U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 125-289
Supplement #:	0133
Drug Name:	Simponi (golimumab) subcutaneous injection
Indication(s):	Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis and Ulcerative Colitis
Applicant:	Janssen Biotech, Inc.
Date(s):	Submission: August 22, 2016 PDUFA: June 22, 2017
Review Priority:	Standard
Biometrics Division:	DB2
Statistical Reviewer:	Yongman Kim
Concurring Reviewers:	Gregory Levin
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Rachel Glaser, Nikolay Nikolov
Project Manager:	Christine Ford

Keywords: clinical studies, failed trial, PREA

Table of Contents

LIST OF FIGURES **3**

1 EXECUTIVE SUMMARY **4**

2 INTRODUCTION **4**

2.1 OVERVIEW 4
2.1.1 Class and Indication *5*
2.1.2 History of Drug Development *5*
2.1.3 Specific Studies Reviewed *5*
2.1.4 Major Statistical Issues *6*
2.2 DATA SOURCES 6

3 STATISTICAL EVALUATION **6**

3.1 DATA AND ANALYSIS QUALITY 6
3.2 EVALUATION OF EFFICACY 7
3.2.1 Study CNTO148JIA3001 ..... *7*
3.3 EVALUATION OF SAFETY 13

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS **13**

4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION 13

5 SUMMARY AND CONCLUSIONS **15**

5.1 STATISTICAL ISSUES 15
5.2 COLLECTIVE EVIDENCE 15
5.3 CONCLUSIONS AND RECOMMENDATIONS 15
5.4 LABELING RECOMMENDATIONS 15

LIST OF TABLES

Table 1. Study included in analysis 6
Table 2. Applicant's analysis of proportion of subjects who did not flare from Week 16 through Week 48, among all randomized subjects 12
Table 3. Applicant's analysis of proportion of subjects who were ACR Ped 30 responders at Week 48, among all randomized subjects 12
Table 4. Applicant's analysis of proportion of subjects who had inactive disease at Week 48, among all randomized subjects 13
Table 5. Applicant's analysis of proportion of subjects who were in protocol defined clinical remission while on medication at Week 48, among all randomized subjects 13
Table 6. Applicant's analysis of proportion of subjects who flare from Week 16 through Week 48 by Week 0 CRP levels; randomized subjects 14

LIST OF FIGURES

Figure 1. Study Schematic 7
Figure 2. Patients Disposition (All Randomized Patients) 11
Figure 3. Applicant's forest plot of proportion of subjects who did not have a flare of disease by demography categories; randomized subjects 14

1 EXECUTIVE SUMMARY

Janssen Biotech, Inc. submitted a supplemental application to update labeling for Simponi (golimumab) with results from a study in polyarticular juvenile idiopathic arthritis (pJIA). The applicant submitted the results from a phase 3 clinical trial, CNTO148JIA3001 (3001 for short hereafter), that evaluated the efficacy of golimumab administered subcutaneously (SC) for the treatment of pJIA. The applicant acknowledged that the results from the trial did not meet the primary and secondary objectives of the study to establish efficacy of the golimumab SC regimen for treatment of the indicated population of pJIA.

Based on my review of the data from the study, I also conclude that the phase 3 trial failed to provide evidence of efficacy based on the primary endpoint of no flare of disease after achieving early improvement on signs & symptoms. Also, the trial did not provide supportive evidence of efficacy based on the secondary endpoints of improvement on signs & symptoms, no disease activity, and clinical remission. As a whole, the results from the study failed to provide substantial evidence of efficacy.

The study 3001 was a randomized withdrawal study in which all subjects received golimumab in an open-label, active treatment period from Week 0 through Week 12, followed by randomization of American College of Rheumatology [ACR] Ped 30 responders at Week 16 to receive placebo or golimumab with methotrexate (MTX) as background therapy. In the subset of patients achieving ACR Ped 30 response at Week 16, there was not a statistically significant difference between golimumab + MTX and placebo + MTX with respect to the primary endpoint of absence of flare between Week 16 and Week 48. Approximately 59% of the golimumab + MTX group and 53% of the placebo + MTX group did not have flares (p=0.414).
The key secondary endpoints also showed no statistically significant differences between the treatment groups as shown below:

1. Proportion of ACR Ped 30 responders at Week 16 with ACR Ped 30 response at Week 48: golimumab + MTX group (52.6%) and the placebo + MTX group (55.3%, p=0.751).
2. Proportion of ACR Ped 30 responders at Week 16 who had inactive disease at Week 48: golimumab + MTX group (39.7%) and the placebo + MTX group (27.6%, p=0.119).
3. Proportion of ACR Ped 30 responders at Week 16 who were in clinical remission at Week 48: golimumab + MTX group (12.8%) and the placebo + MTX group (11.8%, p=0.848).

