

## Cross-Discipline Team Leader Review/ Division Director Summary Review

<b>Date</b>	<i>Electronic Stamp</i>
<b>From</b>	Nikolay P. Nikolov, M.D. Sally Seymour, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review Division Director Summary Review
<b>NDA/BLA # Supplement#</b>	sBLA 125289/133
<b>Applicant</b>	Janssen
<b>Date of Submission</b>	August 22, 2016
<b>PDUFA Goal Date</b>	June 22, 2017
<b>Proprietary Name / Established (USAN) names</b>	Simponi (golimumab)
<b>Dosage forms / Strength</b>	Injection: <ul style="list-style-type: none"> <li>• 50 mg/0.5 mL in a single dose prefilled SmartJect® autoinjector</li> <li>• 50 mg/0.5 mL in a single dose prefilled syringe</li> <li>• 100 mg/1 mL in a single dose prefilled SmartJect® autoinjector</li> <li>• 100 mg/1 mL in a single dose prefilled syringe</li> </ul> (No new dosage forms/strengths are proposed)
<b>Proposed Indication(s)</b>	No new indications are proposed
<b>Recommended:</b>	<i>Approval of labeling changes pertinent to Section 8.4 and PLLR requirements.</i>

## 1. Introduction and Background

Subcutaneous (SC) golimumab (Simponi), a monoclonal anti-TNF-alpha, is currently approved under biologics license application (BLA) 125289 in adults for treatment of moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate (MTX); active psoriatic arthritis (PsA), alone or in combination with MTX; active AS; and moderately to severely active ulcerative colitis (UC) in patients with an inadequate response to or intolerance of prior treatment or requiring continuous steroid therapy. It is administered as a subcutaneous injection via prefilled syringe (PFS) or autoinjector (AI) at a dose of 50 mg once monthly for treatment of RA, PsA, and AS. For treatment of UC, an induction regimen of 200 mg at Week 0, followed by 100 mg at Week 2 is administered, and then maintenance therapy is continued with 100 mg every 4 weeks. Golimumab has been granted Orphan Drug Designation for polyarticular juvenile idiopathic arthritis (PJIA).

The present supplemental BLA is for updating the product labeling with information from study CNTO148JIA3001, conducted as a post-marketing required (PMR) study to fulfill a Pediatric Research Equity Act (PREA)-required pediatric assessment issued with the BLA 125289 approval letter dated April 24, 2009 for rheumatoid arthritis (RA). The letter states:

PMR#1: Assess the pharmacokinetics, safety, immunogenicity, and efficacy of golimumab in pediatric patients 2 to 16 years of age with active polyarticular juvenile idiopathic arthritis (PJIA).

Juvenile Idiopathic Arthritis is an umbrella term used to encompass subtypes of arthritis in pediatric patients defined by International League of Associations for Rheumatology (ILAR), a classification system currently used by the rheumatology academic community. Broadly, JIA is defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age, where other diagnoses (such as infections, malignancy, trauma, reactive arthritis, and specific connective tissue diseases such as systemic lupus erythematosus) have been excluded. JIA affects an estimated 294,000 children between the ages of 0 and 17 in the United States.<sup>1</sup> The incidence, prevalence and disease characteristics of JIA vary worldwide, reflecting genetic and environmental factors that influence the disease phenotype. PJIA, the subject of this application, is most similar to adult RA, with articular manifestations being predominant. In addition to corticosteroids, sulfasalazine and methotrexate, several biologic disease-modifying anti-rheumatic drugs (DMARDs) have been approved for PJIA: etanercept (Enbrel), adalimumab (Humira), and tocilizumab (Actemra) approved for patients 2 years of age and older; and intravenous abatacept (Orencia), approved for patients 6 years of age and older. Recently, several biosimilar products were also approved for PJIA by the FDA: etanercept-szsz (Erelzi) and adalimumab-atto (Amjevita).

