, the treatment difference dropped below 0.1%. According to the MAH the golimumab group had a mean change from baseline in HbA1c increase from 0.08% at Week 45 to 0.356% at Week 52 while a mean increase of 0.072% between these two visits was observed in the placebo group.

Figure 3: LSMean (SE) Change From Baseline in HbA1c (%) Over Time; Full Analysis Set (Study CNTO148DML2001)



LS=least square; SE=standard error.

CHMP comment:

For the secondary endpoints in the double-blind period 0-52 weeks, the change from baseline in insulin use in units per kilogram body weight per day over time was statistically significantly different comparing the golimumab to the placebo group, thus with a bigger change from baseline in daily insulin use in the golimumab as compared to the placebo group.

By contrast the change from baseline in hemoglobin A1c (HbA1c) over time and the hypoglycemic event rates through Week 52 did not differ between the groups, with a rate ratio of 0.90 (95% CI 0.629, 1.286).

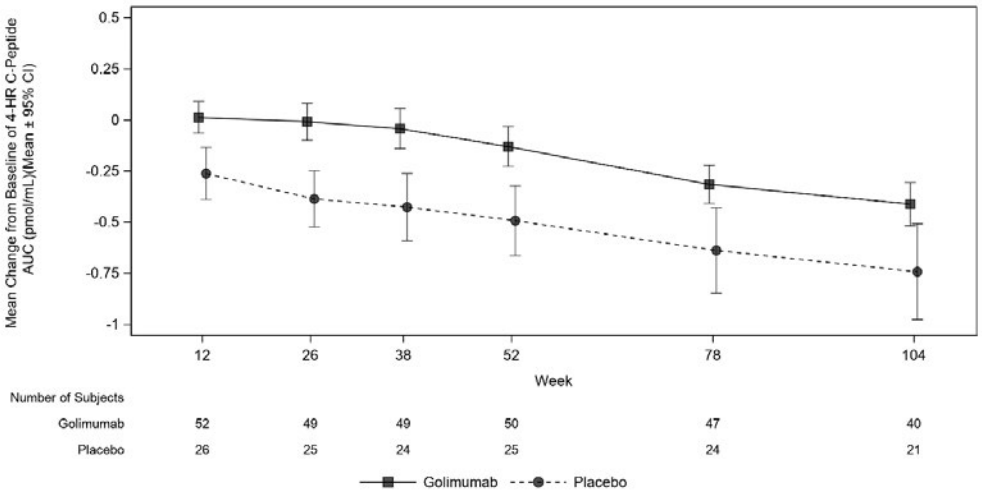
Weeks 52 through 104

MMTT-stimulated 4-hour C-peptide AUC (pmol/mL)

A MMRM model was utilized with all observed post-baseline $\log_{(AUC+1)}$ data through week 104 as the response variable. The model was adjusted for baseline $\log_{(AUC+1)}$, age, time, baseline-by-time interaction, and treatment-by-time interaction. The MAH states that due to the skewed distribution of raw C-peptide AUC data, a normalization transformation of $\log_{(AUC+1)}$ was applied.

The LSMean (95% CI) of the treatment difference at week 104 in $\log_{(AUC+1)}$ scale was 0.11 (0.03, 0.20) with a nominal p-value of 0.012. The observed mean (SD) decrease in C-peptide AUC at Week 104 was 0.74 (0.549) for the placebo group, compared with 0.41 (0.341) for the golimumab group, respectively. For reference, the change from baseline in the raw C-peptide AUC scale was plotted in Figure 4.

Figure 4: Mean Change from Baseline in MMTT-stimulated 4-hour C-peptide AUC (pmol/mL) Over Time Through Week 104; Full Analysis Set (Study: CNTO148DML2001)



T1D disease progression evaluation through 4-hour C-peptide AUC

To evaluate T1D disease progression after 52-weeks' treatment with golimumab, 4-hour C-peptide AUC annual decline of the golimumab group during off-therapy period was compared with the 4-hour C-peptide AUC decline of the placebo group during the double-blind treatment period. Assessment of the disease progression was conducted by applying a random effect model to both groups with $\log_{(AUC+1)}$ as the response variable, age, time (continuous variable), treatment and treatment by time interaction as fixed effects, intercept and slope as random effects.

Through the evaluation in $\log_{(AUC+1)}$ scale, the estimated annual slope was -0.25 in placebo during the treatment period and -0.19 in golimumab during off-therapy with a nominal p-value of 0.153, Table 5. The MAH points out that this result needs to be interpreted with consideration of the unbalanced baseline.