Based on the above findings, I agree with the applicant's approach to not seek an indication claim for pJIA. The applicant only proposes to include results of Study 3001 study in Section 8.4, Pediatric Use, of labeling, and the proposed language is generally reasonable.

2 INTRODUCTION

2.1 Overview

This application (BLA #125,289 S0133) was submitted on August 22, 2016 in support of adding results to labeling regarding golimumab subcutaneous injection for the treatment of pJIA as a supplemental Biological License Application.

2.1.1 Class and Indication

Golimumab is a human monoclonal antibody with an immunoglobulin G (IgG) 1 heavy chain isotype (G1m [1,17] allotype) and a kappa light chain isotype. Golimumab binds with high affinity to both soluble and transmembrane forms of tumor necrosis factor alpha (TNFα) and inhibits TNFα bioactivity. Golimumab is classified according to the Anatomical Therapeutic Chemical Classification System as a TNFα inhibitor. Other members of this therapeutic class include infliximab, etanercept, adalimumab, and certolizumab pegol.

2.1.2 History of Drug Development

The golimumab clinical development program for pJIA was introduced to the Division of Pulmonary, Allergy, and Rheumatology Products under IND 9,925. Communication with the applicant regarding their development plan is documented under this IND. Pertinent parts of the statistical portion of those communications are summarized herein.

As a part of a post-marketing requirement outlined in the 24 April 2009 Simponi (golimumab) approval letter, the applicant was required to conduct a study in pediatric subjects with active pJIA (Protocol CNTO148JIA3001) with subcutaneous golimumab. To fulfill this requirement, the applicant conducted a randomized-withdrawal, double-blind, placebo-controlled, parallel-group, multicenter study of SC golimumab in pediatric subjects with active pJIA despite treatment with methotrexate (MTX).

In December 2015, the applicant requested a meeting with the Division to discuss the possibility of seeking indication claims for pJIA based on the totality of the data and results of post hoc subgroup analyses. The Division provided the following clinical & statistical comments:

- *The Division responded (to the Applicant's question regarding post hoc subgroup analysis to support their efficacy claim for treatment of pJIA) that you state that study CNTO148JIA3001 failed for efficacy because of an unexpectedly low inflammatory burden in the enrolled study population. However, because this conclusion is based on evaluations of efficacy in multiple subgroups without control of overall type 1 error, the observed benefit in the high CRP subgroup may simply be due to chance alone. We therefore view your subgroup efficacy analysis as exploratory, useful for the design of future confirmatory trial(s) for this indication.*

2.1.3 Specific Studies Reviewed

The submission included the results from a phase 3 trial 3001. The objective of the phase 3 study was to evaluate the efficacy and safety of golimumab SC compared with placebo on background methotrexate treatment in pJIA patients. All patients were to receive open-label golimumab for 16 weeks and then only the subset of ACR Ped 30 responders at Week 16 were randomized to double-blind study treatments up to 48 weeks. The primary efficacy outcome variable was the

proportion of patients without a flare from Week 16 through Week 48. Below is the study I analyzed in my review (Table 1).

Table 1. Study included in analysis

	Phase and Design	Active Treatment Period	Randomized Withdrawal Period	# of Subjects per Arm	Study Population
CNTO148JIA3003	*Phase 3 Randomized withdrawal, double blind, placebo-controlled*	*16 weeks*	*48 weeks*	*Golimumab+ MTX (N=78)* *Placebo+ MTX (N=76)*	*pediatric subjects (ages 2 to less than 18 years) with polyarticular juvenile idiopathic arthritis (pJIA) manifested by ≥5 joints with active arthritis despite methotrexate (MTX) therapy for ≥3 months.*

2.1.4 Major Statistical Issues

The study failed to achieve the planned primary and secondary objectives.

2.2 Data Sources

Data were submitted by the applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, program code, and study reports were accessed under the network path \\cdsesub1\evsprod\bla125289\125289.enx.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted efficacy data were acceptable in terms of quality and integrity. I was able to replicate the primary and key secondary efficacy results for the study reviewed. No noticeable deviations between the raw datasets and analysis datasets relevant to primary and secondary endpoints were identified. The statistical analyses of my derived endpoints were consistent with the applicant's analyses.

Based on the information provided in this submission, the study seemed to be conducted properly and was consistent with the history of regulatory interactions and protocol revisions/amendments.