Based on the positive experience with TNF inhibition in PJIA, Simponi was expected to be efficacious in PJIA. However, while appropriately designed and conducted as planned, the study did not meet the primary or major secondary endpoints and the Applicant (b) (4) [REDACTED]. The results from study CNTO148JIA3001 raised questions about the risk:benefit of Simponi in this patient population. Additional limitations of the PJIA development program for SC golimumab were the lack of age-appropriate presentation and the unclear relevance of the body surface area (BSA)-based dosing and the administration method (syringe transfer method) used in study CNTO148JIA3001 to what would have been proposed for marketing. These additional limitations are noted here for completeness but will not be detailed further in this memorandum as they are not directly relevant to this submission. As a result, in a pre-submission communication dated December 17, 2015, the Division advised the Applicant that the results of the study CNTO148JIA3001 alone would not be sufficient to support an indication for Simponi in PJIA. The Division was further concerned that the use of PK extrapolation to support an indication was undermined by the failed clinical study. Thus, the Division advised the Applicant to conduct a controlled dose-ranging study of relatively short duration in which they could consider using baseline CRP levels  $\geq 1.0$  mg/dL as an enrichment strategy to establish efficacy in patients with PJIA and establish a dose-response relationship that could

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<sup>1</sup> M Espinosa and BS Gottlieb, "Juvenile Idiopathic Arthritis," *Pediatrics in Review*, 2012; 33:303-313

support an application for a PJIA indication. The advice on this potential enrichment strategy was based on post-hoc analyses of study CNTO148JIA3001, suggesting that treatment benefit was observed in patients with elevated CRP. Based on the considerations from the pre-submission discussions, the Applicant has decided not to pursue an indication for PJIA at this time but to update Section 8.4 with information from the study in order to fulfill the required PMR and complete the PREA assessment.

Of note, representatives of 2 pediatric rheumatology research networks, the Pediatric Rheumatology International Trials Organization (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG), which contributed to the recruitment for the study, submitted a letter in support of an indication for PJIA for SC golimumab in October 2015. The authors of the letter presented similar justification to support golimumab for PJIA as that presented by the Applicant in the briefing package for the Type C Written Responses in December 2015. They state that Study CNTO148JIA3001 provided open-label PK, effectiveness and safety data of similar type as to be provided for certolizumab and planned for intravenous golimumab in PJIA, and that golimumab offers an advantage over current therapies because of its monthly dosing and subcutaneous administration. It is also noteworthy that in the European Union, the Committee for Medicinal Products for Human Use issued a positive opinion on May 26, 2015 for a PJIA indication for SC golimumab and this was adopted by the EU Commission on June 24, 2016. The Division has carefully considered the community's support of an indication expressed in the letter as well as EMA's decision. However, these considerations were not sufficient to address the Division's concerns with the insufficient evidence of efficacy from study CNTO148JIA3001 to inform the risk:benefit assessment of the proposed dosing regimen of SC golimumab in PJIA.

This submission also updates Simponi labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR) requirements.

## **2. CMC/Device**

No new CMC/Device information was submitted with this supplemental BLA.

## **3. Nonclinical Pharmacology/Toxicology**

*Pharmacology/toxicology Acting Team Leader: Timothy Robison, Ph.D.*

No new preclinical pharmacology/toxicology information was submitted with this supplement. The relevant information was previously reviewed in the original BLA 125289. However, Dr. Robison reviewed the Applicant's proposed labeling and review of the literature and provided recommendations to the PLLR format and content. We agree with his recommendations.

## 4. Clinical Pharmacology/Biopharmaceutics

*Clinical Pharmacology Primary Reviewer: Sze W. Johnny Lau., R.Ph., Ph.D.*

*Clinical Pharmacology Supervisor: Anshu Marathe, Ph.D.*

In study CNTO148JIA3001, samples were collected at Weeks 4, 8, 12, 16, 20, 24, and 48 as well as at final database lock for the determination of golimumab concentration. All patients received golimumab up to the randomized withdrawal at Week 16 showed comparable median trough serum golimumab concentrations at each visit between the 2 groups of patients who were subsequently randomized to either receive placebo or SC 30 mg golimumab/m<sup>2</sup> every 4 weeks at Week 16. Median trough concentrations were maintained for patients who continued on active treatment through Week 48, whereas golimumab concentrations dropped to low concentrations for patients who received the placebo treatment. These data indicate that patients in the study received their assigned treatments supporting a conclusion that the study was conducted as planned. At steady state, the median trough serum golimumab concentration was 0.95 µg/mL in PJIA patients. Given that the Applicant is not seeking an indication with this submission, the Clinical Pharmacology review team concluded, and we agree, that no labeling changes pertaining to Clinical Pharmacology are needed.

