

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125433 Supplement Number: N/A NDA Supplement Type (e.g. SE5): _____

Division Name: DPARP PDUFA Goal Date: 7/18/13 Stamp Date: 9/18/2012

Proprietary Name: Simponi Aria

Established/Generic Name: Golimumab

Dosage Form: IV infusion

Applicant/Sponsor: Janssen Biotech, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____
-

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: JIA

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^Δ	
☒	Neonate	0 wk. 0 mo.	__ wk. 11 mo.	☒	☐	☐	☐
☒	Other	1 yr. 0 mo.	1 yr. 11 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver **(check reason corresponding to the category checked above, and attach a brief justification)**:

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	2 yr. 0 mo.	16 yr. 11 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
Date studies are due (mm/dd/yy): <u>Fourth Quarter 2019</u>							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.		
☐	Other	__ yr. __ mo.	__ yr. __ mo.		
☐	Other	__ yr. __ mo.	__ yr. __ mo.		
☐	Other	__ yr. __ mo.	__ yr. __ mo.		
☐	Other	__ yr. __ mo.	__ yr. __ mo.		
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

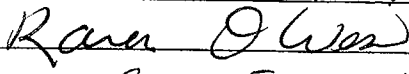
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE H CHUNG
07/15/2013

Debarment Certification

Janssen Research & Development, LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Name	<u>Karen D. Weiss, M.D. M.P.H.</u>
Title	<u>Vice President, Global Regulatory Affairs</u>
Signature	<u></u>
Date	<u>8-15-2012</u>

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 125433	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Simponi Aria Established/Proper Name: golimumab (for intravenous infusion) Dosage Form: 50mg/4 mL (12.5 mg/mL) vial		Applicant: Janssen Biotech Inc Agent for Applicant (if applicable):
RPM: Christine Chung		Division: DPARP
<u>NDA and NDA Efficacy Supplements:</u> NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)		<u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ This application does not rely upon a listed drug. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ This application relies on (explain) <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☐ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.
❖ Actions		
• Proposed action • User Fee Goal Date is <u>July 18, 2013</u>		☒ AP ☐ TA ☐ CR
• Previous actions (<i>specify type and date for each action taken</i>)		☒ None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics ³	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rx-to-OTC full switch ☐ Rolling Review ☐ Rx-to-OTC partial switch ☐ Orphan drug designation ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ MedGuide w/o REMS ☒ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☒ Yes, dates 7/10 &11/2013
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☒ No
❖ Public communications (<i>approvals only</i>)	
Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
Press Office notified of action (by OEP)	☐ Yes ☒ No
Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	AP 7/18/2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	7/17/2013
• Original applicant-proposed labeling	9/18/2012
• Example of class labeling, if applicable	

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	7/17/13
• Original applicant-proposed labeling	9/18/12
• Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	7/12/2013
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	12/11/12 4/2/13, 6/6/13
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☒ RPM 11/28/12 ☒ DMEPA 6/14/13 ☒ DMPP/PLT (DRISK) 7/1/13 ☒ ODPD (DDMAC) 6/28/13 ☒ SEALD 7/15/13 ☐ CSS ☒ Other reviews OBP 7/12/13
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	11/16/12 (entered 7/12/13)
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	☐ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>5/1/2013</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☒ Verified, statement is acceptable

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	2013 – 7/15, 7/9, 7/3, 6/20 (2), 6/5, 5/30, 5/23, 5/2, 5/1, 4/18, 4/17, 4/2, 2/4 2012 - 11/30, 10/24, 10/1
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 9/23/11
• EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg 5/18/09
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 7/18/2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 6/27/13
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 7/xxxx/13 (5)
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Same as CDTL 6/27/13
• Clinical review(s) (<i>indicate date for each review</i>)	6/14/13, 11/9/12
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	In clinical review dated 6/14/13 pg 16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☐ None requested 4/5/13

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		☒ None
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>		☐ None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>		☐ None
Biostatistics		☐ None
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>		☒ None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>		☐ None
Statistical Review(s) <i>(indicate date for each review)</i>		☐ None 6/13/13, 11/17/12
Clinical Pharmacology		☐ None
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>		☒ None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>		☐ None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>		☐ None 6/17/13, 11/8/12
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>		☒ None
Nonclinical		☐ None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) <i>(indicate date for each review)</i>		☒ None
• Supervisory Review(s) <i>(indicate date for each review)</i>		☐ None 6/17/13
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>		☐ None 5/29/13, 11/16/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>		☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>		☒ No carc
❖ ECAC/CAC report/memo of meeting		☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>		☒ None requested
Product Quality		☐ None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		☒ None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		☐ None 6/19/13
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		☐ None 5/29/13, 10/31/12
❖ Microbiology Reviews		☐ Not needed
☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
☒ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		6/20, 5/23, and 2/11/2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Quality TL review 6/19/13
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: 6/25/13 ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

CHRISTINE H CHUNG
07/19/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: July 15, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – Simponi Aria (golimumab)
FDA additional labeling comments

Total no. of pages including cover: 29

Comments: *Response requested no later than Tuesday July 16, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

Your BLA 125433/0 for golimumab for infusion is currently under review, and we have the following labeling comments. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the labeling. Submit revised labeling incorporating the changes noted in the attached marked up label.

Send your responses to me via secure email at christine.chung@fda.hhs.gov no later than COB July 16, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Comments by: EDonohoe, SLimb / 7.15.2013

Drafted by: cchung/ 7.15.2013

Cleared thru: SBarnes/ 7.15.2013

Finalized: cchung/ 7.15.2013

26 Pages of Draft Labeling have been
Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

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

/s/

CHRISTINE H CHUNG
07/15/2013

Chung, Christine

From: Donohoe, Elizabeth A
Sent: Monday, July 15, 2013 1:58 PM
To: Chung, Christine
Cc: Limb, Susan
Subject: RE: Janssen's USPI and MG for SIMPONI ARIA BLA 125433
Attachments: BLA 125433 Simponi Aria Original Format Deficiencies ODE II DPARP July 2013.doc

Hi, Christine -

I have completed my end-of-cycle SRPI review of the SIMPONI ARIA label; attached is a Word version. You will also receive a copy via DARRTS after it has received SEALD Director sign-off. In the SRPI review, deficiencies are identified with a "NO" (# 9, 14, 38, 40, 42). SEALD does not need to see the label again after the SRPI deficiencies are corrected.

In addition to the deficiencies identified in the SRPI, SEALD also has the following recommendations for consideration by the review team:

1) According to 21 CFR 201.57(a)(2), the Product Title must have the dosage form which is "injection." Also, there is no guidance for the Product Title line, but the LRT provides recommendations on page 4. Consider the revision below:

SIMPONI ARIA (golimumab) injection, for intravenous use

The LRT may be found on the SEALD labeling team's internal website:

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabeli>

2) In Dosage Forms and Strengths (both HL and FPI) the dosage form "injection" is missing. See 21 CFR 201.57 (a)(8), (c)(4). HL must contain a concise summary of information provided in the FPI, which must include the dosage form.

In HL, consider: Injection : 50 mg/4 mL (12.5 mg/mL) in a single use vial

In FPI, consider: Injection: 50 mg of golimumab per 4 mL of solution (12.5 mg of golimumab per mL) in each vial.

3) In TOC the spacing in subsection 6.2 is not consistent with the spacing for other subheadings; consider correcting this.

Very nice job, Christine! Please let me know if you have questions....

Liz

Elizabeth A. Donohoe, M.D.
 Labeling Reviewer, Study Endpoints and Labeling Development
 CDER/OND/IO

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	SIMPONI ARIA (golimumab) injection, for intravenous use
Applicant	Janssen Biotech, Inc.
Application/Supplement Number	BLA 125433
Type of Application	Original
Indication(s)	Treatment of adult patients with moderately to severely active Rheumatoid Arthritis in combination with methotrexate
Established Pharmacologic Class ¹	Tumor Necrosis Factor Blocker
Office/Division	ODE II/DPARP
Division Project Manager	Christine Chung
Date FDA Received Application	September 18, 2012
Goal Date	July 18, 2013
Date PI Received by SEALD	July 15, 2013
SEALD Review Date	July 15, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item (**deficiency**).
- **YES:** The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*

Selected Requirements of Prescribing Information

• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment: *The proper name "(golimumab)" should be removed; only the drug product name "SIMPONI ARIA" should be in the HL Limitation Statement.*

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment:

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Selected Requirements of Prescribing Information

Comment:

NO 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

YES Comment: *The statement is not centered; the Final Implementation guidance recommends that this statement be centered within the box.*

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Selected Requirements of Prescribing Information

Comment:

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

28. A horizontal line must separate TOC from the FPI.

Comment:

29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

32. All section headings must be **bolded** and in UPPER CASE.

Selected Requirements of Prescribing Information

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

Selected Requirements of Prescribing Information

12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: The title of subsection 13.1 includes an "and" after "Mutagenesis"; the required title is: "Carcinogenesis, Mutagenesis, Impairment of Fertility".

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[see *Warnings and Precautions (5.2)*]".

Comment: The entire cross reference should be in italics, including the outer brackets. Cross-references in 2.2, 5.1, 5.5, 5.6, 6, 6.1, 6.2, 7.1, 7.2, 7.3 and 8.1 have outer brackets that are not italicized.

- A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- NO** 42. All text is **bolded**.
- Comment:** The cross-references within the boxed warning are not bolded; the LRT and the W&P, Contraindications and BW guidance recommend that all text in the BW be bolded.

- YES** 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

ELIZABETH A DONOHOE
07/15/2013

LAURIE B BURKE
07/15/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: July 9, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – Simponi Aria (golimumab)
FDA labeling comments

Total no. of pages including cover: 30

Comments: *Response requested no later than Thursday July 11, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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Your BLA 125433/0 for golimumab for infusion is currently under review, and we have the following labeling comments. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the labeling. Submit revised labeling incorporating the changes noted in the attached marked up label.

In addition, we have the following carton/container comment.

Remove the statement, (b) (4) located directly below the proper name, golimumab. The placement of the statement is usually reserved for dosage form. The dosage form as defined by USP 36/ NF 31 (5/1/13-12/31/13) Chapter <1> for this product is "for injection". However, presenting the dosage form on Simponi Aria labels may cause confusion because it is not presented on the Simponi label. Additionally, the statement, "for intravenous infusion" which identifies the route of administration is presented appropriately on the label.

Recommended format:

Simponi[®] Aria[™]
(golimumab)

50 mg/4 mL
(12.5mg/mL)

For intravenous infusion

Single-use vial.
Discard unused portion.

Send your responses to me via secure email at christine.chung@fda.hhs.gov no later than COB July 11, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Comments by: KRains / 6.28.2013
Drafted by: cchung/ 7.8.2013
Cleared thru: SBarnes/ 7.8.2013
RNeuner, SLimb/ 7.9.2013
RDavi, JBuenconsejo/ 7.9.2013
Finalized: cchung/ 7.9.2013

27 Pages of Draft Labeling have been
Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

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/s/

CHRISTINE H CHUNG
07/09/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: July 3, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – Simponi Aria (golimumab)
FDA request for information: Postmarketing requirements/commitments

Total no. of pages including cover: 4

Comments: *Response requested no later than Tuesday July 9, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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We refer to original BLA 125433/0 for golimumab for infusion dated September 18, 2012, and to your submissions dated December 21, 2012, and April 15, 2013. We request confirmation of your agreement to conduct the following studies and completion of milestone timelines.

PREA Postmarketing requirements (PMR)

To conduct a trial that will evaluate the safety, efficacy, PK/PD and immunogenicity of IV golimumab in pediatric patients between the ages 2 to 17 years and 11 months with active Juvenile idiopathic arthritis (JIA) despite standard therapy with methotrexate.

PMR Scheduled milestones:

Final Protocol Submission: 12/31/2013
Trial Completion: (b) (4)
Final Report Submission: (b) (4)

Quality Postmarketing commitments (PMC)

PMC #1: Increase in-process control sample size (b) (4) and adjust acceptance criteria (b) (4).
(b) (4)
(b) (4). In addition, implement the new bioburden sample size action and alert limits after production of 10 batches. The Final Report Submission should include the new in-process limits.

PMC Scheduled milestones:

Final Report Submission: 07/20/2014

PMC #2: (b) (4)

PMC Scheduled milestones:

Final Report Submission: 07/20/2014

PMC #3: Perform the Rabbit Pyrogen Test on two batches of Golimumab FVP (IV) DP. Submit the results as a CBE-0 supplement.

PMC Scheduled milestones:

Final Report Submission: 09/30/2013

PMC #4: Perform LAL spiking studies in undiluted golimumab FVP (IV) DP samples and test the samples after different hold times.

PMC Scheduled milestones:

Final Report Submission: 07/20/2014

Submit your response to me via secure email at christine.chung@fda.hhs.gov no later than COB July 9, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Drafted by: RNeuner, SLimb/ 6.19.2013
MCandauchacon, PHughes/ 6.26.2013
Cchung/ 7.3.2013

Initialed by: SBarnes/ 7.3.2013
SSeymour/ 7.3.2013

Finalized: cchung/ 7.3.2013

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/s/

CHRISTINE H CHUNG
07/03/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: June 20, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – golimumab for infusion
FDA carton/container labeling comments

Total no. of pages including cover: 4

Comments: *Response requested no later than Wednesday June 26, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

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Your BLA 125433/0 for golimumab for infusion is currently under review, and we have the following carton and container labeling comments. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the labeling.