3.2 Evaluation of Efficacy

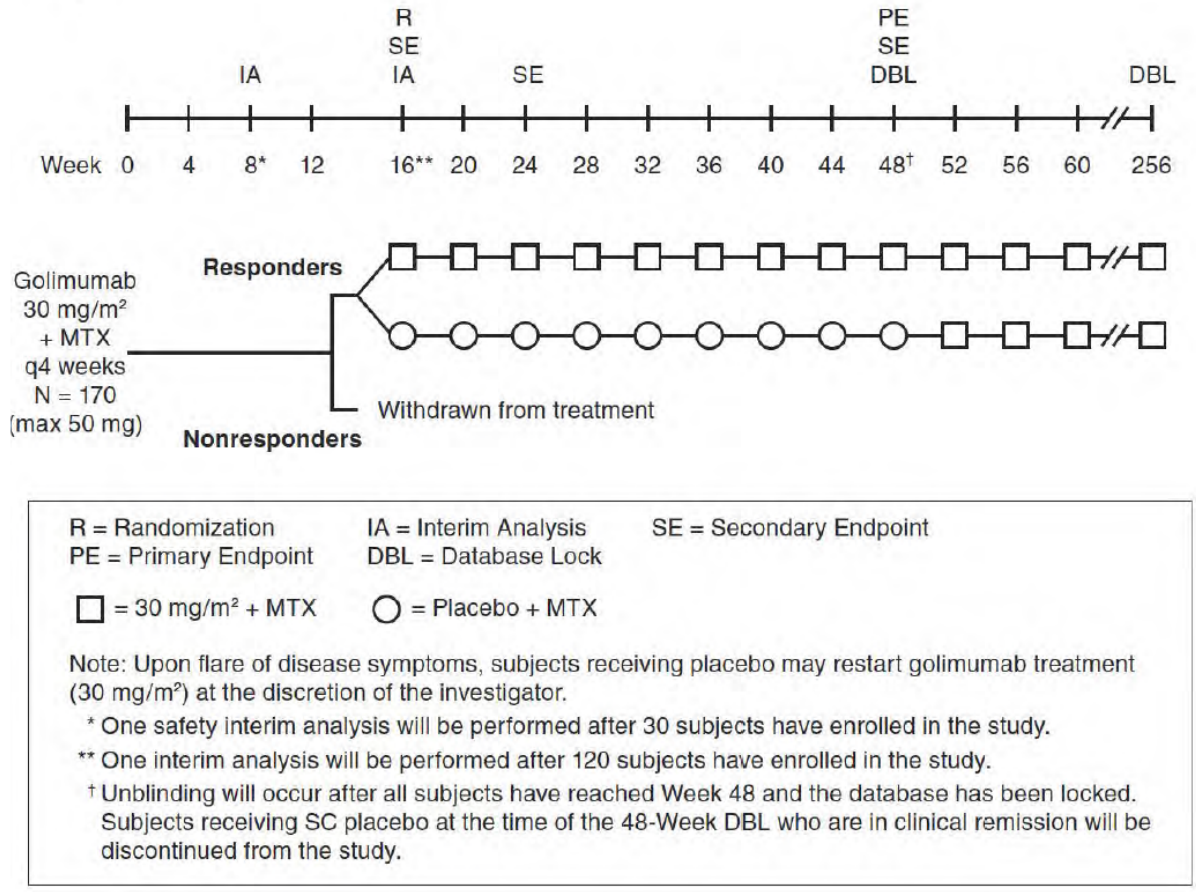
The applicant conducted a phase 3, randomized-withdrawal, double-blind, placebo-controlled efficacy trial, Study 3001.

3.2.1 Study CNTO148JIA3001

3.2.1.1 Study Design and Endpoints

The study was a randomized-withdrawal, double-blind, placebo-controlled, parallel-group, multicenter study of SC golimumab in pediatric subjects with active pJIA despite current treatment with MTX. The study population comprised subjects, ages 2 to less than 18 years with pJIA, receiving MTX with at least a 6-month history of arthritis, and active arthritis in ≥5 joints. Approximately 170 subjects were planned to receive treatment with SC golimumab 30 mg/m^2 (maximum 50 mg) + MTX every 4 weeks (q4w) through Week 12. Subjects who achieved an ACR Ped 30 response at Week 16 were randomized to receive either golimumab 30 mg/m^2 (maximum 50 mg) + MTX or placebo + MTX q4w through Week 48. Subjects who did not achieve an ACR Ped 30 response at Week 16 did not enter the randomized withdrawal portion of the study. Subjects who experienced a flare while on placebo resumed administration of golimumab 30 mg/m^2 injections (Figure 1).

Figure 1. Study Schematic



Source: Excerpted from the Clinical Study Report for Study CNTO148JIA3001 (page 25).