## 5. Clinical Microbiology

Not applicable.

## 6. Clinical/Statistical- Efficacy

*Primary Clinical Reviewer: Rachel Glaser, M.D.*

*Primary Statistical Reviewer: Yongman Kim, Ph.D.*

Study CNTO148JIA3001 was a randomized withdrawal study in pediatric patients, ages 2 to <18 years old, with active polyarticular JIA, including rheumatoid factor (RF)-positive polyarthritis, RF-negative polyarthritis, extended oligoarthritis, juvenile psoriatic arthritis, or systemic JIA with no current systemic symptoms. Through Week 16, all patients received SC golimumab 30 mg/m<sup>2</sup> + MTX (GOL+MTX), and those patients who achieved an ACR Ped 30 response at Week 16 were randomized to blinded treatment with GOL+MTX or placebo + MTX (PBO+MTX). Patients receiving PBO+MTX who experienced a flare of their disease were treated with GOL+MTX during or after the randomized withdrawal period (prior to and after Week 48). Key Design features of the protocol are summarized in Table 1.

**Table 1. Key Design Features of Study CNTO148JIA3001**

Design	Subjects	Treatments	Endpoints
R, W, DB, PC, PG 12 wk OL 32 wk DB, RW 208 wk LTE	173 patients with active PJIA despite MTX enrolled, 154 patients randomized in DB portion	<u>OL (Wk 0-16):</u> <ul style="list-style-type: none"> <li>GOL 30mg/m<sup>2</sup> q4w + MTX</li> </ul> <u>DB (Wk 16-48):</u> <ul style="list-style-type: none"> <li>GOL 30 mg/m<sup>2</sup> q4w + MTX</li> <li>PBO</li> </ul>	Primary: ACRp30 responders at Wk 16 without flare Wks 16-48  Major Secondary: <ul style="list-style-type: none"> <li>ACRp30 responders at Wk 16 with ACRp30 response at Wk 48</li> <li>Responders at Wk 16 with inactive disease at Wk 48</li> <li>Responders at Wk 16 in clinical remission while on medication for JIA at Wk 48</li> </ul>
Source: Adopted from Dr. Glaser's Clinical Review R = Randomized, W = Withdrawal, DB = Double Blind, PC = Placebo Controlled, PG = Parallel Group, OL = Open Label, LTE = Long Term Extension, GOL = Golimumab, MTX = Methotrexate, PBO = Placebo; ACRp30 = ACR Ped 30			

The open-label run-in period and the double-blind, randomized withdrawal periods of the study were conducted and completed as planned; the open-label extension period was discontinued by the Applicant after the results from the efficacy analyses were available. One hundred seventy three (173) patients were enrolled in 33 global sites. Of these, 154 were randomized at Week 16: 78 patients were randomized to GOL+MTX and 76 patients were randomized to PBO+MTX.

Efficacy analyses were conducted based on the intent to treat principle. Efficacy analyses up to Week 16 includes the “all enrolled patients” population, which includes all patients enrolled into the study at Week 0 who received at least 1 dose of study agent treatment. Efficacy analyses from Week 16 through Week 48 are conducted on the “all randomized patients” analysis set, which includes all patients randomized into the randomized withdrawal portion of the study at Week 16.

The primary endpoint was the proportion of patients who were ACR Ped 30 responders at Week 16 who did not experience a flare of disease between Week 16 and Week 48, based on the intent-to-treat population. Forty six patients (59.0%) in the GOL+MTX treatment group were ACR Ped 30 responders who did not experience flare between Week 16 and Week 48, while 40 patients (52.6%) in the PBO+MTX group met the primary endpoint (Table 2); the difference was not statistically significant (p-value 0.414). Sensitivity analyses were consistent with the results of the primary analysis (data not shown). The Applicant’s analyses were also consistent with those by the FDA statistical review team.