1. Container

Indicate how the label is affixed to the vial and where the visual area of inspection is located as per 21 CFR 610.60 (e).

2. Carton

- a. Replace the statement, "Provide the enclosed Medication Guide to each patient." with the statement, "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide" in bold on all carton and container labels per 21 CFR 610.60, 21(7) and 21 CFR 208.24(d).
- b. Replace the statement, [REDACTED] (b) (4) with the statement, "See package insert for dilution, dosage, and administration."

3. Container and Carton

- a. Revise the statement, "Single-Use Vial-Discard unused portion" with the statement, "Single-Dose Vial-Discard unused portion." and move the statement below the route of administration. **See recommended format below.
- b. Move the route of administration adjacent to the proper name, "golimumab" on the line below. FDA has been working to establish a consistent presentation for the proper name, dosage form and route of administration. *See recommended format below.
- c. Please revise the strength presentation, "50 mg/4 mL" to include in close proximity the volume per mL (12.5 mg/mL) to comply with the United States Pharmacopeia, 5/1/13-7/31/13, USP 36/NF 31, General Chapter, Injection <1>, "STRENGTH AND TOTAL VOLUME FOR SINGLE-AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS". *See recommended format below.

4. General comments

- a. Container labels and Carton labeling
 - i. Reduce the size of the colored bar that appears beneath the "For Infusion" statement. As presented, it detracts from the proprietary and established names as well as the strength.
 - ii. Remove the [REDACTED] (b) (4) statement after the proper name.
 - iii. Delete the net quantity statement [REDACTED] (b) (4) because the net quantity is displayed in the strength statement.

b. Professional Sample Container labels and Carton Labeling

Delete the phrase [REDACTED] ^{(b) (4)} from the professional sample label and labeling.

*Recommended format:

Simponi[®] Aria[™]
(golimumab)

50 mg/4 mL
(12.5mg/mL)

For Intravenous Infusion

Single-dose vial
Discard unused portion

5. Ferrule and cap overseal

Provide information on if there is any text on the ferrule and cap overseal. A revised USP standard will go into effect on December 1, 2013. We refer you to the following information:

http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

Submit your response to me via secure email at christine.chung@fda.hhs.gov no later than COB June 26, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Drafted by: KRains, TMcmillan, LMerchant/ 6.14.2013
cchung/ 6.19.2013

Thru: ERead, KBrorson, RNeuner/6.14.2013
SLimb/6.19.2013

Initialed by: SBarnes/ 6.20.2013

Finalized: chung/ 6.20.2013

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/s/

CHRISTINE H CHUNG
06/20/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: June 20, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – golimumab for infusion
FDA labeling comments

Total no. of pages including cover: 32

Comments: *Response requested no later than Wednesday June 26, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

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Your BLA 125433/0 for golimumab for infusion is currently under review, and we have the following labeling comments. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the labeling. Submit revised labeling incorporating the changes noted in the attached marked up label.

In addition and with reference to section 6.1 Clinical Trials Experience, *Immunogenicity* subsection, second paragraph, provide information about how "neutralizing antibodies in vitro" was measured.

Send your responses to me via secure email at christine.chung@fda.hhs.gov no later than COB June 26, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Comments by: ERead, KBrorson / 6.3.2013
RDavi, JBuenconsejo/ 6.14.2013
RNeuner, SLimb/6.19.2013

Drafted by: cchung/ 6.20.2013

Cleared thru: SBarnes/ 6.20.2013

Finalized: cchung/ 6.20.2013

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CHRISTINE H CHUNG
06/20/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration
Silver Spring, MD 20993

IND 9925

Centocor Ortho Biotech Inc.
200 Great Valley Parkway
Malvern, PA 19355

Attention: Bethany Paxson
Senior Director, Global Regulatory Affairs, Immunology

Dear Ms. Paxson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for golimumab.

We also refer to the teleconference between representatives of your firm and the FDA on May 18, 2009. The purpose of the meeting was to discuss the development plan for IV golimumab.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2254.

Sincerely,

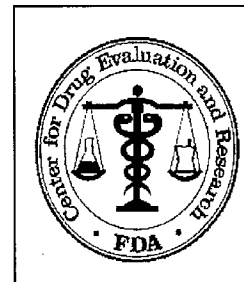
{See appended electronic signature page}

Sharon Turner-Rinehardt
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEETING MINUTES

Meeting Date: May 18, 2009
Location: Teleconference
Product: Golimumab for intravenous (IV) administration
IND: 9925
Indication: Rheumatoid Arthritis
Sponsor: Centocor Ortho Biotech Inc.
Type of Meeting: End-of-Phase 2
Meeting Chair: Sarah Okada, MD
Minutes Recorder: Ramani Sista, RPM



BACKGROUND: Golimumab, a human anti-TNF α monoclonal antibody, is indicated for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. The Sponsor plans to conduct a clinical study of IV golimumab to support an indication in rheumatoid arthritis.

Centocor Ortho Biotech Attendees	
Name	Title
Daniel Baker, MD	Vice President, Clinical R & D
Alan Mendelsohn, MD	Senior Director, Clinical R & D
Zhenhua (Michael) Xu, PhD	Associate Director, Clinical Pharmacology
Jiandong Lu, PhD	Director, Biostatistics
Lilianne (Lee-Lian) Kim, PhD	Manager, Biostatistics
Stella Jones, PhD	Vice President, Global Regulatory Affairs, Immunology
Bethany Paxson	Senior Director, Global Regulatory Affairs, Immunology
Linda Vega	Senior Manager, Global Regulatory Affairs, Immunology
Jerome Boscia, MD	Senior Vice President, Clinical Research and Development
Dennis Decktor	Senior Director, Medical Affairs
Salvatore Morello	Associate Director, Global Regulatory Affairs, Immunology
FDA Attendees	
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Rigoberto Roca, MD	Deputy Director
Sarah Okada, MD	Clinical Team Leader
Erick Brodsky, MD	Medical Officer
Jeffery Siegel, MD	Clinical Team Leader
Deborah Seibel, MD	Medical Officer
Kurt Brorson, PhD	Product Reviewer, DMA
Dionne Price, PhD	Statistical Team Leader
Jonathon Norton, PhD	Statistical Reviewer
Lei Zhang, PhD	Clinical Pharmacology Reviewer
Ramani Sista, PhD, RAC	Regulatory Project Manager
Sharon Turner-Rinehardt	Regulatory Health Project Manager

GENERAL DISCUSSION:

Following introductions, the meeting focused on the responses to the questions included in the April 9, 2009, meeting package for intravenous golimumab for the treatment of RA, under IND 9925. The responses to the questions were provided to the Sponsor on May 15, 2009. The questions are presented below in *italicized* text, the Division's responses, prepared prior to the meeting, are **bolded**. Discussion is presented in normal text.

AGENDA QUESTIONS from SPONSOR and FDA COMMENTS

In our responses, Studies C0524T03, C0524T06, C0524T12, and CNT0148ART3001 will be referred to as Studies 3, 6, 12, and 3001, respectively.

Question 1: Does the Agency agree that the study design, (b) (4) (b) (4) (b) (4), is appropriate to support (b) (4) (b) (4) (b) (4) Golimumab should be given in combination with methotrexate. Does the Agency agree?

FDA Response

With your May 7, 2009, modifications to Study 3001, you propose a golimumab intravenous loading dose, in combination with MTX, (b) (4) (b) (4) (b) (4). In principle, this trial appears adequately (b) (4) designed to explore the efficacy of the (b) (4) regimen proposed. However, the trial, as currently designed, would not be adequate to support a 2-mg/kg q8 week maintenance regimen. Furthermore, the dose regimens proposed may not allow for extrapolation of data from the subcutaneous clinical development program in support of all claims sought (see our response to Question 3) and in support of safety (see our response to Question 4).

Based on the efficacy and safety results of Study 12, and the estimated differences between the subcutaneous and intravenous dosing regimens' pharmacokinetic parameters, we are concerned that your proposed intravenous loading/maintenance dose regimen may not have a similar benefit/risk ratio as your approved subcutaneous dosing regimen in the treatment of RA. As noted in the Division's response to your February 6, 2006 meeting package, dated May 10, 2006, the overall efficacy, safety, and immunogenicity of the intravenous golimumab regimen will need to be comparable to the subcutaneous dosing regimen in order to extrapolate data from the subcutaneous dosing regimen to support

approval (b) (4). **If there are significant differences in efficacy and safety between the subcutaneous and intravenous formulations, then even if Study 3001 were to demonstrate statistically significant differences between the intravenous and placebo treatment groups for the primary and major secondary endpoints, it may not be feasible to approve the intravenous dosing regimen. You should consider studying intravenous dose regimens that would result in similar pharmacokinetic parameters as the subcutaneous dosing regimen (e.g., lower intravenous doses at more frequent intervals). We also recommend you consider utilizing an active-control design with a subcutaneous golimumab treatment group, which would allow for a within-study comparison of the subcutaneous and intravenous dosing regimens.**

Discussion: The Sponsor acknowledged that the proposed intravenous (IV) dosing regimen (b) (4) would result in markedly different pharmacokinetic (PK) profiles than the golimumab subcutaneous (SC) 50 mg q 4 weeks regimen and understood the difficulty of trying to use the SC program data in this circumstance. They stated that they will likely pursue a more frequent IV dosing interval (e.g., 2 mg/kg q 8 weeks with no loading dose) that will result in a similar trough but much greater C_{max} and AUC values (AUC at least 3 times greater) than the SC regimen. (b) (4)

The Division asked the Sponsor if they were planning to propose a new label and different trade name for IV golimumab, since it would be important for prescribers to distinguish between the different characteristics of the IV and SC products (e.g., different routes of administration (ROA), PK, indications, and possibly a different safety profile). The Sponsor replied that they will propose a new label for IV golimumab but plan to keep the trade name (Simponi). The Division expressed concern that this strategy may create medication errors since the practitioners may find it difficult to distinguish between the IV and the SC products. The Sponsor noted that there were some small molecule products (e.g., Zofran) with different ROA, PK, and indications that had the same trade name. The Division agreed to explore how other Divisions dealt with similar situations and provide comment in a post-meeting note.

Post-Meeting Note

The Division has confirmed that there are multiple products with the same drug substance but different formulations and routes of administration that have been approved with the same trade name but different labeling. Therefore, it is possible that IV golimumab may be approved with the same trade name but different labeling. If, as currently planned, there will be major differences between the IV and SC regimens in terms of indications, or if there are major safety differences between the two regimens, the BLA for the IV regimen will need to address how you propose to ensure that prescribers are aware of these differences.

Question 2: Does the agency agree with the 2-sided testing procedure for the major secondary endpoints proposed above?

FDA Response

Our response is based on your proposed modifications to Study 3001 and would apply in principle if different endpoints were substituted in the same decision tree. For the time to flare endpoint (major secondary endpoint 1), you will first compare the 4-mg/kg q 12 dosing regimen to placebo, and then compare the 2-mg/kg q 12 dosing regimen to placebo. It is not clear whether a “win” on 4-mg q12 regimen would be sufficient to continue on to the next secondary endpoint, or whether “wins” are required for both 2- and 4-mg/kg q 12 dosing regimens in order to continue. Requiring a “win” only on the 4-mg q 12 regimen would introduce multiplicity concerns. Also, you propose, “Since major secondary endpoints 2 through 4 (i.e., DAS28 at Week 14, change in SF-36 at Week 14, change in HAQ at Week 14) are in support of the loading regimen, they will be tested in the fixed sequence in the order shown above, if the test for the primary endpoint is statistically significant.” It appears that you are allowing for multiple ways to continue testing after finding that the primary is significant, i.e., test either time to flare or DAS28. Provide clarification on these points and include multiplicity corrections, as needed.

Since RA is a chronic disease that requires chronic treatment, it is essential that both the loading dose and maintenance dose be supported. Therefore, a “win” on the primary endpoint (ACR 20 response at Week 14) and a “loss” (no statistically significant difference) on the major secondary endpoint 1 (time to flare between Weeks 24 and 60) would not support any loading/maintenance dosing regimen for the treatment of RA.

Assuming you account for multiplicity, it is acceptable for you to include time to flare as a major secondary endpoint 1 since this endpoint is important in assessment of your maintenance dose regimen.

We recommend you include a strategy to address multiplicity concerns for any endpoints that may be considered for label claims.

Discussion: The Sponsor asked whether they would be required to strongly control type I error across both doses and endpoints, including the major secondary endpoints. The Division replied that this would be the case, and that when a design was chosen, a statistical analysis plan that strongly controlled type I error would need to be developed.

Post-Meeting Note

It is particularly important to control type I error for secondary endpoints that could lead to an additional label claims.