Subjects were children ages 2 to less than 18 years of age with active polyarticular course JIA (rheumatoid factor positive or negative) ≥6 months before study entry, extended oligoarticular, systemic JIA with no current systemic symptoms but with polyarthritis for ≥6 months before study entry, or polyarticular juvenile psoriatic arthritis. Active disease had to be present at the time of screening and before first injection and was defined by the presence of polyarticular disease involving ≥5 joints with active arthritis as defined by ACR criteria (i.e., presence of swelling, or if no swelling was present, limitation of motion accompanied by pain, tenderness, or both). Subjects with exposure to only 1 prior anti-tumor necrosis factor alpha (TNFα) agent before entering screening for this study were permitted to enroll in the study but were limited to no more than 20% of the total number of subjects.

The primary endpoint was the proportion of subjects without a flare from Week 16 through Week 48, among all randomized subjects. ACR Ped response and flare of disease are composite endpoints measured by the 6 pediatric ACR categories. These are as follows:

1. Physician global assessment of disease, (0-100 mm)
2. Subject/parent global assessment of overall well-being, (0-100 mm)
3. Number of active joints (defined as either swelling, or in absence of swelling, limited range of motion associated with pain on motion or tenderness), (0-73)

4. Number of joints with limited range of motion, (0-69)
5. Physical function by Childhood Health Assessment Questionnaire (CHAQ), (0-3)
6. Erythrocyte Sedimentation Rate (performed at site), (unit = mm/h)

ACR Ped 30 response was defined as ≥30% improvement from baseline in at least 3 of the 6 components with worsening of 30% or more in no more than 1 of the above noted components. Improvement in each of the individual components is indicated by a decrease in score.

Flare according to the JIA pediatric criteria for flare (all criteria must be met) was defined as:

1. ≥30% worsening in at least 3 of the 6 ACR Ped components and ≥30% improvement in not more than 1 of the 6 ACR response components from Week 16.
2. If the Physician or Subject/Parent Global Assessment was one of the 3 ACR response components used to define flare, worsening of ≥20 mm from Week 16 must have been present,
3. If the number of active joints or joints with limitation of motion was one of the 3 ACR response components used to define flare, worsening in ≥2 joints from Week 16 must have been present.
4. If ESR was used in the flare definition, the worsening in ESR had to be to a level above the upper limit of normal (ULN, 20 mm/h). If CRP was used in the flare definition, the worsening in CRP had to be to a level above the ULN, 1.0 mg/dL or 10 mg/L.

For flare of JIA disease determination prior to Week 16 study agent administration, the baseline was the value measured at Week 0. After Week 16 study agent administration, the baseline for flare of disease calculation was the measurement at Week 16.

There were 3 key secondary endpoints. The key secondary analyses in order of importance were as follows:

1. The proportion of subjects with ACR Ped 30 response at Week 48, among all randomized subjects.
2. The proportion of subjects who had inactive disease at Week 48, among all randomized subjects.
3. The proportion of subjects who were in protocol-defined clinical remission while on medication for JIA at Week 48, among all randomized subjects.

Inactive disease was defined as the presence of all of the following:

1. No joints with active arthritis,
2. No fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA,
3. No active uveitis,
4. Normal ESR (ie, <20 mm/hour[h]) or CRP (<1.0 mg/dL or <10 mg/L),
5. Physician Global Assessment of disease activity indicating no active disease (≤5 mm on the VAS).
6. Duration of morning stiffness <15 minutes.

Clinical remission while on medication for JIA was defined as inactive disease at each non-missed visit for a period of ≥6 months (24 weeks) while on medication. All subjects were assumed to be on medication rather than placebo.

3.2.1.2 Statistical Methodologies

The primary analysis population was the ITT population defined as all randomized subjects. Binary categorical data (e.g., the proportion of subjects with an ACR Ped 30 response) were analyzed using the Cochran-Mantel-Haenszel (CMH) test, stratified by JIA disease type, prior anti-TNF therapy, and age. Non-responder imputation was used for dichotomous endpoints when patients dropped out from the study. For a dichotomous composite endpoint, subjects who had completely missing data (i.e., all components of the composite endpoint were missing) were assumed to be a non-responder. When at least 1 of the components was non-missing, last observation carried forward (LOCF) was used for imputing the components with missing data. Continuous data were analyzed using an analysis of variance test, unless otherwise specified. All statistical testing was performed 2-sided at an alpha level of 0.05. Analyses were stratified by JIA disease type, prior anti-TNFα therapy, and age. The missing value was replaced by the last non-missing observation (including baseline).

The primary and key secondary efficacy endpoints were tested in a strategy designed to protect the family-wise type 1 error rate at α=5% (two-sided). If the 2-sided test for the primary endpoint (proportion of subjects without a flare from Week 16 through Week 48, among all randomized subjects) was statistically significant at α=5%, then a hierarchical approach for statistical testing was used for the secondary endpoints. This procedure allowed for preservation of the overall type-1 error probability at the 5% level for the study. Hierarchical ordering of the secondary endpoints was as follows:

1. The proportion of subjects with ACR Ped 30 response at Week 48, among all randomized subjects.
2. The proportion of subjects who had inactive disease at Week 48, among all randomized subjects.
3. The proportion of subjects who were in protocol-defined clinical remission while on medication for JIA at Week 48, among all randomized subjects.