**Table 2. Primary and Major Secondary Endpoints (Randomized Patients), Study CNTO148JIA3001**

	PBO+MTX N = 76 n (%)	GOL+MTX N = 78 n (%)	P value
<b>Primary Endpoint</b>			
ACRPed30 Responders at Wk 16 without flare through Wk 48	40 (52.6)	46 (59.0)	0.414
<b>Major Secondary Endpoints</b>			
ACRPed30 Responders at Wk 16 with ACRPed30 Response at Wk 48	42 (55.3)	41 (52.6)	0.751
ACRPed30 Responders at Wk 16 with inactive disease at Wk 48	21 (27.6)	31 (39.7)	0.119
ACRPed30 Responders at Wk 16 in clinical remission while on medication for JIA at Wk 48	9 (11.8)	10 (12.8)	0.848
Source: Adapted from Dr. Glaser's Clinical Review, Table 6			

- **Statistical and Clinical efficacy conclusions**

Both the clinical and statistical review teams concluded, and we agree, that study CNTO148JIA3001 failed to provide evidence of efficacy of SC golimumab + methotrexate over methotrexate alone in PJIA based on the results from the primary endpoint of no flare of disease after achieving early improvement on signs and symptoms. Also, the results from key secondary endpoints, including improvement on signs and symptoms, no disease activity, and clinical remission were consistent with the primary endpoint and did not support a conclusion of clinical efficacy of SC golimumab + methotrexate over methotrexate alone in PJIA. As a result, the clinical and statistical teams concluded, and we agree, that the results from the study did not provide substantial evidence of efficacy to support an indication of SC golimumab for treatment of PJIA 2 to 18 years of age.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

The reasons why study CNTO148JIA3001 failed are unclear. The ACR Ped 30 response rates to the initial open-label treatment period (87.3%) were similar to those seen with other biologic disease modifying anti-rheumatic drugs (bDMARDs) in similarly designed randomized withdrawal studies that have demonstrated efficacy in PJIA (ACR Ped 30 range 65-94% response to run-in period). However, unlike the other programs, at the end of the randomized withdrawal period, the proportion of patients experiencing flares during the randomized withdrawal period was similar between treatment groups. Given the open-label nature of the data in the run-in period, drawing conclusions on efficacy may be problematic and would not be sufficient, on its own, to provide substantial evidence of efficacy. During the pre-submission review of efficacy, in an effort to identify reasons for why study CNTO148JIA3001 did not meet its objectives, in post-hoc subgroup analyses, the Applicant suggested a treatment benefit of golimumab + MTX over MTX alone in the subgroup of patients with elevated CRP. However, this suggestion was based on evaluations of efficacy in multiple subgroups without control of overall type 1 error. Thus, the observed benefit in the high CRP subgroup may be due to chance alone. Such subgroup efficacy analyses are viewed as exploratory, and potentially useful for the design of confirmatory study(ies) for this indication. This issue was discussed at the pre-submission stages, as summarized in the Introduction and Background section of this document.

## 7. Safety

- **Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing**

### *Summary of Safety*

The current submission contains data from study CNTO148JIA3001. The randomized withdrawal study design, in which all patients receive active treatment, presents limitations in assessment of safety, however, observed safety events were consistent with the known safety profile of golimumab. No new safety signals were identified. Serious infections were similar between treatment groups. While differences in study design, dosing regimens, and duration of follow-up limit direct comparison of frequencies of these events between JIA and RA populations, these are generally similar through Week 16, with a greater proportion of PJIA patients experiencing overall infections and injection site reactions.

### *Immunogenicity*

Anti-drug antibody (ADA) formation was assessed in study CNTO148JIA3001 using a new, more drug-tolerant, enzyme immunoassay (EIA) assay. Of note, this assay has approximately 16-fold higher sensitivity for detection of antibodies to golimumab, with improved drug tolerance, as compared to the original EIA used in the adult rheumatology and UC studies and currently described in Simponi labeling. Thus, comparisons to immunogenicity in described in labeling are limited.

Over the course of the study, ADAs were detected in 81 patients. Through Week 12, ADA were detected in 38 (22.1%) patients and through Week 48, in 69 (40.1%) patients. The overall incidence of neutralizing antibodies was 42.0%, based on Dr. Glaser's analysis. The incidence of neutralizing antibodies was similar across the treatment groups. The observed ADA formation was not associated with clinically significant hypersensitivity reactions, including anaphylaxis. There was no association between positive ADA and injection site reactions.