Question 3: Does the Agency agree that the IV clinical data package, assuming a positive outcome from the CNTO148ART3001 study, will be sufficient to support all of the proposed RA claims anticipated from the SC golimumab clinical program,

(b) (4)

(b) (4)

FDA Response

You propose to support (b) (4) claims (b) (4)

(b) (4) for intravenous golimumab in the treatment of patients with moderately to severely active RA with the following efficacy data:

- **Historical data from subcutaneous golimumab (with approved claims for reducing signs and symptoms and improving physical function)**
- **Future data from your subcutaneous golimumab program for inducing major clinical response and inhibiting the progression of structural damage**
- **Pivotal data from Study 3001 including signs and symptoms data (e.g., ACR response at Week 14) and improvement in physical function data (e.g., change from baseline in HAQ at Week 14, proportion of HAQ responders at Week 14 – change from baseline > 0.25)**
- **Supportive data from Study 12 (although a different dosing regimen was used)**

In Study 3001, according to your pharmacokinetic simulations, the median golimumab concentrations after administration of 4 mg/kg of intravenous golimumab at Weeks 0, 4, and 12 and q 12 weeks would be approximately 70, 6, 0.5, and 0.2 µg/mL at Weeks 12, 14, 20, and 24, respectively. The anticipated exposure to golimumab in the 4 weeks prior to the repeat dosing of the q 12 week regimen would be minimal, and lower than the lowest trough concentrations observed with subcutaneous q 4 week dosing. This gap in exposure with the q 12 week dosing regimen would make it difficult to extrapolate from the subcutaneous data, especially since it is not clear which pharmacokinetic parameters are most influential on the treatment effect observed for the various claims.

Therefore, in order to support (b) (4) claims, the proposed intravenous golimumab study must be of sufficient duration and contain results which directly support all claims sought,

Note our response to Question 2, as well as the statistical comments in the Additional Comments section.

Discussion: The Sponsor asked if the IV dosing regimen in a single Phase 3 IV trial in RA patients achieved similar trough levels and similar signs and symptom responses as the approved SC dosing regimen, would this be sufficient for approval (b) (4)

(b) (4). Assuming that the SC regimen is approved for all the claims sought, the Division stated that similar or greater trough levels and similar or greater ACR responses would support the efficacy of IV golimumab (b) (4)

Post-Meeting Note

Further internal discussion will be required by the Division to assess our response regarding the extrapolation of the data from the SC program to support (b) (4) claims for IV golimumab. We will provide a definitive response as soon as possible.

Question 4: Does the Agency agree that the safety database as outlined in Table 5 will be adequate to characterize the safety profile of IV golimumab administered at Weeks 0, 4, and 12, followed by either a q8 week or q12 week maintenance regimen?

FDA Response

With your May 7, 2009 modifications to Study 3001, you proposed that your safety database for intravenous golimumab will contain

- **Approximately 420 patients with at least 24 weeks of exposure to your proposed golimumab loading dose regimen (about 757 patients with at least 24 weeks of exposure to all intravenous golimumab dosing regimens); and**
- **Approximately 330 patients with at least 48 weeks of exposure to your proposed loading dose with a 2-mg/kg maintenance regimen every 12 weeks (or a higher dose) and about 215 patients with at least 48 weeks of exposure to your proposed loading dose with a 4 mg/kg maintenance regimen every 12 weeks (about 432 patients with at least 48 weeks of exposure to all intravenous golimumab dosing regimens).**

In the two golimumab trials that included the highest golimumab doses tested, there appeared to be a dose-related increase in malignancies (excluding non-melanoma skin cancers). In the Phase 2 trial of subcutaneous golimumab in asthma (Study 3, n=309), there were 0 (0%), 1 (1%), 2 (3%), and 3 (4%) malignancies in the placebo, and 50, 100, and 200 mg groups (approximately 0, 1.1, 2.2, and 3.3 malignancies per 100-patient years, respectively). In Study 12 (intravenous golimumab every 12 weeks, n=643), there were 1 (0.8%), 1 (0.4%), and 4 (1.6%) malignancies in the placebo, 2-mg/kg, and 4-mg/kg groups, respectively, through Week 48. Also according to your pharmacokinetic simulations, the pharmacokinetic profiles of the intravenous and subcutaneous dosing regimens are very different. The C_{max}, AUC, and average concentrations of golimumab after your proposed 4-mg/kg intravenous dose is much greater than the pharmacokinetic parameters seen in your subcutaneous program (50 mg or 100 mg every 4 weeks); although, the trough concentrations of golimumab are lower.

The safety database for your intravenous golimumab program will need to be sufficient to explore the effect of the higher doses and exposure on safety, including the possibility of dose-related increase in malignancy risk. Based on the numbers of patients and malignancies observed in the golimumab asthma trial and Study 12, the numbers of patients proposed for 48 weeks of intravenous exposure in Study 3001 is reasonable, but the adequacy of the data, including the need for additional trials, can only be determined upon review of study results.

Discussion: The Sponsor stated that they will likely have 300 patients exposed to the new IV golimumab dosing regimen (e.g., 2 mg/kg every 8 weeks) for at least one year. The Sponsor asked for further clarification on the size of the safety database to explore the risk of malignancies, since the rate of malignancies is expected to be low and the trial would not be adequately powered to rule out a malignancy signal. The Division noted that since malignancy signals were seen in trials of similar size (Study 3 (N=309) and Study 12 (N=643)), the size of the proposed trial could be sufficient to evaluate an imbalance of malignancies with the new dose regimen. The Sponsor asked the Division how the imbalance of malignancies in Study 12 would be handled. The Division stated that, presuming no imbalance is seen in the IV Phase 3 study, additional postmarketing studies to assess the malignancy risk of IV golimumab may be required. The Sponsor acknowledged that if an imbalance of malignancies were seen with the new IV dosing regimen, the chance of approvability of IV golimumab in RA would be significantly reduced.

Question 5: Does the Agency agree with the definition of a flare as proposed for the CNT0148ART3001 study?

FDA Response

In the randomized withdrawal portion of Study 3001 between Weeks 24 and 60, you propose to define a flare as having all of the following (when compared to corresponding values at Week 20):

- **≥ 20% increase in the tender joint counts**
- **≥ 20% increase in the swollen joint counts**
- **≥ 2 cm increase in Physician Global Assessment of Disease**
- **≥ 2 cm increase in Patient Global Assessment of Disease and/or Patient Assessment of Pain**

Your definition of a flare is acceptable. Patients who discontinue study treatment between Weeks 24 and 60 should be imputed as having a flare.

Discussion: No discussion required for this question.

Additional Comments

- 1. The proposal to use biased coin randomization in Study 3001 raises the concern that the statistical tests may not be valid. If you choose to use adaptive randomization, then you will need to conduct re-randomization tests for the primary and major secondary endpoints. If such tests are not feasible, then you will need to use non-adaptive randomization.**
- 2. We note that you also used biased coin randomization in Study 12. You will need to conduct re-randomization tests for the primary and major secondary endpoints.**

- 3. The protocol for Study 3001 does not specify an analysis for the time-to-flare endpoint. Also, the origin (time 0) is not specified. These must be described in the prospective analysis plan.**
- 4. In the “Summary of Proposed Changes to Study 3001”, you state “The major secondary endpoint of time to flare from Week 24 through Week 60 will compare the 2 mg/kg and 4 mg/kg q 12 week regimens versus placebo.” Clarify what group of patients will comprise the placebo group.**
- 5. For your safety analyses, clarify how you will determine the duration of exposure after intravenous golimumab administration (e.g., 8 weeks after last infusion, when concentrations of golimumab are expected to reach the trough levels seen after subcutaneous administration).**
- 6. According to your May 7, 2009, modifications to the protocol of Study 3001, you propose that patients who are randomized to Group II and receive intravenous placebo infusions who have less than a 20% improvement in both tender and swollen joint count from Week 0 to Week 16 will enter early escape and will receive 2 mg/kg of intravenous golimumab at Weeks 16, 20, and then 8 weeks thereafter. Clarify whether patients in Group I (intravenous golimumab at Weeks 0, 4, and 12) have less than a 20% improvement in both tender and swollen joint count from Week 0 to Week 16 will enter early escape.**
- 7. According to your May 7, 2009, modifications to the protocol of Study 3001, you propose those patients in the randomized withdrawal portion of the trial “who are re-randomized to receive placebo and experience a flare of their RA ... will be started on 2 mg/kg every 8 weeks.” Clarify whether patients who are re-randomized to receive 2 or 4 mg/kg of intravenous golimumab every 12 weeks experience an RA flare will receive additional treatment.**
- 8. Provide information on the golimumab dosage formulation for Study 3001 and clarify all significant differences in formulation and container closure from the dosage formulation used in Study 12.**
- 9. Provide product stability information for the Study 3001 dosage form.**

Discussion: No further discussion required for the additional comments.

Action Items for IND 9925

1. The Sponsor will clarify plan for controlling type I error across major secondary endpoints and doses.
2. The Sponsor will submit CMC information on the new dosage form.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 9925

CENTOCOR ORTHO
BIOTECH INC

Golimumab (Human Monoclonal Antibody
to Tumor Necrosis Factor Alpha,
rTNV148B, CNTO 148)

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/s/

SHARON M TURNER RINEHARDT
06/17/2009



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: June 5, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – golimumab for infusion
FDA request for information: Clinical drug-demographic safety analysis

Total no. of pages including cover: 4

Comments: *Response requested no later than Monday June 10, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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We refer to original BLA 125433/0 for golimumab for infusion dated September 18, 2012, and have the following request for information.

In order for us to complete our safety review of your application, submit the drug-demographic analyses for age, gender, race and weight as shown in the attached table for the Week 24 time point for Study CNTO148ART3001.

Submit your response to me via secure email at christine.chung@fda.hhs.gov no later than COB June 10, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Proportion of Patients with an Infectious AE by Age, Gender, Race, and Weight by
Randomized Treatment Group Through the 24-Weeks of Controlled Treatment in Study
CNTO148ART3001

		Placebo ¹	Golimumab 2 mg/kg every 8 wks ¹
Entire Population		197	395
Age	<65 years		
	≥ 65 years		
Gender	Female		
	Male		
Race	Caucasian		
	Asian		
	Black		
Weight	≤ 25 th percentile		
	> 25 th percentile to ≤ median		
	> median to ≤ 75 th percentile		
	> 75 th percentile		

¹Based on treatment assigned at randomization. Patients who escaped are not included in this table.

Drafted by: RNeuner, SLimb/ 6.4.2013
cchung/ 6.5.2013

Initialed by: SBarnes/ 6.5.2013

Finalized: chung/ 6.5.2013

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/s/

CHRISTINE H CHUNG
06/05/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 30, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – golimumab for infusion
FDA request for information – Clinical hematology and LFT lab data

Total no. of pages including cover: 5

Comments: *Response requested no later than June 5, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

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We refer to original BLA 125433/0 for golimumab for infusion dated September 18, 2012, and have the following request for information.

In order for us to complete our review of your application, submit mean change over baseline at Week 24 for both hematology and liver function data formatted as shown in the attached tables for Study CNTO148ART3001.

Submit your response to me via secure email at christine.chung@fda.hhs.gov no later than June 5, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Mean Change in Hematology Parameters in Study CNTO148ART3001

Indices	PLO + MTX		PLO +MTX to Golimumab 2 mg/kg + MTX		Golimumab 2 mg/kg + MTX		Golimumab Combined	
	Baseline	Wk 24	Baseline	Wk 24	Baseline	Wk 24	Baseline	Wk 24
Hemoglobin (g/L) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
Hematocrit (%) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
WBC (x10³/mcl) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
Basophils (%) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
Eosinophils (%) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
Lymphocytes (%) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
Monocytes (%) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
Neutrophils (%) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
Platelets (x10³/mcl) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								

Mean Change in Liver Function Tests for Study CNTO148ART3001

Liver Function test	PLO + MTX		PLO +MTX to Golimumab 2 mg/kg + MTX		Golimumab 2 mg/kg + MTX		Golimumab Combined	
	Baseline	Wk 24	Baseline	Wk 24	Baseline	Wk 24	Baseline	Wk 24
Alk phos (U/L) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
ALT/SGPT (U/L) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
AST/SGOT (U/L) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
GGT (U/L) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
LDH <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								
Total bili (mg/dl) <i>N</i> <i>Mean (SD)</i> <i>Median</i> <i>(Min, Max)</i>								

Drafted by: RNeuner, SLimb/ 5.29.2013
cchung/ 5.29.2013

Initialed by: SBarnes/ 5.29.2013

Finalized: chung/ 5.30.2013

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/s/

CHRISTINE H CHUNG
05/30/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 23, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – golimumab for infusion
FDA request for information - Clinical

Total no. of pages including cover: 3

Comments: *Response requested no later than May 28, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

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We refer to original BLA 125433/0 for golimumab for infusion dated September 18, 2012, and have the following request for information.

According to the study report for Protocol CNTO148ART3001, 197 subjects were randomized to treatment with placebo+MTX, out of which 68 subjects qualified for early escape and 6 subjects discontinued study treatment, leaving 123 patients to continue study agent at Week 24. Provide an account for the discrepancy shown in Table 1 located on page 45 of the 52-week report which lists 121 placebo + MTX patients switched to treatment with golimumab 2 mg/kg at Week 24 instead of 123 patients.

Submit your response to me via secure email at christine.chung@fda.hhs.gov no later than May 28, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Drafted by: RNeuner, SLimb/ 5.23.2013
cchung/ 5.23.2013

Initialed by: SBarnes/ 5.23.2013

Finalized: chung/ 5.23.2013

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CHRISTINE H CHUNG
05/23/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 2, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – golimumab for infusion
FDA request for information - Clinical

Total no. of pages including cover: 3

Comments: *Response requested no later than May 10, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

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We refer to original BLA 125433/0 for golimumab for infusion dated September 18, 2012, and have the following request for information.

Submit identification of the 6 patients who were reported to have infusion reactions with skin manifestations as noted in Attachment 4.15 (CSR CNTO148ART3001), and provide a line listing of all adverse events reported for each patient.