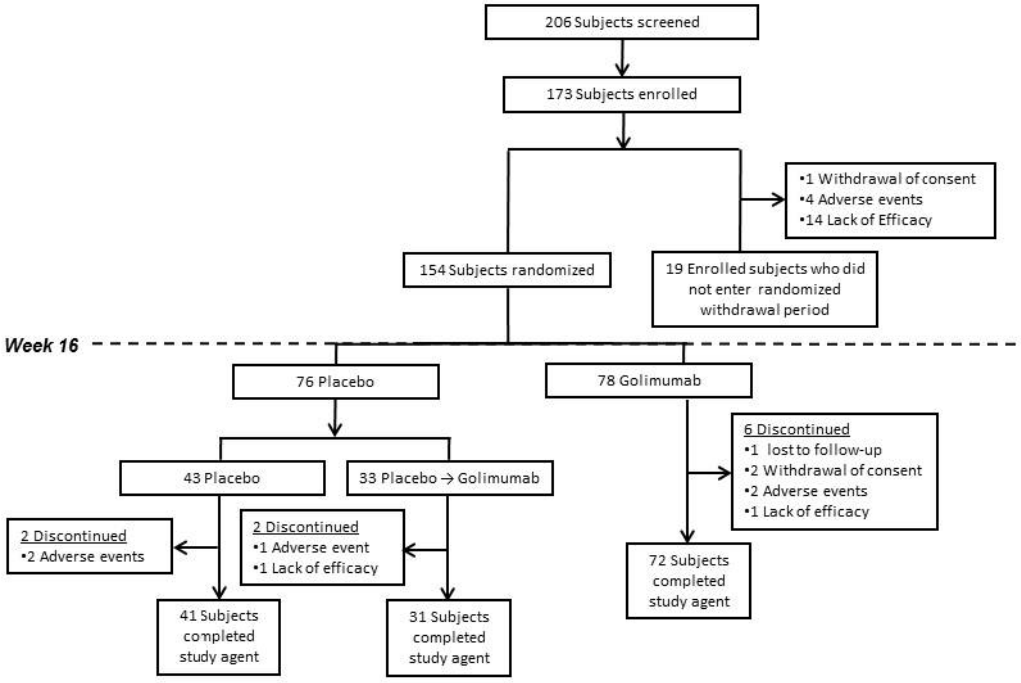
<u>Sample Size Calculation</u>

Power calculations were performed using a chi-squared test with flare of JIA disease as the response variable and treatment group as the independent variable. Assuming 65% and 37% of subjects experienced a flare of disease from Week 16 through Week 48 for the placebo + MTX, and golimumab + MTX treatment groups, respectively, 134 subjects who were responders at Week 16 (67 subjects from each treatment group) would be required to enter the randomized withdrawal portion of the study to obtain 90% power to detect a significant difference between treatment groups. These percentages of disease flares were observed in the adalimumab study in juvenile rheumatoid arthritis (JRA).

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

At Week 0, 173 subjects enrolled and received golimumab + MTX. Among them, 19 subjects did not enter the randomized withdrawal period because they did not meet the ACR Ped 30 response at Week 16. Of the 154 remaining subjects, 78 subjects were randomized to golimumab + MTX, and 76 subjects were randomized to placebo + MTX at Week 16. I found that among the 154 subjects, 151 subjects met the ACR Ped 30 response at Week 16 and 3 subjects (1 from placebo and 2 from golimumab) did not meet the ACR Ped 30 response at Week 16.
Through Week 48, 10 randomized subjects discontinued study agent or study participation, including 4 (5.3%) in the placebo + MTX group and 6 (7.7%) in the golimumab + MTX group. The most common reason for discontinuation was due to an AE.

Figure 2. Patients Disposition (All Randomized Patients)



Source: Excerpted from the Clinical Study Report CNTO148JIA3001 (page 53)

Demographic characteristics of enrolled subjects at baseline were generally well-balanced across treatment groups:

1. Majority of subjects were female (75.7%).
2. Most subjects were Caucasian (87.9%).
3. Median age was 12.0 years.
4. Median weight was 43.0 kg.

Baseline clinical disease characteristics were generally well-balanced across treatment groups including enrolled subjects who did not enter randomized withdrawal and the subjects

randomized to placebo + MTX or golimumab + MTX. All treatment groups had median ESR levels in the normal range, <20 mm/h, and median CRP levels in the normal range, <1.0 mg/dL. The majority (52.0%) of enrolled subjects had polyarticular RF-negative JIA, and 15 (8.7%) subjects had JPsA. All enrolled subjects had joints with active arthritis, and 52.6% to 64.5% of the subjects across the treatment groups had morning stiffness greater than 15 minutes. Across treatment groups, 85.7% to 100% of subjects had received prior corticosteroid injections and 14.3% to 17.4% of subjects had undergone prior arthrocentesis.