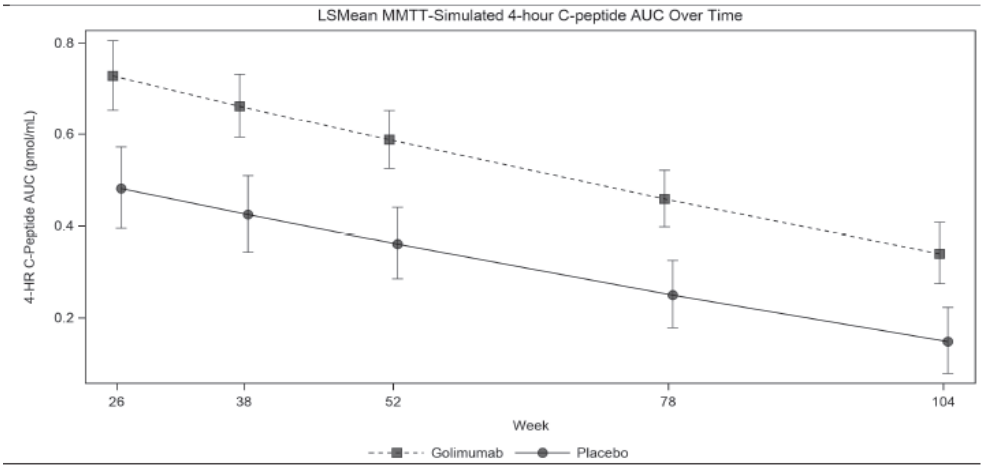
Table 5: Summary of Secondary Endpoints; Full Analysis Set (Study CNTO148DML2001)

	Placebo	Golimumab
Analysis Set: Full	28	56
Annual Disease Progression		
N	28	50
Slope estimate based on model Mean (SE)	-0.25 (0.031)	-0.19 (0.026)
p-value between placebo through Week 52 and golimumab from Weeks 52 through 104		0.153

Note: Evaluation was made between placebo in treatment period and golimumab group during off-therapy period.

During Weeks 0 through 52, the annual mean (SD) AUC decline observed was 0.49 (0.437) for placebo with a mean percent decrease of 56%. During Weeks 52 through 104, the annual mean (SD) AUC decline was 0.27 (0.270) for golimumab with 45% of mean percent decrease. However, the early golimumab treatment did delay this fall in C-peptide. According to the model, the decline in β-cell function with golimumab paralleled to that with placebo after 26 weeks of treatment. Thus, the estimated lag time of the mean C-peptide AUC of the golimumab treatment group was 46.8 weeks (95% CI [28.7, 64.9]) or 10.8 months to drop to the same level as the placebo treatment group at Week 26, resulting in an overall numerically greater preservation of β-cell function in the golimumab treatment group, Figure 5.

Figure 5: LSMean (SE) Change From Baseline in HbA1c (%) Over Time; Full Analysis Set (Study CNTO148DML2001)



Note1: LSMean of C-Peptide AUC was the back-transformation exp(estimate) -1, where the estimate was based on log(AUC+1).
Note2: Lag time 46.8 weeks (95% CI [28.7, 64.9]).

According to the MAH, at Week 104, the mean (SD) change from baseline in HbA1c (%) was 1.68 (2.324) with the golimumab treatment group versus 1.25 (1.84) with the placebo treatment group. The mean (SD) HbA1c at Week 104 was observed as 8.53 (2.25) for the golimumab treatment group and 8.13 (1.67) for the placebo treatment group.

The MAH further states that the mean (SD) change from baseline in daily insulin usage (units/kg) at Week 104 was 0.279 (0.452) for the golimumab treatment group compared with 0.348 (0.305) for the placebo treatment group. The mean (SD) daily insulin usage at Week 104 was 0.726 (0.302) and 0.822 (0.317) for the golimumab and placebo treatment groups, respectively.

CHMP comment:

For MMTT-stimulated 4-hour C-peptide AUC (pmol/mL) from 52 throughout 104 weeks the LSMean (95% CI) of the treatment difference at week 104 in log(AUC+1) scale was 0.11 (0.03, 0.20) with a nominal p-value of 0.012. Further the observed mean (SD) decrease in C-peptide AUC at Week 104 was 0.74 (0.549) for the placebo group, compared with 0.41 (0.341) for the golimumab group, respectively.

To evaluate T1D disease progression after 52-weeks' treatment with golimumab, 4-hour C-peptide AUC annual decline of the golimumab group during off-therapy period was compared with the 4 hour C-peptide AUC decline of the placebo group during the double-blind treatment period.

This resulted (using an evaluation in log(AUC+1) scale) in an estimated annual slope of -0.25 in placebo during the treatment period and -0.19 in golimumab during off-therapy with a nominal p-value of 0.153.

Open-Label Extension

According to the MAH the MMTT assessments, C-peptide, and proinsulin data are based on data available only from the OLE screening i.e., there was no on-treatment OLE data available to assess these parameters. Alternatively, for the HbA1c (%), daily insulin use, and resulting IDAA1C score parameters, the results were based on limited on-treatment OLE data collected during this period.

Pharmacokinetics

According to the MAH golimumab was administered subcutaneously (SC) at 60 mg/m^2 for participants <45kg or 100 mg for participants ≥45 kg at Week 0 and Week 2 followed by 30 mg/m^2 for participants <45kg or 50 mg for participants ≥45 kg at Week 4 and every 2 weeks thereafter. Median trough serum golimumab concentrations after the induction doses of 60 mg/m^2 for participants <45kg or 100 mg for participants ≥45 kg at Week 2 and Week 4 were 4.44 µg/mL (mean ± SD: 4.64±1.51) and 6.44 µg/mL (mean ± SD: 6.85±2.17), respectively. At Week 12, the median trough serum golimumab concentration was 3.56 µg/mL (mean ± SD: 3.74±2.03) and were maintained through Week 52. Steady-state trough golimumab levels in T1D participants through Week 52 were according to the MAH similar across different age groups, body weight quartiles, and body weight categories. Serum samples for the measurement of golimumab were collected at Weeks 78 and 104 in the off-therapy follow-up period. The MAH states that golimumab was eliminated from the body at both Weeks 78 and 104, respectively.