Submit your response to me via secure email at christine.chung@fda.hhs.gov no later than May 10, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Drafted by: RNeuner, SLimb/ 5.2.2013
cchung/ 5.2.2013

Initialed by: SBarnes/ 5.2.2013

Finalized: chung/ 5.2.2013

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CHRISTINE H CHUNG
05/02/2013



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

ELECTRONIC CORRESPONDENCE

Date: May 1, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – golimumab for infusion
FDA request for information

Total no. of pages including cover: 3

Comments: *Response requested no later than May 7, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

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We are currently reviewing labeling for golimumab for infusion (most recent proposed labeling submitted December 14, 2012) and have the following request for information.

Provide the mean steady state human exposure ($AUC_{0-8 \text{ weeks}}$) value at an interval of 0-8 weeks for the proposed dosing regimen of 2 mg/kg IV at 0 and 4 weeks and every 8-week thereafter.

Submit your response to me via secure email at christine.chung@fda.hhs.gov no later than May 7, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Drafted by: MDe, TRobison/ 5.1.2013
cchung/ 5.1.2013

Initialed by: SBarnes/ 5.1.2013

Finalized: chung/ 5.1.2013

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/s/

CHRISTINE H CHUNG
05/01/2013

Chung, Christine

From: Suggs, Courtney
Sent: Wednesday, May 01, 2013 11:43 AM
Chung, Christine
Greeley, George
Subject: Golimumab Partial Waiver/Deferral/Plan May 1 PeRC Review

Hi Christine,

We wanted you to provide you with the results review at PeRC on May 1 as well as any PeRC recommendations. The minutes are excerpted below.

Simponi (Golimumab) Partial Waiver/Deferral/Plan

- BLA 125433, Simponi (golimumab), was studied for the treatment of rheumatoid arthritis in adult patients.
- The application was submitted September 18, 2012 and has a PDUFA date of July 18, 2013.
- It triggers PREA as a new dosage form, dosing regimen, and route of administration.
- The Division is requesting a partial waiver in neonates and pediatric patients up to 1 year, 11 months of age because studies are impossible or highly impracticable.
 - JIA does not present at birth.
 - There are a small number of pediatric patients up to 1 year, 11 months of age that are diagnosed with JIA and JIA is not typically clinically evident before 1 year of age.
- The Division is requesting a partial deferral in pediatric patients >2 years to 16 years, 11 months of age because adult studies are completed and ready for approval.
The PeRC agrees with the waiver in pediatric patients <2 years of age and to the deferral in patients >2 years of age to 16 years, 11 months of age.
- PeRC recommendation(s):
 - The PeRC recommends the Division modify the study submission date and change it to a date that is closer to the study completion date.

Thanks,
Courtney

LCDR Courtney M. Suggs, PharmD, MPH
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6404
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: April 18, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – golimumab for infusion
FDA request for information – Microbial quality #4

Total no. of pages including cover: 3

Comments: *Response requested no later than April 23, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

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We refer to original BLA 125433/0 for golimumab for infusion and have the following request for information.

Amend the BLA to include integrity test (b) (4) in section 3.2.P.3.4 “Control of Critical Steps and Intermediates.”

Submit your response (with responses to information request dated April 17, 2013) to me via secure email at christine.chung@fda.hhs.gov no later than April 23, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Drafted by: MCandauchacon, PHughes, ERead, DFrucht/ 4.18.2013
cchung/ 4.18.2013

Initialed by: SBarnes/ 4.18.2013

Finalized: chung/ 4.18.2013

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/s/

CHRISTINE H CHUNG
04/18/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: April 17, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – golimumab for infusion
FDA request for information – Product Quality submission dated 4/16/2013

Total no. of pages including cover: 4

Comments: *Response requested no later than April 23, 2013*

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We refer to original BLA 125433/0 for golimumab for infusion and to your submission dated April 16, 2013, and have the following request for information.

Your April 16, 2013, responses in *italic font* are followed by our comments in normal font.

Janssen's response 6a and 6b:



FDA comment



Janssen's response 17c

The Applicant acknowledges that CFR 610.13, Purity, includes the requirement to test products to be used by injection for pyrogenic substances by utilizing the rabbit pyrogen test, as the test can detect both endotoxin and exotoxin pyrogens. The Applicant commits to submit RPT results on at least one commercial batch of Simponi (b) (4) DP no later than 30 days prior to FDA's PDUFA date for BLA 125433. The applicant commits to submit RPT results on two additional commercial DP lots to the BLA, postapproval. The Applicant plans to use the RPT results to validate the absence of exotoxin pyrogens in the Simponi (b) (4) drug product. The Applicant proposes that RPT be discontinued

for commercial batches after the initial three batches, and that RPT not be included in the drug product specifications.

The Applicant acknowledges the need to execute LAL spiking studies, and will therefore conduct these studies and commits to report the results to the FDA in the first Annual Report.

FDA comment

Indicate when results from the Rabbit Pyrogen Test for two additional golimumab
(b) (4) DP lots will be submitted to the Agency.

Submit your response to me via secure email at christine.chung@fda.hhs.gov no later than April 23, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Drafted by: MCandauchacon, PHughes/ 4.16.2013
cchung/ 4.16.2013

Initialed by: SBarnes/ 4.16.2013
MCandauchacon, PHughes/ 4.17.2013

Finalized: cchung/ 4.17.2013

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/s/

CHRISTINE H CHUNG
04/17/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: April 2, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0 – golimumab for infusion
FDA request for information – Product Quality submission dated 2/20/2013

Total no. of pages including cover: 6

Comments: *Response requested no later than April 15, 2013*

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We refer to original BLA 125433/0 for golimumab for infusion and to your submission dated February 20, 2013, and have the following request for information.

Your February 20, 2013, responses in *italic font* are followed by our comments in normal font.

Janssen's response 2d:

The sensitivities of the dye ingress and microbial ingress methods are (b) (4), respectively.

FDA comment

Submit information about how sensitivity of either method (microbial ingress and dye ingress) was determined. Sensitivity should be correlated to breach size using breached containers. Since the microbial and dye ingress validations were conducted with different pressure and time challenges, in order to assess if the dye ingress method is more sensitive than the microbial ingress method, sensitivity of both methods should be correlated to breach size. Otherwise, both methods should be validated using the same challenge conditions.

Janssen's response 4a and b

a. *The bioburden acceptance criterion (b) (4) (b) (4) The final bioburden bulk sample for the Simponi (b) (4) DP, (b) (4) has an acceptance criterion (b) (4) which is consistent with the requirement for the maximum acceptable bioburden level prior to (b) (4) as stated in EMEA Guidance CPMP/QWP/486/95, Note for Guidance on Manufacture of Finished Dosage Form (April 1996).*

The Applicant agrees to implement the proposed (b) (4) sample volume (b) (4) for future production, and will at the same time tighten the specifications for bioburden for these samples as stated in response 4b. The more stringent acceptance criteria for the FB (b) (4) will be (b) (4)

The acceptance criteria for the final bioburden sample taken immediately before (b) (4). These acceptance criteria are based on impact to product quality and process understanding.

These changes will be filed as a post-approval supplement once the validation of the new sample size is complete. The applicant considers the implementation of alert and action levels unnecessary given the change in sample size and tighter specifications that will be implemented, but will re-evaluate the need to implement a two tier system after 10 batches.

b. *The Applicant agrees with increasing the (b) (4) bioburden sample volume (b) (4). Revalidation of the bioburden assay with a sample volume (b) (4) is currently in progress. After the revalidation is complete, the acceptance criterion for the (b) (4) will be adjusted (b) (4) and the acceptance criterion (b) (4) will be adjusted (b) (4)*

The applicant agrees to implement the (b) (4) bioburden sample volume (b) (4) for future production, to be filed as a post-approval supplement.

FDA comment

Submit information regarding the new sample size, new acceptance criteria, and reevaluation of alert and action limits in the next Annual Report to the Agency for BLA 125433 once approved.

Janssen's response 6a



FDA comment



Janssen's response 6b



FDA comment

[REDACTED] (b) (4)

Janssen's response 11f

[REDACTED] (b) (4)

FDA comment

[REDACTED] (b) (4)

Janssen's response 14b

[Last paragraph]

The container closure integrity (CCI) of (b) (4) DP was evaluated separately after subjecting the drug product vials to a standardized simulated transportation profile (see CPV-12071). The simulated transportation profile is designed to subject the drug product and primary packaging to conditions the drug product may experience during transport. Three loaded corrugated shippers (b) (4) were used for this study and a total of 500 vials were collected as samples from the 3 shippers after transportation simulation. All the drug product vials were visually examined and showed no defects. All the sampled vials were also tested for CCI using the blue dye ingress test and met the test acceptance criteria. The container closure integrity of all the vials was maintained after simulated transport.

FDA comment

Provide an explanation [REDACTED] (b) (4)
[REDACTED] (DS-REF-17726).

Janssen's response 17c

[Last paragraph]

The LAL test is considered to be appropriate and sufficient for Simponi (b) (4) DP, based on the measures in place during manufacturing of Simponi (b) (4) DP to control bioburden and the in-process microbiological test results presented to date.

FDA comment

Non-endotoxin pyrogens will not be detected by the LAL test. Your response is adequate provided the rabbit pyrogen test was performed for the approved BLA 125289. Otherwise, the rabbit pyrogen test should be performed as per

21 CFR 610.13.b. In addition, the Agency has recently been informed that the LAL endotoxin assay may underestimate the amount of endotoxin in DP formulated with polysorbate. Specifically, inhibition of endotoxin recovery has been observed in undiluted samples that are spiked and then tested after different hold times. Perform small scale endotoxin recovery studies spiking known amounts of endotoxin standard in the DP and include simulations of hold times and processing conditions.

Submit your response to me via secure email at christine.chung@fda.hhs.gov no later than April 15, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Drafted by: MCandauchacon, PHughes/ 3.28.2013
cchung/ 3.29.2013

Initialed by: SBarnes/ 3.29.2013
MCandauchacon, PHughes/ 4.1.2013

Finalized: cchung/ 4.2.2013

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/s/

CHRISTINE H CHUNG
04/02/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: February 4, 2013

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0/0 – golimumab for infusion
FDA request for information – Microbial Quality

Total no. of pages including cover: 3

Comments: *Response requested by February 18, 2013*

Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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We refer to original BLA 125433/0/0 for golimumab for infusion dated September 18, 2012, and have the following request for information.

1. Information and validation of washing, depyrogenation, and sterilization processes of product-contact parts and equipment is included in the Appendix section. Amend the BLA to include that information in Module 3.
2. P.2.5 Microbial Attributes
 - a. Clarify if the samples used in the container closure integrity tests (microbial and dye ingress) have been validated outside the normal operating range for crimping speed and crimping forces. Crimping speed and crimping forces should reflect worst-case operating conditions.
 - b. Clarify if the microbial ingress test has been validated (b) (4).
 - c. Include the (b) (4) test as part of your acceptance criteria for the microbial ingress test.
 - d. Provide sensitivity (limit of detection) of both methods (microbial and dye ingress) correlated to breach size.
 - e. Describe dye ingress controls and submit control results.
3. P.3.3 Description of Manufacturing Process and Process Controls



2 Pages have been Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

14. P.3.5.6 Shipping Validation

- a. Indicate shipping routes and conditions of golimumab IV to the packaging and labeling site and to its final destination.
- b. Submit shipping validation protocol and shipping validation report. The shipping validation report should demonstrate the ability of the shipping containers to maintain controlled temperatures and to protect drug product and container closure integrity from shock and vibration during shipping under worst-case conditions.

15. P.5.1 Specifications for Release and End of Shelf-life

Conduct container closure integrity in lieu of sterility as your end of shelf-life specification.

16. P.5.2 Analytical Procedures

- a. Submit description of the sterility test and indicate the number of DP vials used for the test.
- b. The endotoxin analytical method is referred to section 3.2.S.4.2 of the BLA. However this BLA does not have a Drug Substance section. Submit your endotoxin analytical method to the Agency, and amend the BLA to include the method in section 3.2.P.5.2.

17. P.5.3 Validation of Analytical Procedures

- a. Describe the sterility suitability test, (b) (4)
 (b) (4)
- b. Clarify what “Placebo” stands for in the endotoxin interference test.
- c. Provide information and summary data for the rabbit pyrogen test of golimumab IV in conformance to 21CFR610.13 (b) or provide justification for not performing the test.

18. P.5.4 Batch Analysis

Submit in-process results related to microbial quality (endotoxin, bioburden, and sterility) for all DP batches manufactured to the current date.

19. P.8.2 Post-Approval Stability Protocol and Stability Commitment

Include container closure integrity in lieu of sterility as part of your stability program. Container closure integrity should be assessed annually and at expiry.

 (b) (4)

Submit your response to me via secure email at christine.chung@fda.hhs.gov no later than February 18, 2013. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Drafted by: MCandauchacon, PHughes/ 2.4.2013
cchung/ 2.4.2013

Initialed by: SBarnes/ 2.4.2013
Finalized: chung/ 2.4.2013

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/s/

CHRISTINE H CHUNG
02/04/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Type of Meeting: Proprietary Name Review

Meeting Date: December 3, 2012; 11:00 AM
Meeting Location: FDA White Oak, Bldg 22, Room 4396, Teleconference

Application: BLA 125433
Proposed Proprietary Name: [REDACTED] (b) (4)
Established Name: golimumab
Applicant: Janssen Biotech, Inc.