3.2.1.4 Results and Conclusions

Primary Efficacy Endpoint:

The analysis of the primary endpoint failed to show a statistically significantly lower flare rate through Week 48 for golimumab compared to placebo (Table 2). As pre-specified in the protocol, all dropouts prior to Week 48 were treated as having flare(s).

Table 2. Applicant's analysis of proportion of subjects who did not flare from Week 16 through Week 48, among all randomized subjects

	Treatment Group	n/N (%)	Comparison	Difference (%)	p-value
Primary analysis with NRI	Golimumab (N=78)	46/78 (59)	vs. Placebo	6	0.414
	Placebo (N=76)	40/76 (53)			

Note: P-value based on CMH test, stratified by JIA disease type, prior anti-TNF therapy, and age.
Source: Excerpted from the Clinical Study Report for Study CNTO148JIA3001 (page 78).

Key Secondary Efficacy Endpoints:

1. *Proportion of Subjects who were ACR Ped 30 Responders at Week 48, among all randomized subjects*

There was not evidence of a difference between treatment groups in the proportion of subjects with ACR Ped 30 response at Week 48, with a p-value=0.751 (Table 3). Note that golimumab was numerically inferior to placebo. Subjects who flared after Week 16 were considered non-responders for this analysis.

Table 3. Applicant's analysis of proportion of subjects who were ACR Ped 30 responders at Week 48, among all randomized subjects

	Treatment Group	n/N (%)	Comparison	Difference (%)	p-value
Primary analysis with NRI	Golimumab (N=78)	41/78 (53)	vs. Placebo	-2	0.751
	Placebo (N=76)	42/76 (55)			

Note: P-value based on CMH test, stratified by JIA disease type, prior anti-TNF therapy, and age.
Source: Excerpted from the Clinical Study Report for Study CNTO148JIA3001 (page 79).

2. *Proportion of Subjects who Had Inactive Disease at Week 48, among all randomized subjects*

There was not evidence of a difference between treatments in the proportion of subjects who

had inactive disease at Week 48, with a p-value of 0.119 (Table 4). Note that subjects who flared after Week 16 were considered non-responders for this analysis.

Table 4. Applicant's analysis of proportion of subjects who had inactive disease at Week 48, among all randomized subjects

	Treatment Group	n/N (%)	Comparison	Difference (%)	p-value
Primary analysis with NRI	Golimumab (N=78)	31/78 (40)	vs. Placebo	12	0.119
	Placebo (N=76)	21/76 (28)			

Note: P-value based on CMH test, stratified by JIA disease type, prior anti-TNF therapy, and age.
Source: Excerpted from the Clinical Study Report for Study CNTO148JIA3001 (page 79).

3. *Proportion of subjects who were in clinical remission while on medication for JIA at Week 48, among all randomized subjects*

There was not evidence of a difference between treatments in the proportion of ACR Ped 30 responders at Week 16 who were in clinical remission at Week 48, with a p-value of 0.848 (Table 5).

Table 5. Applicant's analysis of proportion of subjects who were in protocol defined clinical remission while on medication at Week 48, among all randomized subjects

	Treatment Group	n/N (%)	Comparison	Difference (%)	p-value
Primary analysis with NRI	Golimumab (N=78)	10/78 (13)	vs. Placebo	1	0.848
	Placebo (N=76)	9/76 (12)			

Note: P-value based on CMH test, stratified by JIA disease type, prior anti-TNF therapy, and age.
Source: Excerpted from the Clinical Study Report for Study CNTO148JIA3001 (page 80).

Summary of Results

In summary, the phase 3 study failed to demonstrate that golimumab was statistically superior compared to placebo with respect to the primary endpoint or any of key secondary endpoints.

3.3 Evaluation of Safety

The assessment of the safety of the study drug was conducted by the reviewing medical team. The reader is referred to Dr. Rachel Glaser's review for information regarding the safety profile of the drug.