In the OLE responders could restart treatment with SC golimumab, trough serum golimumab concentrations increased from Week 4 to Week 12, after which steady-state concentrations were observed. OLE Week 12 trough serum golimumab concentrations were similar to the Week 12 levels from the beginning of the study. The MAH states that higher serum golimumab concentrations were observed at Week 28 and Week 52 because only 2 participants remained in the study.

CHMP comment:

Golimumab was administered subcutaneously (SC) at 60 mg/m^2 for participants < 45 kg or 100 mg for participants ≥45 kg at Week 0 and Week 2 followed by 30 mg/m^2 for participants <45kg or 50 mg for participants ≥45 kg at Week 4 and every 2 weeks thereafter. This is acknowledged. According to the data submitted by the MAH there were no clear associations observed between efficacy endpoints and pharmacokinetics (PK).

Immunogenicity

According to the MAH antibodies to golimumab were assessed with a highly sensitive drug tolerant assay method and were detected in 30 of 56 participants (54%) of whom 29 (97%) had titers of less than 1:1000. Twelve of these 29 (41%) participants were positive for neutralizing antibodies. The MAH states that presence of antibodies to golimumab did not have apparent effects on PK unless peak titers were >1:100 and had no impact on efficacy endpoints. There was no impact of antibodies to golimumab on injection site reactions. Six (23.1%) of the 26 participants classified as negative and 7 (23.3%) of the 30 participants classified as positive for antibodies to golimumab had an injection site reaction through Week 52. None of the injection site reactions through Week 52 were, according to the MAH considered to be severe or serious. There was 1 subject positive for antibodies to golimumab who had an injection site reaction leading to drug discontinuation in the peak titer group ≥100 to <1000.

Through Week 104, 7 participants became newly positive during the off-therapy period as compared to those reported through Week 52. The MAH stats that at the Week 52 analysis, most of the participants who were antibody positive had low titers; all participants had titer levels 1:1000 except for 1 subject who had a titer of 1:6144 previously reported through Week 52. Of the 7 participants newly positive for antibodies to golimumab, 6 were positive for neutralizing antibodies.

According to the MAH in the OLE, most of the participants were positive for antibodies to golimumab (4 of 5 golimumab treated participants with appropriate samples). Three of the four participants who were antibody positive had low titers (<1:48), except for one participant who had a titer of 1:12,288 at OLE Week 4 whose titers reduced to 1:768 by their OLE early termination visit. One of 4 participants was positive for neutralizing antibodies to golimumab, therefore overall, the number of participants with neutralizing antibodies is 1 in 5 participants. A total of 35 golimumab injections were administered to

participants who were negative for antibodies to golimumab and 167 golimumab injections to participants who were positive for antibodies to golimumab. The MAH states that there was no impact of antibodies to golimumab on injection-site reactions. One participant classified as negative and of 4 participants classified as positive for antibodies to golimumab had an injection-site reaction through the OLE. None of the injection-site reactions in the OLE for the 1 antibody negative participant were considered to be severe or serious.

Limited conclusions can be drawn about immunogenicity due to the small number of participants remaining in the OLE.

CHMP comment:

Antibodies towards golimumab were detected in 30 of 56 participants (54%). These were detected using a highly sensitive drug tolerant assay method according to the MAH. Among these 29 (97%) had titers of less than 1:1000. The MAH states that presence of antibodies to golimumab did not have apparent effects on PK unless peak titers were >1:100 and had no impact on efficacy endpoints. There seemed to be no impact of antibodies on the risk for golimumab injection site reactions.

The following text is included in the current SmPC: " *A drug-tolerant EIA method was used in the pJIA study for the detection of antibodies to golimumab. Due to the higher sensitivity and the improved drug tolerance, a higher incidence of antibodies to golimumab was expected to be detected with the drug-tolerant EIA method compared to the EIA method. In the Phase III pJIA study through week 48, antibodies to golimumab were detected by the drug-tolerant EIA method in 40% (69/172) of golimumab treated children of which a majority had a titre lower than 1:1000. An effect on serum golimumab concentrations was seen at titres of > 1:100 while an effect on efficacy was not seen until titres of > 1:1000, though the numbers of children with titres of > 1:1000 were low (N = 8). Among the children who tested positive for antibodies to golimumab, 39% (25/65) had neutralising antibodies. The higher incidence of antibodies with the drug-tolerant EIA method, because they were mainly low titre antibodies, did not have an apparent impact on drug levels, efficacy and safety and therefore does not represent any new safety signal.*

The presence of antibodies to golimumab may increase the risk of injection site reactions (see section 4.4). The small number of patients positive for antibodies to golimumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

Because immunogenicity analyses are product-and assay-specific, comparison of antibody rates with those from other products is not appropriate."

Thus, the reported ADA-rate seems somewhat higher than what has previously been reported for golimumab-treated children although comparisons may be hampered by differences in ADA-methodology. However, the rates are not markedly higher, based on rather few subjects and also the studied diabetic population may be somewhat different from the pediatric population for which golimumab is currently approved (i.e. JIA) with regards to factors of importance for ADA-development such as concurrent immunosuppression. Thus, the significance of this finding for the currently approved indications are considered limited. However, if the development programme in diabetic children is pursued, monitoring of ADA-development (ADA-testing and monitoring for clinical events potentially associated with ADA) will be very important.