Meeting Chair: Lubna Merchant, Team Leader, DMEPA
Meeting Recorder: Nichelle Rashid, Safety Regulatory Health Project Manager

FDA Attendees:

Lubna Merchant, Team Leader, DMEPA
Teresa McMillan, Safety Evaluator, DMEPA
Nichelle Rashid, Safety Regulatory Health Project Manager

Applicant Attendees:

Salvatore Morello, Director, Global Regulatory Affairs
Bethany Paxson, Sr. Director, Global Regulatory Affairs
Valerie Donnelly, Director, Global Trademark Development
Colleen Tavani, Manager, Global Trademark Development
Adrienne Minecci, Group Product Director
Brian Smith, Director, Marketing
David Lockhart, Director, Marketing
Jocelyn Leu, Associate Director, Clinical Pharmacology
Phil Weck, Vice President, Clinical R&D

Background:

DMEPA requested a teleconference to inform Janssen Biotech, Inc., of the findings regarding the proposed proprietary name, [REDACTED] (b) (4), and to inform them of their regulatory options.

Product Information:

Simponi (golimumab) Solution for Injection was initially approved for subcutaneous use on April 24, 2009. It is used for treatment of rheumatoid arthritis, active psoriatic arthritis, and active ankylosing spondylitis. It is available in 50 mg/0.5 mL single dose pre-filled SmartJect autoinjector and 50 mg/0.5 mL single dose pre-filled syringe.

Simponi IV Solution for Injection is used for treatment of rheumatoid arthritis. It will be available as 50 mg/4 mL (12.5 mg/mL) vials.

Discussion:

This is a courtesy call to notify Janssen of DMEPA's preliminary findings and safety concerns with regards to the proposed proprietary name, (b) (4) submitted on October 19, 2012.

DMEPA's preliminary review has identified that the proposed proprietary name, is unacceptable for the following reasons:

The Office of Prescription Drug Promotion (OPDP) objects to the proposed name

(b) (4)

Additionally, DMEPA identified that the proposed name, (b) (4)

(b) (4) is not acceptable for this product.

As stated in the Proprietary Name Review Concept Paper DMEPA published in September 2008, proprietary names should not include USAN stems 'because the USAN stems are intended to indicate a pharmacological or chemical trait of a drug, a single stem will be applicable to multiple drug products. Use of these stems in proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names.

It was also conveyed to Janssen Biotech, Inc. that DPARP has not made a decision on the use of Simponi in the proprietary name.

Regulatory Options:

1. Wait for DMEPA to complete the review of [REDACTED] (b) (4) by the OSE PDUFA goal date of 01/17/13 and issue a formal decision (most likely denial).
2. Withdraw the proposed name, [REDACTED] (b) (4) and submit another name for review.

Questions:

Janssen Biotech, Inc. asked if the safety evaluation of the proposed proprietary name was performed. DMEPA stated that the safety evaluation was not conducted since there were promotional and safety issues identified during the preliminary review of the proposed proprietary name.

Janssen also asked about an expected timeline of DPARP's decision on the use of Simponi in the proprietary name. DMEPA stated that the Division has not provided an expected timeline as to when a decision would be made regarding the use of the root name Simponi. Janssen was advised to contact the division directly.

Conclusions:

Janssen Biotech, Inc. indicated that they will withdraw the proposed proprietary name by December 10, 2012, and submit a new name for review.

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/s/

NICHELLE E RASHID
12/11/2012



BLA 125433

FILING COMMUNICATION

Janssen Biotech, Inc.
Welsh & McKean Roads
P.O. Box 776
Spring House, PA 19477

Attention: Salvatore Morello
Director, Global Regulatory Affairs

Dear Mr. Morello:

Please refer to your Biologics License Application (BLA) dated and received September 18, 2012, submitted under section 351(a) of the Public Health Service Act for intravenous (IV) golimumab, 50 mg/4 mL vial.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 18, 2013.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 21, 2013.

During our filing review of your application, we identified the following potential review issues:

1. We have concerns regarding the adequacy of the safety database in support of IV golimumab. Based on preliminary review, the systemic exposure from the proposed golimumab IV regimen appears higher than the exposure from golimumab SC. This observation heightens the concerns about possible dose-related adverse events like malignancy and serious infections. We question whether there are adequate data to make an informed benefit-risk assessment for IV golimumab because of the limited safety database for the to-be-marketed dose regimen, the uncertainty regarding the clinical impact of differences in PK characteristics between IV and SC regimens, and the absence of a direct,

head-to-head comparison of the IV and SC formulations that would enable a descriptive clinical comparison. The adequacy of the safety database may impact the viability of the application.

2. We have concerns regarding the adequacy of the efficacy data submitted in support of the proposed 2 mg/kg IV dosing regimen for golimumab. The application relies on the results from a single efficacy trial with IV golimumab that met its prespecified primary endpoint (Trial CNTO148ART3001). As discussed at the Pre-BLA filing meeting on October 3, 2011, we require independent substantiation of efficacy for IV golimumab. The adequacy of your proposed bridging to efficacy data for subcutaneous (SC) golimumab on the basis of pharmacokinetic comparisons will be a review issue, but determination is made more difficult by a lack of data derived from a direct comparison of the to-be-marketed IV dose regimen and the SC regimen.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

- A. Provide re-randomization tests for the following major secondary efficacy endpoints; proportion of subjects with moderate or good DAS 28 scores (using CRP) at week 14, change from baseline in HAQ at week 14, and proportion of subjects with ACR50 improvement at week 24. If these are already included in the submission, provide their location.
- B. Provide subgroup analyses by age, gender, and race of the primary and major secondary efficacy endpoints using the protocol specified primary analysis methods. Also provide tests for the interaction of treatment with each of age, gender, and race in the overall patient group. If these are already included in the submission, provide their location.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

- C. In the Boxed Warning for the HIGHLIGHTS section, the heading must be *centered* and contain the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS AND MALIGNANCY**”).
- D. For the Boxed Warning in FULL PRESCRIBING INFORMATION: CONTENTS and FULL PRESCRIBING INFORMATION, the heading must be in UPPER-CASE and contain the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the

subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS AND MALIGNANCY**”).

- E. Under FULL PRESCRIBING INFORMATION, section 17, change the statement to the following: “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”.

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by December 19, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21U.S.C. 355c)], all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. However, since the IV formulation represents a new dosage form, dosing regimen, and route of

administration, the application triggers PREA. Given the differences between the IV and SC formulations on preliminary review, we do not agree with your proposed justification for waiver on the basis of the ongoing pediatric trial for SC golimumab. Within 30 days of the date of this letter, please submit a pediatric plan for review.

If you have any questions, call Christine Chung, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.

Director

Division of Pulmonary, Allergy, and Rheumatology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
11/30/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: October 24, 2012

To: Salvatore Morello, Director Global Regulatory Affairs	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1210	Fax number: 301-796-9728
Email: smorell@its.jnj.com	Phone number: 301-796-3420

Subject: BLA 125433/0/0 – golimumab for infusion
FDA request for information

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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We refer to original BLA 125433/0/0 for golimumab for infusion dated September 18, 2012, and have the following request for information.

1. Provide all principal clinical site investigator contact information, if updated recently: current complete street address, phone number and e-mail.
2. Provide research study patient data listings (By: clinical site and clinical investigator number) for your studies C0524t12 and CNTO148art3001 in PDF electronic format. The data listings should be unmodified and should be based on the BLA submission to the Agency. The study subject data listings should capture the following:
 - a. subject discontinuations (if applicable per treatment group: site subject number, screening visit date, date of first dose/last dose, date of discontinuation, reason for discontinuation).
 - b. concomitant or prohibited medications (non-study medications): [if applicable per treatment group: site subject number, type (prior and/or concomitant meds), medication (preferred term), indication/reason taken, date started, date stopped].
 - c. adverse events [if applicable, per treatment group: MEDRA preferred term/investigator entry, date start/stopped, severity/resolution, Serious Adverse Event? (yes, no)].
 - d. primary efficacy endpoint or co-endpoint [if applicable per treatment group: site subject number, visit # and corresponding date (screening, baseline, week 1...etc), provide sub-item # raw score or measurement, other primary efficacy relevant score or measurement)].
 - e. protocol deviations or violations (Study C0524t12 ONLY).

Submit requested information as an official response to the BLA no later than October 31, 2012, or provide a timeline for when the information will be submitted. If you have any questions, please contact me at 301-796-3420.

Drafted by: AOrencia, RNeuner, SLimb/ 10.24.2012
cchung/ 10.24.2012

Initialed by: SBarnes/ 10.24.2012
Finalized: chung/ 10.24.2012

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/s/

CHRISTINE H CHUNG
10/24/2012



BLA 125433

BLA ACKNOWLEDGEMENT

Janssen Biotech, Inc.
Welsh & McKean Roads
P.O. Box 776
Spring House, PA 19477

Attention: Salvatore Morello
Director, Global Regulatory Affairs

Dear Mr. Morello:

We have received your Biologics License Application (BLA) submitted under section 351(a)/351(k) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Intravenous golimumab

Date of Application: September 18, 2012

Date of Receipt: September 18, 2012

Proposed Use:



(b) (4)

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CHRISTINE H CHUNG
10/01/2012



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B, Pre-BLA

Meeting Category: IND

Meeting Date and Time: September 23, 2011

Meeting Location: Teleconference

Application Number: 9925

Product Name: Simponi®

Received Briefing Package August 23, 2011

Sponsor Name: Janssen Biotech, Inc.

Meeting Requestor: Salvatore Morello, Director, Global Regulatory Liaison

Meeting Chair: Badrul Chowdhury, M.D., Ph.D.

Meeting Recorder: Miranda J. Raggio, BA, BSN, MA, RPM

Meeting Attendees:

FDA Attendees:

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Sarah Yim, M.D., Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Theresa M. Michele, M.D., Clinical Team Leader, DPARP

Eric Brodsky, M.D., Clinical Reviewer, DPARP

Molly Topper, Ph.D., Nonclinical Supervisor, DPARP

Suresh Doddapaneni, Ph.D, Deputy Director, Division of Clinical Pharmacology II, Office of Clinical Pharmacology

Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, Office of Clinical Pharmacology

Kurt Brorson, Ph.D., Product Quality Reviewer, Office of Biotechnology Products Division of Monoclonal Antibodies

David Fruchts, Ph.D., Team Leader, Product Quality Reviewer, Office of Biotechnology Products Division of Monoclonal Antibodies

Joan Buenconsejo, Ph.D, Acting Biostatistics Team Leader, Office of Biostatistics, Division of Biometrics II

Robert Abugov, Ph.D., Office of Biostatistics, Division of Biometrics II

Joan Buenconsejo, Ph.D, Acting Biostatistics Team Leader, Office of Biostatistics, Division of Biometrics II

Jamie Wilkins Parker, Pharm.D., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)

Miranda Raggio, Senior Regulatory Project Manager, Division of Pulmonary and Allergy Products

Sponsor Attendees:

Daniel Baker, MD, Vice President, Clinical Research

Carolina Giuseppi, MD, Global Medical Safety

Stella Jones, PhD, Vice President, Global Regulatory Affairs, Immunology

Lee-Lian (Lilianne) Kim, PhD, Senior Manager, Biostatistics

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Karen Nelson, Senior Director, CMC Regulatory

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Amy Rahn, Senior Manager, Programming and Data Management

Linda Vega, Senior Manager, Global Regulatory Affairs, Immunology

Phillip Weck, PhD, Vice President & Compound Development Team Leader

Shujian Wu, MD, Director, Global Medical Safety

Zhenhua (Michael) Xu, PhD, Director, Pharmacokinetics and Pharmacometrics

Jerome Boscia, MD, Head of Immunology Department

BACKGROUND

Janssen Biotech, Inc. (Janssen) requested a Type B Pre-BLA meeting in correspondence dated July 7, 2011. The stated purpose of this meeting was to discuss their proposed development program for an intravenous formulation of golimumab for rheumatoid arthritis. Upon review of the meeting package, received on August 23, 2011, the Division provided responses to Janssen's questions via a letter sent electronically to Salvatore Morello on September 21, 2011. The content of the letter is printed below, with the Janssen's questions in ***bold italics***, the Division's responses in *italics*, and the requests for clarification and discussion in normal font. In a September 22, 2011, email, Janssen notified the Division that they wanted further

clarification on Introductory Comments 2 and 3, Questions 2, 7, 8, 9, and Additional Comments 1, 2, and 3, and Janssen included specific clarification requests in the email. Summary comments of the meeting discussion are found in normal font following the specific questions.

INTRODUCTORY COMMENTS

In our responses, Studies C0524T12, CNT0148ART3001, C0524T05, C0524T06, and C0524T11 are referred to as Studies 12, 3001, 5, 6, and 11, respectively.

You propose to submit a sBLA for intravenous (IV) golimumab (2 mg/kg at Weeks 0 and 4 and then every 8 weeks thereafter) in combination with methotrexate (b) (4) in patients with moderately to severely active rheumatoid arthritis (RA). You propose that the primary support of the efficacy and safety of this IV dose regimen will be from Study 3001. You propose to provide supportive evidence of efficacy and safety from different IV dosage regimens in patients with RA (dose regimens of 2 and 4 mg/kg IV every 12 weeks in Study 12) and data from different SC dose regimens in patients with RA (50 and 100 mg SC every 4 weeks in Studies 5, 6, and 11).