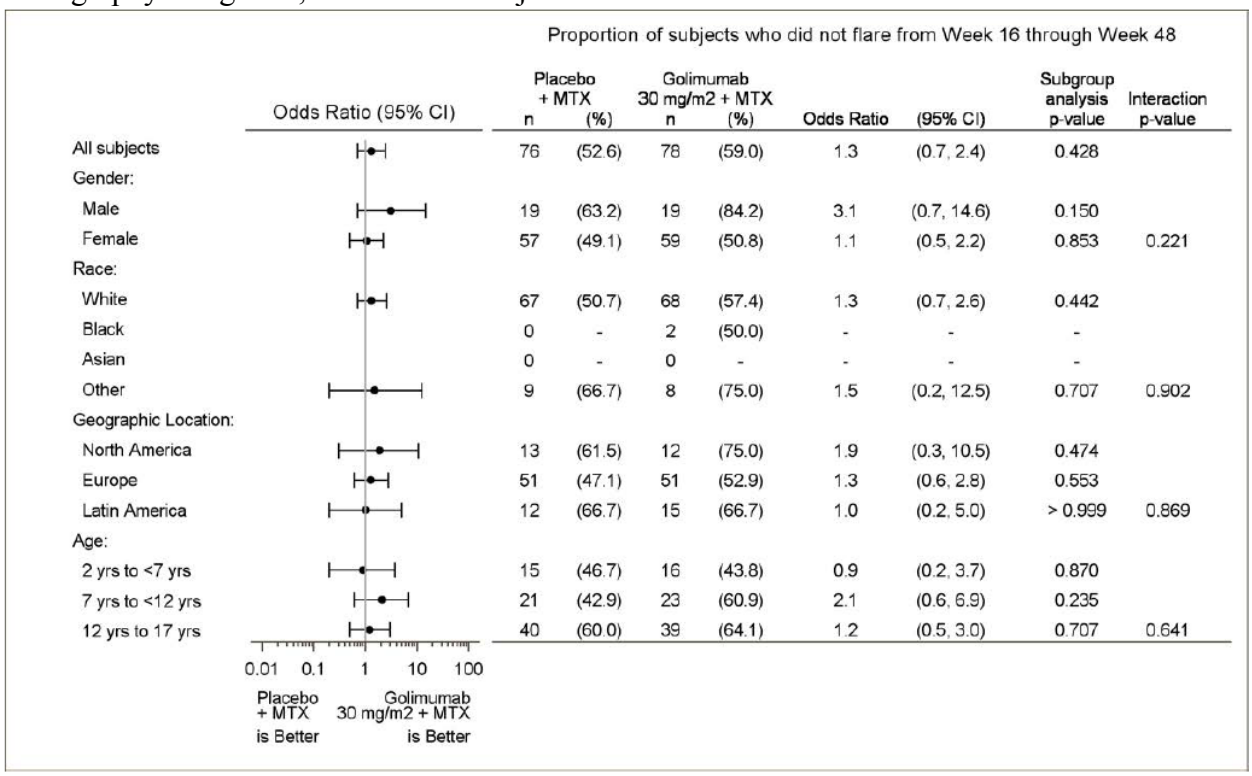
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The results from subgroup analyses by gender, race, age, and geographic region in terms of the primary endpoint could be found in the Clinical Study Report section 6.3.1.1 Subgroup Analyses

for the Primary Endpoint (pages 84-85). The results for various subgroups were consistent with the result for all subjects (Figure 3).

Figure 3. Applicant's forest plot of proportion of subjects who did not have a flare of disease by demography categories; randomized subjects



	Placebo + MTX n	(%)	Golimumab 30 mg/m2 + MTX n	(%)	Odds Ratio	(95% CI)	Subgroup analysis p-value	Interaction p-value
All subjects	76	(52.6)	78	(59.0)	1.3	(0.7, 2.4)	0.428	
Gender:								
Male	19	(63.2)	19	(84.2)	3.1	(0.7, 14.6)	0.150	
Female	57	(49.1)	59	(50.8)	1.1	(0.5, 2.2)	0.853	0.221
Race:								
White	67	(50.7)	68	(57.4)	1.3	(0.7, 2.6)	0.442	
Black	0	-	2	(50.0)	-	-	-	
Asian	0	-	0	-	-	-	-	
Other	9	(66.7)	8	(75.0)	1.5	(0.2, 12.5)	0.707	0.902
Geographic Location:								
North America	13	(61.5)	12	(75.0)	1.9	(0.3, 10.5)	0.474	
Europe	51	(47.1)	51	(52.9)	1.3	(0.6, 2.8)	0.553	
Latin America	12	(66.7)	15	(66.7)	1.0	(0.2, 5.0)	> 0.999	0.869
Age:								
2 yrs to <7 yrs	15	(46.7)	16	(43.8)	0.9	(0.2, 3.7)	0.870	
7 yrs to <12 yrs	21	(42.9)	23	(60.9)	2.1	(0.6, 6.9)	0.235	
12 yrs to 17 yrs	40	(60.0)	39	(64.1)	1.2	(0.5, 3.0)	0.707	0.641

Note: Odds ratio and its confidence interval based on logistic regression model with terms of JIA disease type, prior anti-TNF therapy, and age.
Source: Excerpted from the Clinical Study Report for Study CNTO148JIA3001 (page 316).