Safety results

According to the MAH the safety findings are consistent with the safety profile of golimumab.

Weeks 0 through 52

A summary of key safety events is provided in table 6. The incidence of adverse events was 91% (51 of 56 participants) in the golimumab group and 82% (23 of 28) in the placebo group. No severe or serious infections occurred in either group. Infections were reported in 40 of 56 participants (71%) in the golimumab group and 17 of 28 (61%) in the placebo group; all were considered mild or moderate

The incidence of injection site reactions was similar in both trial groups. One serious adverse event was reported in each trial group; According to the MAH neither was deemed by trial investigators to be related to the trial regimen nor led to withdrawal from the trial or discontinuation of the trial regimen.

In addition to being a secondary efficacy endpoint, hypoglycemic events were also reported as adverse events at the discretion of the investigators. These events were reported in 13 participants (23%) in the golimumab group and in 2 participants (7%) in the placebo group; none of these events were reported as severe or serious. Of the 13 hypoglycemic adverse events reported in the golimumab group, 7 were reported at a single trial site, which recorded hypoglycemic adverse events in all the participants at the site (including the 2 events in the placebo group); the other 6 hypoglycemic adverse events were reported across five different trial sites.

No cases of diabetic ketoacidosis, neoplasia, serious or opportunistic infections, tuberculosis, or anaphylactic reactions were reported. The percentage of participants who had a post-baseline decrease in the neutrophil count was higher in the golimumab group than in the placebo group (29% [16 of 56 participants] vs. 19% [5 of 27]); transient fluctuations in the neutrophil count were observed among the participants in the golimumab group while they were receiving treatment. Four participants in the golimumab group had neutropenia grade 3 or 4 according to the Common Terminology Criteria for Adverse Events (CTCAE). One participant who had a low neutrophil baseline count discontinued treatment at 6 months. The MAH states that limited data (Valle 2013) also suggest that neutropenia may precede and accompany the onset of T1D.

Table 6: Adverse Events (Safety Analysis Population) Through Week 52

All participants	Placebo (N=28)	Golimumab (N=56)
Any adverse event	23 (82)	51 (91)
Leading to discontinuation*	0	2 (4)
Related to trial agent†	12 (43)	24 (43)
Any serious adverse event‡	1 (4)	1 (2)
Death	0	0
Pregnancy	0	0
Any infection	17 (61)	40 (71)
Serious infection	0	0
Opportunistic infection	0	0
Active tuberculosis	0	0
Neoplasia	0	0
Hypoglycemia¶	2 (7)	13 (23)
Any injection-site reaction	8 (29)	13 (23)
New or worsening autoimmune disease	1 (4)	0

* One participant in the golimumab group was withdrawn from the trial on day 113 because of pain at the injection site, and another patient in the golimumab group was withdrawn on day 183 because of intermittent leukopenia and neutropenia that was deemed to be possibly related to the trial drug. The latter participant also had low white-cell counts at baseline.

† An adverse event related to the trial agent was defined as any event that was deemed by the trial investigators to be very likely, probably, or possibly related to the trial drug or placebo or if the data regarding the relationship to the trial agent were missing.

‡ One participant in the golimumab group had diplopia due to an orbital floor fracture after an automobile accident, and one participant in the placebo group had cholelithiasis and underwent ambulatory cholecystectomy. Both events were reported to have resolved and were not deemed by trial investigators to be related to golimumab or placebo; the patients did not discontinue their assigned regimen because of these adverse events.

¶ Hypoglycemic events were reported as adverse events at the discretion of the investigators.

The secondary end points at Week 52 are presented in Table 7.

Table 7: Secondary End Points at Week 52*

Outcome	Placebo	Golimumab	Treatment Effect (95% CI)†	p-Value‡
Glycated hemoglobin level				
All participants - no.	28	56		
Mean glycated hemoglobin level at baseline - %	7.1±1.2	7.0±1.1		
Mean glycated hemoglobin level at Week 52 - %	7.6±1.2	7.3±1.5		
LS mean (±SE) change from baseline at Week 52	0.56±0.29	0.47±0.21	–0.09 (–0.81 to 0.63)	0.80
Insulin use				
All participants - no.	28	56		
Mean dose at baseline - U/kg/day	0.44±0.20	0.42±0.26		
Mean dose at Week 52 - U/kg/day	0.69±0.26	0.51±0.28		
LS mean (±SE) change from baseline to Week 52 - U/kg/day	0.24±0.04	0.07±0.03	–0.18 (–0.27 to –0.08)	0.001
Participants <18 yr of age - no.	21	47		
Mean dose at baseline - U/kg/day	0.44±0.20	0.42±0.26		
Mean dose at Week 52 - U/kg/day	0.69±0.26	0.51±0.28		
LS mean (SE) change from baseline to Week 52 - U/kg/day	0.27±0.05	0.08±0.03	–0.19 (–0.31 to –0.08)	
Participants ≥18 yr of age - no.	7	9		
Mean dose at baseline - U/kg/day	0.40±0.19	0.31±0.3		
Mean dose at Week 52 - U/kg/day	0.51±0.33	0.37±0.23		
LS mean (SE) change from baseline to Week 52 - U/kg/day	0.16±0.05	0.03±0.04	–0.14 (–0.27 to 0.00)	
Hypoglycemic events from baseline through Week 52§				
All participants - no.	28	56		
Mean number of hypoglycemic events§	42.9±4.0	38.2±35.7	0.90 (0.63 to 1.29)	0.80
Level 1	26.0±23.5	25.0±26.1	0.99 (0.65 to 1.49)	
Level 2	14.3±15.1	10.7±11.4	0.72 (0.50 to 1.04)	
Level 3	0	0		
Participants <18 yr of age - no.	21	47		
Mean number of hypoglycemic events	48.2±34.8	40.6±36.3	0.87 (0.58 to 1.29)	
Level 1	28.0±23.5	26.2±26.3	0.99 (0.62 to 1.57)	
Level 2	17.6±16.1	11.5±12.0	0.64 (0.42 to 0.96)	
Participants ≥18 yr of age - no.	7	9		
Mean number of hypoglycemic events	27.0±27.7	27.1±31.7	1.09 (0.40 to 2.98)	
Level 1	20.0±24.2	18.8±25.7	1.05 (0.32 to 3.47)	
Level 2	4.4±3.8	6.4±5.9	1.33 (0.48 to 3.72)	