We have the following concerns/comments about your proposal:

- 1. We consider the IV and SC formulations of golimumab to be two separate and distinct products because they have different pharmacokinetic characteristics, dosing regimens, and product presentations, despite having the same drug substance. Unless clinical data demonstrate that the safety and efficacy profile are sufficiently similar to support interchangeability of the products, you will need to complete a stand-alone program demonstrating both safety and efficacy of the IV formulation.*
- 2. Given the greater maintenance dose regimen with the IV vs. the SC regimen (80 mg/month vs. 25 mg/month considering 50% bioavailability of the SC regimen), greater exposure of IV vs. SC regimen (AUC is about 3 times greater, Cmax is at least 10 times greater), and possible dose-related increase in serious adverse events including malignancy in trials of TNF inhibitors, we will require additional safety data prior to the BLA submission to evaluate your proposed IV dosage regimen.*

Sponsor clarification response: The Sponsor acknowledges the FDA's comments, and plans to adopt the FDA's advice and not submit the IV RA file as previously planned in November 2011.

Discussion: No discussion.

Post-Meeting Comment: We have the following clarification to our response above: "Given the greater maintenance dose regimen with the IV vs. the SC regimen [(80 mg/month (**assuming a mean weight of 80 kg per person**)) vs. 25 mg/month considering 50% bioavailability of the SC regimen]."

- 3. You have provided data from only one trial using your proposed dosing regimen (Study 3001). Given the differences of the IV and SC regimens, you will need to provide evidence of independent substantiation of the efficacy of IV golimumab. See the 1998 "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" Guidance for more details.*

We also note our responses to you from our May 2009 end-of-phase II meeting for IV golimumab:

"If there are significant differences in efficacy and safety between the subcutaneous and intravenous formulations, then even if Study 3001 were to demonstrate statistically significant differences between the

intravenous and placebo treatment groups for the primary and major secondary endpoints, it may not be feasible to approve the intravenous dosing regimen. You should consider studying intravenous dose regimens that would result in similar pharmacokinetic parameters as the subcutaneous dosing regimen (e.g., lower intravenous doses at more frequent intervals). We also recommend you consider utilizing an active-control design with a subcutaneous golimumab treatment group, which would allow for a within-study comparison of the subcutaneous and intravenous dosing regimens.”

Sponsor Clarification Response: The Sponsor acknowledges the FDA’s comment. In accordance with Section II.C.2.a. of the 1998 Guidance, since the PK profile of the new IV route differs from the approved SC product, the Sponsor plans to use the signs and symptoms and physical function efficacy data from the approved SIMPONI SC route of administration to independently substantiate the “efficacy” results observed in Study 3001. [see excerpted FDA guidance below, under section II.C.2.a.]

II.C.2.a. Different doses, regimens, or dosage forms

As discussed in Sections II.C.1.d, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial where blood levels and exposure are not very different or, even if quite different, there is a well understood relationship between blood concentration and response.

Where the relationship between blood concentration and response is not so well understood and the pharmacokinetics of the new dose, regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness of a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient. For example, a single controlled trial was needed to support the recent approval of a once daily dose of risperidone because the once daily and twice daily regimens had different pharmacokinetics and risperidone’s PK/PD relationship was not well understood.

Discussion: Janssen outlined their proposal to support the efficacy of IV golimumab (2 mg/kg at Weeks 0 and 4 and then every 8 weeks thereafter) in combination with methotrexate (b) (4) for the RA indication. Janssen proposed that (b) (4) data from Study 3001 (using the proposed IV regimen) and the following data would provide independent substantiation of the efficacy of the proposed IV regimen: (b) (4) data using IV golimumab in Study 12 (different IV regimen) and (b) (4) data from 3 RA trials using SC golimumab (given that the proposed IV regimen resulted in greater exposures than the SC regimen and that the IV and SC formulations had the same drug substance).

The FDA stated that in general positive results from two adequate and well-controlled trials using the proposed regimen are required to support efficacy of a new product. Although the 1998 Guidance outlines situations where a single positive trial using the proposed dose regimen could be used to support efficacy (i.e., Study 3001), the adequacy of this approach would be a review issue. The FDA recommended that Janssen provide data from another IV trial or a thorough rationale and justification for their single study approach in their sBLA submission. The FDA stated that robust radiographic results at Week 24 from Study 3001 may help provide supportive evidence for the efficacy of the IV regimen in their sBLA submission.

The FDA expressed the following concerns about Janssen’s proposed data to independently substantiate efficacy:

1. Exposure to golimumab after IV administration may not be greater than exposures after SC administration at all times during the dosing intervals. If exposures were lower at any point during the dosing interval, then it may not be possible to extrapolate efficacy data from the SC golimumab

RA program. Median trough levels observed after IV golimumab administration in Study 3001 (i.e., 0.28 and 0.22 µg/mL at Weeks 12 and 20, respectively) may be lower than median trough levels observed in a similar population after SC dosing in Study 6 (0.57 µg/mL at Weeks 12 and 20). Janssen stated that inter-study PK variability accounted for the differences in observed values across different studies and PK simulations showed that the median trough concentrations across studies were similar (0.3 µg/mL). The FDA responded that Janssen may have to account for the differences in the observed and simulated results or provide a rationale of why the lower trough levels with IV vs. SC golimumab are not clinically meaningful to support their proposal to extrapolate the SC efficacy data.

2. Study 12 does not provide independent substantiation of efficacy given that it used different dosing regimens than the proposed regimen and that the primary efficacy endpoint was not successful.

QUESTIONS AND PRELIMINARY RESPONSES

Question 1: Does the Agency agree with the Sponsor's proposal for including both the SC and IV routes of administration in one SIMPONI® USPI?

Division Response: No, the data that you plan to submit in your sBLA is insufficient to support the use of a single U.S. prescribing information (USPI) for both the SC and IV routes of administration (ROA).

We recommend that the SC and IV ROA of golimumab have separate USPI because they have different pharmacokinetic characteristics (e.g., C_{max} and AUC), dosing regimens (flat vs. weight based dose, amount of product, frequency, bioavailability), may have different indications (RA vs. RA, PsA, and AS), may have different claims [REDACTED] (b) (4) and may have differences in efficacy or safety.

Furthermore, to reduce the chance of possible medication errors (e.g., use of IV liquid in a vial presentation for subcutaneous use due to two products in the market), we recommend separate USPI for the SC and IV products.

Discussion: No discussion.

Question 2: Based on the described statistical analyses and to be consistent with the current SIMPONI SC and other anti-TNFα agent labels, does the Agency agree that the selected RA signs and symptoms and physical function data are clinically relevant to display in the USPI for IV golimumab? If so, will the Agency accept a retrospective multiplicity adjustment to control the Type 1 error in order to support these labeling statements?

Division Response: You propose to include the following data in the IV golimumab USPI: Proportion of subjects with ACR 20, 50, and 70 responses at Weeks 14 and 24; median percent improvement from baseline in the individual ACR components at Week 14; percent of subjects achieving ACR 20 response by visit; change in HAQ-DI score from baseline to Week 24; and proportion of HAQ responders (change from baseline ≥ 0.22 at Week 24). Because additional data are needed in your BLA program, we cannot make specific comments regarding labeling at this time. We have the following general comments about endpoints relevant to labeling:

- In general, ACR responses, ACR response over time, improvement in ACR components, and HAQ results have been included in the USPI of other products approved for RA. However, many of these endpoints in Study 3001 did not have appropriate multiplicity adjustments, which may limit inclusion in the label.

- *If results from the proportion of patients with a DAS28(CRP) score less than 2.6 are included, it is likely that the proportion of patients with 0, 1, 2, and 3 or more active joints will be included.*
- *Your proposal to include the percent of subjects achieving an ACR response (b) (4) may be potentially misleading if the ACR responses (or continuous sign and symptom endpoints) decrease at Week 4 (golimumab exposure is lower).*

In addition, we have the following comments on your proposed statistical approach in Study 3001.

- *You propose application of multiplicity adjustments retrospectively in Study 3001. We consider retrospective adjustments as post hoc analyses.*
- *Randomization in your Phase 3 trials was adaptive. As such, we consider re randomization tests, rather than Cochran Mantel Haenszel tests or analyses of covariance, appropriate to evaluate statistical significance of endpoints proposed for inclusion on the label.*
- *Your protocol for Study 3001 states that patients will be considered ACR20 treatment failures at Week 14 if they discontinue study agent infusions due to an unsatisfactory therapeutic effect; increase in baseline MTX or baseline oral steroid dose for RA; or initiate new DMARDs or oral, IV, or IM steroids for RA. In your sBLA submission, submit a sensitivity analysis for all dichotomous endpoints including the primary endpoint where all patients who discontinue treatment for any reason prior to the endpoint assessment are treatment failures (non-responder imputation).*
- *In your sBLA submission, submit 'retrieved dropout' analyses on any continuous endpoints proposed for inclusion in the USPI. Such analyses use data observed after termination of assigned treatment, if collected, analyzed according to originally assigned treatment group.*

Sponsor Clarification Request: The Sponsor would like the FDA to provide further clarity on this analysis at the meeting.

Discussion: The FDA stated that the "retrieved dropout" analyses are intention to treat analyses which include data collected after patients change from their initial treatment regimen assigned at randomization. The FDA reminded Janssen to provide adequate information in the data files to identify these patients in their sBLA submission.

Post Meeting Clarification: For ACR response endpoints in your sBLA submission, consider as treatment failures (or nonresponders) all patients who discontinue randomized treatment, increase MTX or steroid doses or initiate DMARDS for any reason prior to endpoint assessment.

(b) (4)

Division Response: *No, see our Introductory Comments and our response to Question 1.*

Discussion: No discussion.

Question 4: *Does the Agency agree with the Sponsor's proposal for describing the IV safety data in the USPI?*

Division Response: *No, see our Introductory Comments and response to Question 1.*

Discussion: No discussion.

Question 5: Does the Agency agree with the Sponsor's approach for cross-referencing previously submitted information from the SIMPONI® SC BLA 125289 to support the BLA for IV golimumab?

Division Response: Your proposal to cross reference data that has been previously submitted as per the "Providing Regulatory Submission in Electronic Format - Human Pharmaceutical Product Applications and Related Submission Using the eCTD specifications" Guidance and per 21 CFR 314.50 (g)(1) is acceptable.

Discussion: No discussion.

Question 6: Does the Agency agree with Sponsor's proposal to request a waiver for conducting a pediatric study in pJIA with IV golimumab?

Division Response: In general, your proposal for a waiver for conducting a pediatric study of IV golimumab in patients with polyarticular JIA is reasonable. However, the final decision will depend upon a review of your waiver request including your justification for the waiver in your sBLA submission.

Discussion: No discussion.

(b) (4)

Sponsor Clarification Request: The Sponsor notes that in this response and in other responses, the FDA refers to the initial file for IV RA as an sBLA. The Sponsor would like to confirm at the meeting if the initial file is a BLA or an sBLA.

Discussion: The FDA informed Janssen that the submission for the IV formulation of golimumab should come in as a supplemental BLA; not an original BLA. The FDA stated that this decision is not made at the division level and suggested that Janssen contact Mike Jones of the User Fee Office if they wanted further clarification.

(b) (4)

Overall Safety Presentation, Plan for Evaluating the Safety of Golimumab, and Proposed Approach for Narratives and CRFs

Question 9: *Does the FDA agree that the IV safety database that will be included in the initial BLA and the 4-month Safety Update as outlined in Table 1 is adequate to characterize the safety profile of IV golimumab?*

Division Response: *No, we do not agree. At the time of the sBLA submission you will have about 394 and 80 patients exposed to your proposed IV dose regimen for about 6 and 12 months, respectively. The amount of safety information at the time of the sBLA submission should be sufficient to assess the safety profile of your proposed IV dose regimen as a stand alone program.*

Sponsor Clarification Response: As discussed above, the Sponsor is adopting FDA's advice in not making the IV RA submission in Nov 2011 as previously planned. In accordance with FDA's recommendation, the Sponsor plans to delay our submission in order to collect additional safety data with the IV dosage form. As such, in our new plan for the initial BLA file, we propose to provide safety data from Study 3001 from approximately 550 patients exposed for 24 weeks and approximately 350 patients exposed with the recommended maintenance IV dosing regimen for 1-year. This proposal is consistent with the discussions at the EoPII meeting for the IV program as follows:

At the EoPII meeting held on May 18th, 2009 (FDA Meeting Minutes, response to Question 4, pages 6-7):

- The FDA noted that since malignancy signals were seen in trials of similar size (C0524T03 in asthma (N=309) and C0524T12 (N=643)), the size of the proposed trial could be sufficient to evaluate an imbalance of malignancies with the new dose regimen.
- The Sponsor indicated that we would have around 300 patients treated with the new IV regimen (2 mg/kg q 8 wks) for at least one year.

Further, Study 3001 has not shown an imbalance in malignancies.

In addition, as requested by the FDA in their additional pre-meeting comments, the Sponsor will include available safety data (e.g., deaths, serious adverse events, serious infections, malignancies) from all IV golimumab studies including Study CNTO148ART3002 (switch study in patients with RA) and Study C0524T16 (PURSUIT, induction Phase 3 trial in patients with ulcerative colitis) in the initial BLA.

Discussion: The FDA acknowledged Janssen's plan to include additional safety data from Study 3001 in their initial sBLA submission. However, the FDA stated additional safety data will be required in the initial sBLA submission to support the safety of the proposed IV regimen because:

1. IV dosing results in much greater exposures (C_{max} and AUC) than the SC regimen.
2. Dose-related increases in adverse reactions have been seen in several TNF inhibitor trials.