The applicant tried to find the reason for the failure of the study to provide evidence of efficacy by exploring subgroup results, including results by baseline CRP levels, and claimed that the failure might be due to a lower inflammatory burden among randomized subjects compared to studies with other products. However, given that the analysis was one of many post hoc subgroup analyses (in small subsets of the randomized population) and exploratory in nature, it is not clear whether observed differences across CRP subgroups may be real or due to chance (Table 6). Such a hypothesis should be confirmed in an independent study.

Table 6. Applicant's analysis of proportion of subjects who flare from Week 16 through Week 48 by Week 0 CRP levels; randomized subjects

CRP	Golimumab	Placebo	p-value
≥1.0	40% (6/15)	86.67% (13/15)	0.0068
<1.0	38.33% (23/60)	38.6% (22/57)	
≥0.8	36.84% (7/19)	88.89% (16/18)	0.0015
<0.8	39.29% (22/56)	35.19% (19/54)	
≥0.6	39.13% (9/23)	77.27% (17/22)	0.0048
<0.6	38.46% (20/52)	36% (18/50)	
≥0.4	39.29% (11/28)	76.92% (20/26)	0.0026
<0.4	38.3% (18/47)	32.61% (15/46)	
≥0.3	42.42% (14/33)	66.67% (20/30)	0.0505
<0.3	35.71% (15/42)	35.71% (15/42)	
≥0.2	44.44% (16/36)	63.64% (21/33)	0.1004
<0.2	33.33% (13/39)	35.9% (14/39)	
≥0.1	38.64% (17/44)	63.16% (24/38)	0.0199
<0.1	38.71% (12/31)	32.35% (11/34)	

Source: Excerpted from the Clinical Study Report for Study CNTO148JIA3001 (page 367).

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Because the phase 3 study 3001 failed to demonstrate a statistically significant difference between golimumab and placebo with respect to the primary and secondary endpoints, there is insufficient evidence supporting effectiveness.

5.2 Collective Evidence

The phase 3 trial which was the only study conducted in pJIA patients and it failed to show evidence of efficacy based on the primary endpoint of no flare of disease after achieving early improvement on signs & symptoms (ACR Ped 30). Also, the trial did not provide supportive evidence of efficacy based on the secondary endpoints of improvement on signs & symptoms, no disease activity, and clinical remission. Therefore I conclude that the results from the study failed to provide substantial evidence of efficacy.

More specifically, the primary endpoint of proportion of subjects with no flare from Week 16 throughout Week 48 was not statistically significantly different between the golimumab + MTX group (59.0%) and the placebo + MTX group (52.6%, p=0.414).

The key secondary endpoints did not show statistically significant differences between the treatment groups:

1. Proportion of subjects with ACR Ped 30 response at Week 48: golimumab + MTX group (52.6%) and the placebo + MTX group (55.3%, p=0.751).
2. Proportion of subjects who had inactive disease at Week 48: golimumab + MTX group (39.7%) and the placebo + MTX group (27.6%, p=0.119).

3. Proportion of subjects who were in clinical remission at Week 48: golimumab + MTX group (12.8%) and the placebo + MTX group (11.8%, p=0.848).

5.3 Conclusions and Recommendations

In my opinion, based on the above non-positive findings, I agree with the applicant's approach to not seek an indication claim for pJIA and to include results of Study 3001 in Section 8.4, Pediatric Use, of labeling.

5.4 Labeling Recommendations

The following is an excerpt from the USPI Section 8.4, Pediatric Use in the proposed label. I generally agree with the description of the study and non-positive analysis results and their interpretation, but will propose a few suggested edits to the language.

8.4 Pediatric Use

(b) (4) effectiveness of SIMPONI in pediatric patients less than 18 years of age (b) (4) not been (b) (4) established.

The safety and efficacy of SIMPONI were evaluated in a multicenter, placebo-controlled, double-blind, randomized-withdrawal, parallel group study (b) (4) in 173 children (2 to 17 years of age) with active polyarticular juvenile idiopathic arthritis (pJIA). (b) (4)

(b) (4)

Subjects were maintained on their stable dose of MTX at the same dose (mg/week) at study entry (b) (4) In the 16 week open-label phase, patients received MTX and SIMPONI 30 mg/m2 (maximum 50 mg) subcutaneously every 4 weeks. Patients who achieved an ACR Ped 30 response at Week 16 entered the randomized withdrawal phase of the study and received MTX and either SIMPONI 30 mg/m^2 (maximum 50 mg) or placebo every 4 weeks through Week 48.

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

In this study, the frequency and type of the adverse reactions seen in children were (b) (4) to those observed in adults.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YONGMAN KIM
05/19/2017

GREGORY P LEVIN
05/21/2017