* Plus–minus values are means ±SD unless otherwise indicated.

† For insulin use, the treatment effect is shown as the least-squares (LS) mean between-group difference in the change from baseline at week 52 (golimumab minus placebo). For hypoglycemic events, the treatment effect is shown as the ratio of the rate of hypoglycemic events (the number of events per patient-year of exposure) in the golimumab group to that in the placebo group.

‡ P values were calculated with the use of the Hochberg approach to control for multiple comparisons. Additional details are provided in the Supplementary Appendix.

§ Hypoglycemia was defined in the protocol as a biochemically confirmed blood glucose level of 70 mg per deciliter (3.9 mmol per liter) or less, irrespective of clinical symptoms and events related to severe hypoglycemia (with severe hypoglycemia defined as an event characterized by altered mental or physical status [or both] that requires assistance from another person for recovery). Hypoglycemic events were further assessed according to American Diabetes Association levels: level 1 is a blood glucose reading of 54 to less than 70 mg per deciliter (3.0 to <3.9 mmol per liter); level 2, a blood glucose reading of less than 54 mg per deciliter; and level 3, a severe event characterized by altered mental or physical status (or both) that requires assistance from another person for recovery. The analysis of hypoglycemic events according to age group (<18 years or ≥18 years) was performed post hoc.

Weeks 52 through 104

According to the MAH the incidence of TEAEs was similar in both treatment groups. During this period, 38 (77.6%) of 49 participants from the golimumab treatment group and 19 (76.0%) of 25 participants from the placebo treatment group experienced at least 1 TEAE. The highest number of TEAEs were reported in the SOC of Infections and infestations for both the golimumab (17 [34.7%] participants) and placebo (14 [56.0%] participants) treatment groups followed by Metabolism and nutrition disorders (golimumab: 15 [30.6%] participants; placebo: 3 [12.0%] participants). Overall, 9 (18.4%)

participants from the golimumab treatment group and 2 (8.0%) participants from the placebo treatment group reported at least 1 TEAE that was assessed by the investigator as reasonably related to the study treatment.

Pregnancy was reported in 1 participant in the golimumab treatment group during the off-therapy period. On Day 563, the pregnancy was reported. The participant completed the off-treatment period and 3 months later delivered a healthy baby (gestational age 37 weeks) through C-section (polyhydramnios).

The number of hypoglycemia events from Week 52 through Week 104 is presented in Table 8. The mean (SD) number of hypoglycemia episodes was 18.5 (45.8) versus 32.8 (69.45) in the golimumab and placebo treatment groups, respectively, during the off-therapy period (Week 52 through Week 104). There was no severe hypoglycemia event reported through Week 104 per American Diabetes Association definition.

Table 8: Number of Categorized Hypoglycemia Events from Week 52 Through Week 104; Off-Therapy Analysis Set (Study CNTO148DML2001)

	Placebo	Golimumab
Analysis Set: Off-therapy	25	49
The number of hypoglycemia episodes		
Mean (SD)	32.8 (69.45)	18.5 (45.79)
Median	14.0	6.0
Range	(0; 333)	(0; 296)
Symptomatic hypoglycemia[a]		
Mean (SD)	24.5 (67.73)	14.8 (43.18)
Median	5.0	3.0
Range	(0; 333)	(0; 295)
Asymptomatic hypoglycemia[b]		
Mean (SD)	8.4 (16.76)	3.7 (9.37)
Median	1.0	1.0
Range	(0; 74)	(0; 59)
Probable symptomatic hypoglycemia[c]		
Mean (SD)	0.0 (0.00)	0.0 (0.00)
Median	0.0	0.0
Range	(0; 0)	(0; 0)
ADA-defined severe hypoglycemia[d]		
Mean (SD)	0.0 (0.00)	0.0 (0.00)
Median	0.0	0.0
Range	(0; 0)	(0; 0)

Note: [a] Symptomatic hypoglycemia is an event with symptoms of hypoglycemia accompanied by a measured plasma glucose (PG) concentration ≤70 mg/dL, which has symptom and BG<=70;
[b] Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured PG concentration of ≤70 mg/Dl, which has no symptom but BG<=70;
[c] Probable symptomatic hypoglycemia is an event during in which symptoms of hypoglycemia but without an accompanying PG determination, which has symptom but missing BG value.
[d] ADA-defined severe hypoglycemia denotes severe cognitive impairment requiring external assistance for recovery.