3. There were a greater number of deaths in the golimumab IV groups compared to the control group in Study 12 (6 and 0 deaths, respectively); although, no firm conclusions could be made because of the imbalance of exposure.
4. There was a greater number of malignancies in the 4 mg/kg IV dose regimen compared to the 2 mg/kg and control groups in Study 12; although, no firm conclusions could be made because of the imbalance of exposure.

Janssen stated that there was a lower rate of deaths and malignancies in the IV golimumab group (the proposed to-be-marketed regimen) compared to the control group in Study 3001, and noted that TNF inhibitors as a class are generally well-characterized. The FDA answered that their recommendations on the adequacy of the size of the safety database are determined by a complete review of all the safety data available, not just a single study. The FDA stated that Janssen needs to provide enough data to clearly show an adequate benefit/risk for the use of the proposed IV regimen.

Question 10(a): Does the FDA agree with the proposed plan for presenting safety data in the IV BLA?

Division Response: *Yes, your proposal seems reasonable.*

Discussion: No discussion.

Question 10(b): *Does the FDA agree with the proposed plan for presenting safety data in the 4-month safety update*

Division Response: *Yes, your proposal seems reasonable.*

Discussion: No discussion.

Question 11: *Does the FDA agree with the proposed approach for providing narratives and CRFs in the BLA?*

Division Response: *Yes, your proposal seems reasonable. However, we may need additional narratives and CRFs if we detect safety signals during our BLA review.*

Discussion: No discussion.

Additional Comments

1. *Provide a description of the intravenous dosage form used in Studies 12 and 3001 and the proposed to-be-marketed dosage form. The descriptions should address the formulation, container/closure, and a summary of manufacturing, batch release and stability information.*

Sponsor Clarification Request: The Sponsor would like the FDA to provide further clarity on this request at the meeting.

Discussion: Janssen stated their intention to include all required descriptions of the to-be-marketed 12.5 mg/ml vial intravenous dosage form in the pharmaceutical development section and other relevant parts of the sBLA. The information will include a summary of the formulation development, a container/closure description, a manufacturing description, a batch analysis of the new formulation lots, as well as a biochemical comparability study with the PFS form, including extended characterization, stability information and lot release testing. Information regarding the lots used in studies 12 and 3001 has been submitted to IND 9925, serial number 118 FDA stated that this seems comprehensive.

2. *For your sBLA submission, include safety data (e.g., deaths, serious adverse events, serious infections, malignancies) from all your studies of IV golimumab including Study CNTO148ART3002 (switch study*

in patients with RA) and Study C0524T16 (PURSUIT, induction Phase 3 trial in patients with ulcerative colitis).

Sponsor Clarification Response: The Sponsor acknowledges the FDA's comment. See our response to Question 9 above.

Discussion: No discussion.

3. *Study CNTO148ART3002 cannot be used to support comparative claims of golimumab to adalimumab or etanercept because there is no blinded controlled comparison and there is no heterogeneous TNF inhibitor control group. In general, two adequate and well-controlled superiority trials are needed to support a comparative efficacy claim.*

Sponsor Clarification Response: The Sponsor agrees and did not ever intend to use this trial to support comparative claims in the USPI.

Discussion: No discussion.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

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

/s/

MIRANDA B RAGGIO
10/03/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125433Orig1s000

Trade Name:

SIMPONI ARIA, 50mg/4 mL vial

Generic Name:

golimumab

Sponsor:

Janssen Biotech, Inc.

Approval Date:

July 18, 2013

Indications:

Treatment of moderately to severely acute Rheumatoid Arthritis (RA) in adults in combination with methotrexate.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
125433Orig1s000

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

APPROVAL LETTER



BLA 125433/0

BLA APPROVAL

Janssen Biotech, Inc.
Welsh & McKean Roads
P.O. Box 776
Spring House, PA 19477

Attention: Salvatore Morello
Director, Global Regulatory Affairs

Dear Mr. Morello:

Please refer to your Biologics License Application (BLA) dated and received September 18, 2012, submitted under section 351(a) of the Public Health Service Act for Simponi Aria (golimumab), 50 mg/4 mL vial.

We acknowledge receipt of your amendments dated October 19, November 8 and 13, and December 6, 14, and 21, 2012, and January 2 and 17, February 20, March 1, April 16, May 2, 7 (two), 10 (two), and 28, June 3, 5, 10, 14, 26, and 27, and July 1, 9, 12, and 17, 2013.

LICENSING

We have approved your BLA for Simponi Aria (golimumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Simponi Aria under your existing Department of Health and Human Services U.S. License No. 1864. Simponi Aria is indicated for treatment of moderate to severely active Rheumatoid Arthritis (RA) in adults in combination with methotrexate.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture golimumab (for infusion) drug substance at Janssen Biologics/Barnahely, Ringaskiddy, Co. in Cork, Ireland, and Janssen Biologics B.V. in Leiden, The Netherlands. The final formulated product will be [REDACTED] ^{(b) (4)}, labeled, and packaged at Cilag AG, Schaffhausen, Switzerland. The drug product may also be labeled and packaged at AndersonBrecon, Inc. at Rockford, Illinois, USA. You may label your product with the proprietary name, Simponi Aria, and will market it in single use sterile solution of 50 mg/4 mL vials.

DATING PERIOD

The dating period for Simponi Aria shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as [REDACTED] (b) (4)

Any changes in the manufacturing, testing, packaging, or labeling of Simponi Aria, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your July 12, 2013, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for golimumab (for intravenous infusion) was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues in the intended population.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for neonates and infants up to 1 year and 11 months of age years because necessary studies are impossible or highly impracticable. This is because juvenile idiopathic arthritis (JIA) does not present at birth and a small number of children in this age group are diagnosed with JIA.

We are deferring submission of your pediatric study for children 2 years of age to 17 years and 11 months for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

PMR #1: To conduct a trial that will evaluate the safety, efficacy, PK/PD and immunogenicity of IV golimumab in pediatric patients between the ages 2 to 17 years and 11 months with active juvenile idiopathic arthritis (JIA) despite standard therapy with methotrexate.

The timetable you submitted on July 9, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	12/2013
Trial Completion:	06/2018
Final Report Submission:	12/2018

Submit the protocol(s) to your IND 9925, with a cross-reference letter to this BLA.

Report of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the report, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We remind you of your postmarketing commitments:

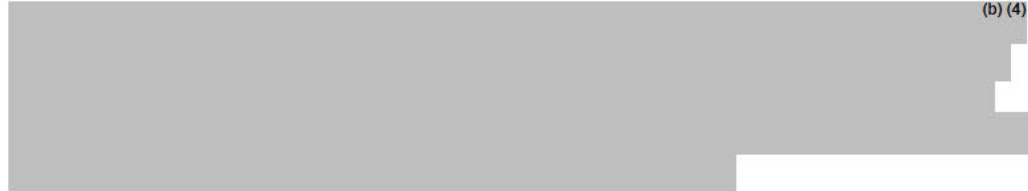
PMC #2: Increase in-process control sample size to (b) (4) and adjust acceptance criteria to (b) (4)

In addition, implement the new bioburden sample size action and alert limits after production of 10 batches. The Final Report Submission should include the new in-process limits.

The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2014

PMC #3:



The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2014

PMC #4: Perform the Rabbit Pyrogen Test on two batches of Golimumab FVP (IV) DP. Submit the results as a CBE-0 supplement.

The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2013

PMC #5: Perform LAL spiking studies in undiluted golimumab FVP (IV) DP samples and test the samples after different hold times.

The timetable you submitted on July 9, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2014

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected study completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

If you have any questions, call Christine Chung, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

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/s/

SARAH K YIM
07/18/2013
Signing for Badrul Chowdhury, M.D., Ph.D.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

CHEMISTRY REVIEW(S)

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing³ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: July 19, 2013

Applicant Name: Janssen Biotech, Inc.

U.S. License #: 1864

STN(s): 125433/0

Product(s): Simponi® (golimumab for infusion)

Short summary of application: Original BLA for the use of golimumab for infusion for the treatment of Rheumatoid Arthritis.

FACILITY INFORMATION

Manufacturing Location: Ireland
Firm Name: Janssen Biologics (Ireland)
Address: Barnahely, Ringaskiddy, Co.
Cork, Ireland

FEI: 3007029098

Short summary of manufacturing activities performed: DS manufacture, Release testing of DP, stability testing.

This site was inspected by IOG [REDACTED] ^{(b) (4)} and classified VAI. This was a routine GMP surveillance inspection covering golimumab manufacturing and testing operations. The CBI and TRP profiles were updated and are acceptable.

Manufacturing Location: Switzerland
Firm Name: Cilag AG
Address: Hochstrasse 201, CH-8200
Schaffhausen, Switzerland
FEI: 3002806695

Short summary of manufacturing activities performed: Drug Product manufacturing, release testing of DP, labeling and packaging.

This site was inspected by IOG [REDACTED] (b) (4) and classified VAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing operations. The SVS profile was updated and is acceptable.

Manufacturing Location: The Netherlands
Firm Name: Janssen Biologics B.V.
Address: Einsteinweg 101, 2333 CB
Leiden, The Netherlands
FEI: 3002806632

Short summary of manufacturing activities performed: Release testing of DP, stability testing.

This site was inspected by IOG [REDACTED] (b) (4) and classified VAI. This was a routine GMP surveillance inspection covering biotech drug product testing operations. The CBI profile was updated and is acceptable.

Manufacturing Location: Illinois
Firm Name: AndersonBrecon, Inc.
Address: 4545 Assembly Drive
Rockford, IL 61109, USA
FEI: 1421377

Short summary of manufacturing activities performed: Drug Product labeling and packaging.

This site was inspected by CHI-DO [REDACTED] (b) (4) and classified NAI. This was a routine GMP surveillance inspection covering drug product labeling and packaging operations. The [REDACTED] (b) (4) profile was updated and is acceptable.

OVERALL RECOMMENDATIONS:

There are no pending or ongoing compliance actions that prevent approval of this BLA.

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other

procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

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/s/

RANJANI PRABHAKARA
06/25/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies, WO Bldg 64, HFD-123
10903 New Hampshire Ave., Silver Spring MD 20903

The Quality Team Leader's Executive Summary

From: Kurt Brorson, Ph.D., Product Quality Team Leader
Division of Monoclonal Antibodies (DMA)

Through: Kathleen A. Clouse, Ph.D., Director, DMA

BLA Number: 125433

Product: Simponi aria

Sponsor: Janssen, Inc.

Date of Review: May 28, 2013

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of Simponi aria is well controlled, and leads to a high quality product that is sufficient to meet quality parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use from a product quality perspective (under conditions specified in the package insert).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable (language subject to ongoing negotiation)

None.

II. Summary of Quality Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- Golimumab is a recombinant human monoclonal antibody that binds human TNF. It is a second generation version of Remicade (a chimeric anti-TNF mAb currently marketed for RA, Crohn's disease and other clinical indications). Golimumab is a human IgG1κ monoclonal antibody, with an approximate molecular weight of 149,700 daltons and isoelectric points between 8.7 and 9.3. The golimumab expression construct was generated from xeno-mice, which are genetically altered to express human immunoglobulins. The antibody drug substance is manufactured using standard bioprocess technology at (b) (4) and takes place at Centocor BV (CBV) Leiden, Holland and Centocor Biologics Ireland Limited (CBIL), Cork Ireland.
- The currently marketed Simponi liquid pre-filled syringe drug product is filled (b) (4)
- Simponi aria will be indicated for similar rheumatologic indications as the prefilled syringe Simponi dosage form licensed in 2009.
- Simponi aria uses the same drug substance (as well as DS process and analytical assays) used to produce the Simponi (golimumab) pre-filled syringe (PFS) approved in BLA 125289. The presentation has changed from a PFS containing 100 mg/mL mAb to a vial/stopper format with 12.5 mg/mL mAb intended for IV injection.

- Simponi aria final drug product (FDP) will be supplied as a sterile, preservative-free liquid formulation in vials. The formulation components are as follows: 12.5 mg/ml golimumab, 9.5 mM histidine, 4.5% w/v sorbitol, and 0.015% w/v polysorbate 80 at pH 5.5. Except for the golimumab antibody itself, all ingredients meet compendial requirements (USP/NF, Ph. Eur. and/or JP) and are commonly used for formulation of biopharmaceuticals. No excipients are of human or animal origin. All are present in the approved pre-filled syringe product, but in some cases at lower concentrations. As this is a diluted version of the pre-filled syringe formulation, it represents a lower risk dosage form.
- The container closure system is comprised of USP Type I (b) (4) glass vials (b) (4) stoppers (b) (4).
- Simponi aria drug product is manufactured at the Cilag AG facility in Schaffhausen, Switzerland. Certain release tests may be performed at Janssen BV (Leiden Holland) or Janssen Biologics (Ireland). Inspection of the Cilag AG drug product manufacturing site was waived by BMAB/OC (b) (4) on the basis of previous inspectional history of this multi-product fill/finish site.
- The validated commercial lot size range is (b) (4) vials, with each vial having a fill volume of 4.0 mL.
- Sufficient drug product batches were analyzed to validate the vial fill manufacturing process. Product-and process-related contaminants are within proposed specification limits. Validated testing to assure microbial and viral safety (controlled during drug substance manufacture) is in place.
- Drug product lot testing utilizes the same or similar analytical assays as those validated in the approved and licensed BLA (STN 125289) for PFS golimumab.
- Studies of the compatability of Simponi aria were conducted (b) (4) mg/mL to 0.25 or 6.0 mg/mL in PVC/DEHP and PO-PA infusion bags containing 0.9% (b) (4). (b) (4) The results of testing for bioactivity, protein concentration, appearance, pH, visible particulate matter, sub-visible particulate matter, turbidity, aggregates, and monomer, indicate that (b) (4) are comparable and conform with all test acceptance criteria.
- Simponi aria should be stored at 2-8°C; it does not contain preservatives. Based on stability data trend analysis of Simponi aria, the data support the requested 24-month commercial expiry period at the 2-8°C (intended) storage condition inside the original carton protected from light.