It is notable that the incidence of ADA appears significantly higher than the reported immunogenicity of SC golimumab in the Simponi labeling (2% in RA, PsA, and AS patients treated with concomitant MTX). This is not unexpected given the increased sensitivity of the new assay. To more accurately compare immunogenicity across the studied indications, the Applicant has previously submitted data comparing the older assay with the newer drug-tolerant assay. When ADA were re-assessed in samples from the phase 3 rheumatologic studies using the new EIA assay, the incidence of ADA through Week 52 was 31.7%, similar to the observed rate in the GOL+MTX group through Week 48 in study CNTO148JIA3001.

(b) (4)

- **Discussion of primary reviewer's comments and conclusions**

Dr. Glaser has concluded, and we concur, that the types and rates of adverse events submitted with this supplement are generally consistent with those reviewed with the SC golimumab BLA and has not identified any new safety signals.

## **8. Advisory Committee Meeting**

No Advisory Committee meeting was convened for this supplement. The Division acknowledged the interest in the community of discussing the findings from study CNTO148JIA3001, however, given that the study did not meet its primary and key secondary objectives, the Division did not consider that Advisory Committee input was warranted at this time.

## **9. Pediatrics**

As mentioned in the section on relevant regulatory history above, study CNTO148JIA3001 submitted to support this supplement was conducted as a required study under PREA. As per the PREA requirement from the BLA approval of SC golimumab for RA, this study was required to assess the pharmacokinetics, safety, immunogenicity, and efficacy of [SC] golimumab in pediatric patients 2 to 16 years of age with active polyarticular juvenile idiopathic arthritis (PJIA), and has done so. Therefore, we recommend this postmarketing requirement (PMR) be designated as fulfilled and the pediatric assessment of SC golimumab under PREA complete. This application was discussed at the Pediatric Review Committee (PeRC) on May 31, 2017 and PeRC agreed with the Division's assessment and recommendations.

## **10. Other Relevant Regulatory Issues**

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues of concern**—No issues.
- **Financial disclosures**— Not applicable.
- **Other GCP issues**—Not applicable.
- **OSI audits**—OSI inspection of clinical sites was not warranted in this case because the Applicant is not seeking an indications based on the results from the core study
- **Other discipline consults**—None requested.
- **Any other outstanding regulatory issues**—None identified.

## **11. Labeling**

- **Proprietary name**—No issues, already approved.
- **DDMAC, DMEPA and OSE Division comments**— No issues.
- **Physician labeling**

The primary proposed changes included:

- 1) Updates to Section 8.4 to include a statement that “Effectiveness of SIMPONI in pediatric patients less than 18 years of age has not been established” and a summary of Study CNTO148JIA3001
- 2) Changes to labeling to meet the requirements of PLLR.
  - **Carton and immediate container labels (if problems are noted)**—No issues.
  - **Patient labeling/Medication guide (if considered or required)**—No changes.

## 12. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

We recommend approval of this supplement, provided agreement can be reached with the applicant on revisions to the proposed label.

- **Risk Benefit Assessment**

The current supplemental BLA updates Simponi labeling with information in Section 8.4 based on the results from study CNTO148JIA3001. This study was conducted as a post-marketing required study to address PREA with the approval of Simponi for RA. Given that the study did not meet its primary and key secondary objectives, the efficacy of the studied SC dosing regimen of golimumab in PJA 2 to <18 years of age has not been established and thus the risk:benefit profile of the SC golimumab has not been well defined to support an indication for this patient population at this time. While the study did not meet its efficacy objectives, it provided sufficient data to inform the adequate labeling for the studied population and thus to complete the pediatric assessment under PREA.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies (REMS)**

The review of the sBLA has not identified new serious safety concerns. Therefore a Risk Evaluation and Mitigation Strategy (REMS) is not required for this application.

- **Recommendation for other Postmarketing Requirements and Commitments**

None.

- **Recommended Comments to Applicant**—None.

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/s/  
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06/21/2017

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