According to the MAH a higher number of participants from the golimumab treatment group compared to the placebo treatment group reported Grade 2 hematology AEs. Between Week 52 through Week 104, two participants from the golimumab treatment group reported Grade 3 and 4 decreased neutropenia. There were no reports of neutropenia in the placebo treatment group.

Five SAEs were reported: all of them diabetic ketoacidosis. All 5 SAEs were assessed by the investigator as not related to the study drug and had resolved. All participants completed the off-therapy period of the study.

Open-Label Extension

According to the MAH 3 participants reported at least 1 TEAE. Two participants reported at least 1 or more reasonably related TEAEs which were related to hypoglycemic episodes; these TEAEs presented with several symptoms most commonly nausea, nervousness, shakiness etc.

Two participants developed mild to moderate infections such as nasopharyngitis, sinusitis or oropharyngeal pain, which resolved with no impact and assessed as not likely associated with golimumab.

One participant developed mild injection site erythema, which was reported twice and assessed as probably related to golimumab SC injection.

One participant experience seizure a serious TEAE, ten days after last dose of golimumab, which resolved 3 days later and assessed as not related to golimumab.

Post-baseline hematology values of (CTCAE) Grade 2 toxicity included neutropenia (Study Day 183) and decreased platelet counts (Study Day 267). No deaths, opportunistic infections, malignancies, or tuberculosis were reported.

CHMP comment:

It is agreed with the MAH that the safety findings from this study are overall consistent with the safety profile of golimumab. The most common adverse events were infections and injection site reactions. No deaths, opportunistic infections, malignancies, or tuberculosis were reported. Of note, a higher number of participants from the golimumab treatment group compared to the placebo treatment group reported Grade 2 hematology AEs. Between Week 52 through Week 104, two participants from the golimumab treatment group reported Grade 3 and 4 decreased neutropenia. There were no reports of neutropenia in the placebo treatment group.

With regards to the reported number of infections, it is rather high as compared to rates presented in the SmPC. However, the reported rates in the golimumab group are not very much higher than the reported rates in the placebo group and there were no serious infections, supporting that this finding does not evoke any new safety concerns.

Similarly, the incidence rate of injection site reactions was also rather high as compared to rates presented in the SmPC. However, as the rates were comparable in the active group and the placebo group, the issue will not be further pursued.

The reported events of hypoglycemia are of interest as it is not listed as an adverse event in the current SmPC. From weeks 0 through 52, hypoglycemic events reported as adverse events were reported in 13 participants (23%) in the golimumab group and in 2 participants (7%) in the placebo group. However, the mean number of hypoglycemic events seemed to be higher in the placebo group, event rate (based on actual number of events as stated in Table 4) in golimumab group 39.01 versus event rate 43.36 in placebo group (Rate Ratio 0.90 95% CI 0.629-1.286). The implications of these findings, that are not consistent and based on a rather small dataset, for the overall populations for which golimumab are currently approved seem currently uncertain but this has to be carefully followed in the on-going development diabetic programme.

However, the MAH should also, within this procedure, provide a thorough discussion regarding the potential relevance of this finding for the use of golimumab according to the current label (i.e., within the patient groups covered by the approved indications, with approved doses and existing contra-indications/precautions for use).

2.3.3. Discussion on clinical aspects

Conclusions according to the MAH

Weeks 0 through 52

The MAH states that in children and adolescents (aged 6 to 21 years) with newly diagnosed T1D, treatment with golimumab for 52 weeks resulted in:

-A statistically significant difference versus placebo in C-peptide AUC

-Less insulin use in the golimumab treatment group compared to the placebo group

-No statistically significant difference in the incidence of hypoglycemia events between the placebo and golimumab treatment.

-Relatively stable proinsulin/insulin ratio compared to an increase in the placebo group

-Higher proportion of participants meeting pre-defined responder criteria compared to the placebo group.

-A treatment separation in HbA1c change from baseline was observed as early as Week 8 and appeared to trend closer over time with a significant difference only at Week 12.

-No clear relationship was observed between efficacy endpoints and PK or antibodies to golimumab.

Overall, this study met its key primary endpoint and showed improvements in secondary endpoints. No new safety signals were observed. Altogether, the data suggest a favorable efficacy profile and a safety and tolerability profile consistent with previous findings.

Weeks 52 through 104

In children and adolescents (aged 6 to 21 years) with newly diagnosed T1D, treatment with golimumab for 52 weeks followed by a 52-week off-therapy period resulted in:

-The rate of decline of C-peptide in the golimumab treatment group during off-therapy period appeared to be similar as that observed in the placebo treatment group. However, the early golimumab treatment did delay a fall in C-peptide AUC, as compared to the placebo treatment group, by 46.8 weeks or 10.8 months.

-In addition, there were no new or unexpected safety issues/signals during off-therapy period.

Open-Label Extension

In children and adolescents (aged 6 to 21 years) with newly diagnosed T1D who restarted golimumab during the OLE, the results indicate that:

-Firm conclusions on efficacy during the OLE cannot be drawn due to the low number of participants, prior trends during off-treatment period, and the (partial) lack of on-treatment OLE data.

-There were no new or unexpected safety issues/signals during the OLE.

The MAH concludes that based upon the data of study CNTO148DML2001, there is no need to update the product information or risk management plan. The overall benefit-risk balance of golimumab remains positive.

References

Quattrin T, Haller MJ, Steck AK, et al. Golimumab and Beta-Cell Function in Youth with New-Onset Type 1 Diabetes. Clinical Trial N Engl J Med. 2020;383(21):2007-2017.

Valle A, Giamporcaro GM, Scavini M, et al. Reduction of Circulating Neutrophils Precedes and Accompanies Type I Diabetes. Diabetes. 2013;62(6):2072-2077.

3. CHMP overall conclusion and recommendation

This submission includes 3 clinical study reports (CSRs) for the golimumab Phase 2a study CNTO148DML2001 (T1GER**.**) Study CNTO148DML2001 is a completed Proof of Concept (POC), multicenter, randomized, double blind, placebo-controlled study of the efficacy, safety, pharmacokinetics (PK) and immunogenicity of golimumab compared with placebo in 84 participants 6 through 21 years of age who have been recently diagnosed with Type 1 Diabetes (T1D). The study took place in the USA. The rationale behind the study is that both preclinical and clinical studies have demonstrated that tumor necrosis factor alpha (TNFα) has a role in T1D development and progression given immune, direct β-cell toxic, and metabolic effects of TNFα suggesting that inhibiting this cytokine might be an approach to further investigate clinically.

The study includes 3 phases: i) Weeks 0 to 52 (double-blind treatment phase), ii) Weeks 52 to 104 (off-therapy follow-up phase), and iii) the Open-Label Extension (OLE) phase (62 weeks). The overall

aim was to determine whether golimumab administered subcutaneously (SC) in participants 6 to 21 years of age with newly diagnosed T1D has the potential to maintain residual β-cell function and improve metabolic control.

The primary endpoint was the Mixed-Meal Tolerance Test (MMTT) -stimulated 4-hour C-peptide area under the concentration-time curve (AUC) at Week 52. The secondary outcomes include 1) change from baseline in insulin use in units per kilogram body weight per day over time, 2) change from baseline in hemoglobin A1c (HbA1c) over time, 3) hypoglycemic event rates through Week 52 and 4) MMTT-stimulated 4-hour C-peptide AUC over time. In addition, pharmacokinetics, immunogenicity and safety aspects were evaluated.

Results

In total 84 patients were randomized, 56 patients to the golimumab-, and 28 patients to the placebo group. The baseline characteristics were substantially similar in the two groups although the MAH points out that the placebo group has a somewhat higher the 4 h C peptide AUC (nmol/L) at baseline as compared to the golimumab group. This imbalance was however very small.

Efficacy

According to the MAH, overall golimumab significantly slowed disease progression as measured by Mixed-Meal Tolerance Test (MMTT)-stimulated C-peptide AUC decline. The least square (LS)Mean (95% CI) of the treatment difference in log(AUC+1) scale was 0.17 (0.08, 0.26) with a p value of 0.0004. Thus, the primary endpoint of the study was reached. However, a critical assessment of the efficacy claims made by the MAH is beyond the scope of this procedure.

Immunogenicity and Safety aspects

Antibodies towards golimumab were detected in 30 of 56 participants (54%). There were no observed associations between efficacy endpoints and PK or antibodies to golimumab.

The following text is included in the current SmPC: "In the Phase III pJIA study through week 48, antibodies to golimumab were detected by the drug-tolerant EIA method in 40% (69/172) of golimumab treated children of which a majority had a titre lower than 1:1000."

Thus, the reported ADA-rate seems somewhat higher than what has previously been reported for golimumab-treated children although comparisons may be hampered by differences in ADA-methodology. However, the rates are not markedly higher than previously reported and based on a dataset with rather few subjects. Further, the studied diabetic population may be somewhat different from the pediatric population for which golimumab is currently approved (i.e. JIA) with regards to factors of importance for ADA-development such as concurrent immunosuppression. Thus, the significance of this finding for the currently approved indications are considered limited, not warranting any current PI or RMP-changes. However, if the development programme in diabetic children is pursued, monitoring of ADA-development (ADA-testing and monitoring for clinical events potentially associated with ADA) will be very important.

It is agreed with the MAH that the safety findings from this study are overall consistent with the safety profile of golimumab. The most common adverse events were infections and injection site reactions. No deaths, opportunistic infections, malignancies, or tuberculosis were reported.

With regards to the reported number of infections, it is rather high as compared to reported rates in the SmPC. However, the reported rates in the golimumab group are not very much higher than the reported rates in the placebo group and there were no serious infections, supporting that this finding does not evoke any new safety concerns.

Similarly, the incidence rate of injection site reactions was also rather high as compared to rates presented in the SmPC. However, as the rates were comparable in the active group and the placebo group, the issue will not be further pursued.

The reported events of hypoglycemia are of interest as it is not listed as an adverse event in the current SmPC. From weeks 0 through 52 hypoglycemic events reported as adverse events were reported in 13 participants (23%) in the golimumab group and in 2 participants (7%) in the placebo group. However, the mean number of hypoglycemic events seemed to be higher in the placebo group. The implications of these findings, that are thus not fully consistent and based on a rather small dataset, for the overall populations for which golimumab are currently approved, seem currently uncertain. Upon request from the CHMP, the MAH provided a thorough discussion regarding the potential relevance of this finding for the use of golimumab according to the current label. The lack of consistency regarding measurement and reporting of hypoglycemia and the low number of observed events in the rather small TIGER study make the evaluation of the observed differences between the two treatment arms difficult. Further, the implications of the findings for the overall population for which golimumab is currently approved seem uncertain. However, it is agreed that the signal, at present, is not strong enough to warrant any PI changes. Nevertheless, the CHMP considered that it is of great importance to carefully follow and monitor hypoglycemia in a structured way in the on-going and planned development diabetic programme of golimumab. See section 4 below.

In conclusion, no clear, new safety signals were observed within the submitted data. Based on the submitted data the overall benefit-risk balance of golimumab remains positive. No update of the product information or risk management plan is considered needed.

☒ **Fulfilled**

No regulatory action required.

4. Additional clarification requested

1. Please provide a thorough discussion regarding the observed imbalance in subjects that reported hypoglycemic events as adverse events between the golimumab and the placebo group in the T1GER study. This could preferably also take into account other data available on the topic, e.g. from the literature as well from post marketing reporting, to allow for a fulsome review. Does the finding have any relevance for the use of golimumab according to the current label i.e. for use in the patient groups covered by the approved indications treated with the approved doses? And if so, would it merit to be reflected in the PI?

MAH responses to Request for supplementary information

In the T1GER study (CNTO148DML2001), the site Principal Investigators (PIs) were to assess and label hypoglycemic episodes (ie a Blood Glucose (BG) $\leq$ 70 mg/dL and/or symptoms of hypoglycemia) according to their clinical judgement. As such that left the ability of site PIs to label different participants with, for example, the same BG with different levels of adverse events (AEs), if at all. As hypoglycemia is an expected (adverse) event and is a sequalae of the underlying disease of Type 1 Diabetes (T1D) (due to treatment with insulin), not all site PIs would record a specific BG value or symptoms the same, at least in terms of AE reporting. We found that there were sites that appeared to have a (much) lower threshold for reporting hypoglycemia events as AEs at all and higher level AEs than others. Note, there were no Serious Adverse Events (SAEs) reported due to hypoglycemia. It is this subjective data and some imbalance with treatment group recruitment according to site, that appears to support that there were more hypoglycemic AEs in the treatment group vs placebo group.

When the data is looked at objectively considering both BG levels and symptoms according to the current ADA/EASD guidance on hypoglycemia reporting on all participants *(Diabetes Care 2017 Jan; 40(1): 155-157)*, although not statistically significant, those in the treatment group had numerically lower rates of any hypoglycemia, Level 1 (BG 70mg/dL to 54 mg/dL) and Level 2 hypoglycemia (BG level of 54mg/dL or less). *(Quattrin et al N Engl J Med. 2020 Nov 19;383(21):2007-2017)* Note, no participant experienced Level 3 hypoglycemia (severe cognitive impairment requiring external assistance for recovery) in either group.

In the pediatric participants (18 year old and less), treatment with golimumab was associated with statistically significant fewer Level 2 hypoglycemia events than with placebo. (Quattrin et al)

Taken together, because of the nature of T1D and the expected AE of hypoglycemia due to comanagement with insulin, the subjective nature of AE reporting and the objective data showing no difference (and lower rates of hypoglycemia in some), the MAH feels that the data do not suggest that there is an intrinsic hypoglycemic effect of golimumab. Therefore, the MAH is of the opinion that an update of the Product Information is not warranted.

CHMP comment:

The MAH explains that assessing and labelling hypoglycemic episodes in the T1GER (CNTO148DML2001) study was up to the principal investigator at each site, leading to a different threshold for reporting such episodes as an adverse event. It is further stated that the rates of *reported hypoglycemic events* (level 1 and level 2, the assessment reflecting both BG levels and symptoms) in both adult and paediatric study participants were higher in the placebo-arm. The MAH also argues that hypoclycemic events are expected due to the nature of type 1 diabetes, and the concomitant treatment with insulin. Thus, according to the MAH there are no signals of any intrinsic hypoglycemic effect of golimumab warranting an update of the Product Information (PI).

Overall, it is acknowledged that the lack of consistency regarding measurement and reporting of hypoglycemia and the low number of observed events in the rather small T1GER study make the evaluation of the observed differences between the two treatment arms difficult. The implications of the findings for the overall populations for which golimumab are currently approved seem uncertain, and at present, it is agreed that the signal is not strong enough to warrant any PI-changes.

However, occurrence of hypoglycemia following the initiation of TNF-inhibitors treatment in patients with diabetes mellitus has previously been reported in a number of case series and reports.[1] A biological reasonable explanation might be that blocking TNF-alfa leads to decreased insulin resistance, decreased β-cell apoptosis, and improvement in blood sugar control in patients with diabetes.[2] In the light of this, it is of great importance to carefully follow and monitor hypoglycemia in a structured way in the on-going and planned development diabetic programme of golimumab.

References:

1.Etanercept-Induced Hypoglycemia in a Patient With Psoriatic Arthritis and Diabetes Pfeifer et al. Investig Med High Impact Case Rep. 2017

2. The association between the biological disease-modifying anti-rheumatic drugs and the incidence of diabetes: A systematic review and meta-analysis Lin et al.,Pharmacol Res. 2020