B. Description of How the Drug Product is Intended to be Used

- Simponi aria is intravenous (IV) golimumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). The BLA claims a treatment benefit for IV golimumab in combination with methotrexate (MTX) (b) (4) (b) (4) adult patients with moderately to severely active rheumatoid arthritis (RA). Based upon efficacy and safety data through 52 weeks, the BLA proposes an IV golimumab dosing regimen of 2 mg/kg at Weeks 0 and 4 and q8w thereafter.

C. Basis for Approvability

- Simponi aria is manufactured by a robust process with precautions for contamination. It is manufactured consistently, leading to a safe and effective product for the intended indication; sufficient product quality data support its licensure.
- **ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION.** Janssen contends that Simponi aria qualifies for a categorical exclusion under 21 CFR 25.31(c), and to their knowledge, no extraordinary circumstances exist. We concur with this conclusion. There is minimal impact expected of Simponi aria manufacturing on the environment.

I. LIST OF DEFICIENCIES TO BE COMMUNICATED

None.

IV. ADMINISTRATIVE

A. Reviewer's Signature

Product Quality Reviewer: Erik Read, Ph.D

B. Endorsement Block

Product Division Team Leader: Kurt Brorson, Ph.D.

Product Division Director: Kathleen A. Clouse, Ph.D.

C. CC Block

DMA LCB Chief: David Frucht, M.D.

OBP Office Director: Steven Kozlowski, M.D.

Medical Officer: Rosemarie Neuner, M.D.

Clinical Team Leader: Sarah Yim, M.D.

Division of Monoclonal Antibodies File: BLA STN 125433

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/s/

KURT A BRORSON
06/19/2013

KATHLEEN A CLOUSE STREBEL
06/19/2013

BLA STN 125433

Golimumab

Janssen Biotech, Inc

**Erik Read, Ph.D., Senior Staff Fellow
Kurt Brorson, Ph.D., Research Biologist
Kathleen Clouse, Ph.D., Director, DMA**

Division of Monoclonal Antibodies

OBP CMC Review Data Sheet

1. **BLA#:** STN 125433
2. **REVIEW DATE:** unknown
3. **PRIMARY REVIEW TEAM:**
Medical Officer: Rosemarie Neuner, MD, MPH
Pharm/Tox:
Product Quality Team: Erik Read, Ph.D; Kurt Brorson, Ph.D
BMT or Facilities: Maria Candau-Chacon
Clinical Pharmacology: Liang Zhao
Statistics: Ruthanna Davi
OBP Labeling: Kim Rains
RPM: Christine Chung

4. **MAJOR GRMP DEADLINES**
Filing Meeting: unknown
Mid-Cycle Meeting: February 20, 2013
Wrap-Up Meeting: June 11, 2013
Primary Review Due: June 13, 2013
Secondary Review Due: unknown
CDTL Memo Due: not set
PDUFA Action Date: July 19, 2013

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)

7. **DRUG PRODUCT NAME/CODE/TYPE:**
 - a. **Proprietary Name:** CNTO 148
 - b. **Trade Name:** Simponi Aria
 - c. **Non-Proprietary/USAN:** golimumab
 - d. **CAS name:** 476181-74-5

- e. **Common name:** golimumab
- f. **INN Name:** golimumab
- g. **Compndial Name:** not applicable
- h. **OBP systematic name:** MAB HUMAN (IGG1) ANTI CAA26669 (TNF-alpha_HUMAN) [CNTO 148]
- i. **Other Names:** ATC L04AB06; ChEMBL1201833; PubChem 47206264; KEGG D04358; UNII 91X1KLU43E; IMMUNOGLOBULIN G1, ANTI-(HUMAN TUMOR NECROSIS FACTOR .ALPHA.) (HUMAN MONOCLONAL CNTO 148 .GAMMA.1-CHAIN), DISULFIDE WITH HUMAN MONOCLONAL CNTO 148 .KAPPA.-CHAIN), DIMER

- 8. **PHARMACOLOGICAL CATEGORY:**
- 9. **DOSAGE FORM:** viald liquid
- 10. **STRENGTH/POTENCY:** 12.5 mg/mL
- 11. **ROUTE OF ADMINISTRATION:** intravenous
- 12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
		(b) (4)	Yes	Exists
			Yes	Exists

- 13. **INSPECTIONAL ACTIVITIES:** WAIVED
- 14. **CONSULTS REQUESTED BY OBP:** NONE
- 15. **QUALITY BY DESIGN ELEMENTS**

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

- 16. **PRECEDENTS**
- 17. **ADMINISTRATIVE**

A. Signature Block

Kathleen Clouse, Ph.D., Director, Division of Monoclonal Antibodies	
Kurt Brorson, Ph.D., Research Biologist, Division of Monoclonal Antibodies	
Erik K. Read, Ph.D. Primary Reviewer Division of Monoclonal Antibodies	

B. CC Block

Recipient	Date
Christine Chung	
Patrick Swann	

21 Pages have been Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

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/s/

ERIK K READ
05/29/2013

KURT A BRORSON
05/29/2013

**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: March 7, 2013

From: Reyes Candau-Chacon, Ph.D., OC/OMPQ/DGMP/BMAB
Kurt Brorson, Ph.D., OPS/OBP/DMA

To: BLA File, STN 125433/0

Through: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMP/BMAB

Subject: BLA

Applicant: Janssen Biotech, Inc.

Facility: Cilag AG, Hochstrasse 201, CH-8200 Schaffhausen, Switzerland (FEI #1018495)

Product: Simponi IV (golimumab)

Dosage: Sterile, single-use solution at a concentration of 12.5 mg/mL (50 mg/4 mL solution) in glass vials to be delivered by intravenous infusion at 2 mg/kg

Indication: Treatment of moderate to severely active Rheumatoid Arthritis (RA) in adults in combination with methotrexate

Waiver Recommendation

Based on the compliance history of the firm, the current GMP status, and the fact that Cilag AG, Schaffhausen, Switzerland has been approved to manufacture several licensed products using similar manufacturing processes, we recommend that the pre-license inspection of Cilag AG drug-product manufacturing facility in Schaffhausen, Switzerland (FEI # 3002806695) be waived for STN 125433/0.

Summary

PAS 125433/0 was submitted by Janssen Biotech, Inc. to license golimumab for infusion. Cilag AG is the drug product manufacturing facility for this BLA.

Golimumab is a monoclonal antibody that binds to the trans-membrane bioactive forms of human tumor necrosis factor TNF α preventing the binding of TNF α to its receptor and inhibiting TNF α biological activity. A 100 mg/L pre-filled syringe version of this product was approved in 2009 under STN 125289. Golimumab IV is intended to be used in combination with methotrexate in adult patients with moderate to severely active Rheumatoid Arthritis.

Janssen Biotech, Inc. seeks approval of a more dilute version of the existing product in a lower risk container closure system. The new version is 12.5 mg/mL (50 mg/4 mL) solution in glass vials to be delivered by intravenous infusion. The drug substance or excipients have not changed.

Facility Information



Supporting Information for the inspection waiver:

The following information is provided in support of waiving the pre-approval inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

Cilag AG, Schaffhausen is approved to manufacture (b) (4) other US-licensed products.

2. *FDA has not inspected the establishment in the last 2 years.*

The establishment was inspected by FDA Team Biologics from (b) (4)

3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

The inspection was classified VAI with acceptable GMP status.

4. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities / buildings / areas.*

Cilag AG, Schaffhausen is approved to manufacture multiple products. The last inspection (b) (4) covered the SVS profile of several biological products (b) (4)

. In addition, the inspection covered (b) (4) other 11 NDA/ANDA APIs marketed in the U.S.

5. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.*

The manufacturing process for Simponi IV (golimumab) is similar to other drug product processes manufactured in the same facility. The drug substance has been reviewed and approved by FDA previously under STN 125289 under a more concentrated protein formulation (100 mg/mL) and a higher-risk container/closure system (pre-filled syringes).

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/s/

REYES CANDAU-CHACON
03/07/2013

PATRICIA F HUGHES TROOST
03/11/2013

KURT A BRORSON
03/11/2013

KATHLEEN A CLOUSE STREBEL
03/11/2013

JOSEPH D DOLESKI
03/11/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing³ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: July 19, 2013

Applicant Name: Janssen Biotech, Inc.
U.S. License #: 1864
STN(s): 125433/0
Product(s): Golimumab for infusion

Short summary of application: Original BLA for the use of golimumab for infusion for the treatment of Rheumatoid Arthritis.

FACILITY INFORMATION

Manufacturing Location: USA
Firm Name: AndersonBrecon, Inc.
Address: AndersonBrecon, Inc.; 4545 Assembly Drive; Rockford, IL 61109, USA
FEI: 1421377

Short summary of manufacturing activities performed: Drug Product labeling and packaging.

Inspected by CHI-DO [REDACTED] ^{(b) (4)} and classified NAI. This CGMP inspection covered packaging and labeling operations and found them acceptable.

OVERALL RECOMMENDATION:

There are no pending or ongoing compliance actions that prevent approval of this BLA. Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation.

³ The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

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/s/

MAHESH R RAMANADHAM
02/08/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

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- 2) a final TB-EER 15-30 days prior to the action date

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APPLICATION INFORMATION

PDUFA Action Date: July 19, 2013

Applicant Name: Janssen Biotech, Inc.
U.S. License #: 1864
STN(s): 125433/0
Product(s): Golimumab for infusion

Short summary of application: Original BLA for the use of golimumab for infusion for the treatment of Rheumatoid Arthritis.

FACILITY INFORMATION

Manufacturing Location:
Firm Name: Cilag AG
Address: Hochstrasse 201, CH-8200 Schaffhausen, Switzerland
FEI: 3002806695

Short summary of manufacturing activities performed: Drug Product manufacturing, release testing of DP, labeling and packaging.

Inspected by IOG [REDACTED] (b) (4) and classified VAI. This CGMP inspection covered sterile manufacturing operations and found the SVL / SVS profiles updated and acceptable.

FACILITY INFORMATION

Manufacturing Location:
Firm Name: Janssen Biologics B.V.
Address: Einsteinweg 101, 2333 CB Leiden, The Netherlands
FEI: 3002806632

Short summary of manufacturing activities performed: Release testing of DP, stability testing.

Inspected by IOG [REDACTED] (b) (4) and initially classified OAI. This CGMP inspection observed CGMP deficiencies related to the failure to prevent microbial and endotoxin contamination [REDACTED] (b) (4). Action on this BLA should not be taken without an updated compliance recommendation.

FACILITY INFORMATION

Manufacturing Location:

Firm Name: Janssen Biologics (Ireland)

Address: Barnahely, Ringaskiddy, Co. Cork, Ireland

FEI: 3007029098

Short summary of manufacturing activities performed: Release testing of DP, stability testing.

Inspected by IOG [REDACTED] ^{(b) (4)} and classified VAI. This CGMP inspection covered golimumab operations and found the TRP profile updated and acceptable.

OVERALL RECOMMENDATION:

The compliance status of Janssen Biologics B.V. is initially unacceptable. Please resubmit this TB-EER 30 days prior to the planned action date for an updated compliance evaluation.

³

The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

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/s/

MAHESH R RAMANADHAM
02/01/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

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- 2) a final TB-EER 15-30 days prior to the action date

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APPLICATION INFORMATION

PDUFA Action Date: July 19, 2013

Applicant Name: Janssen Biotech, Inc.
U.S. License #: 1864
STN(s): 125433/0
Product(s): Golimumab for infusion

Short summary of application: Original BLA for the use of golimumab for infusion for the treatment of Rheumatoid Arthritis.

FACILITY INFORMATION

Manufacturing Location:
Firm Name: Cilag AG
Address: Hochstrasse 201, CH-8200 Schaffhausen, Switzerland
FEI: 3002806695

Short summary of manufacturing activities performed: Drug Product manufacturing, release testing of DP, labeling and packaging.

Inspected by IOG [REDACTED] (b) (4) and classified VAI. This CGMP inspection covered sterile manufacturing operations and found the SVL / SVS profiles updated and acceptable.

FACILITY INFORMATION

Manufacturing Location:
Firm Name: Janssen Biologics B.V.
Address: Einsteinweg 101, 2333 CB Leiden, The Netherlands
FEI: 3002806632

Short summary of manufacturing activities performed: Release testing of DP, stability testing.

Inspected by IOG [REDACTED] (b) (4) and classified NAI. This CGMP inspection covered operations for golimumab and found them acceptable. The BTP profile was updated and found acceptable.

FACILITY INFORMATION

Manufacturing Location:

Firm Name: Janssen Biologics (Ireland)

Address: Barnahely, Ringaskiddy, Co. Cork, Ireland

FEI: 3007029098

Short summary of manufacturing activities performed: Release testing of DP, stability testing.

Inspected by IOG [REDACTED] ^{(b) (4)} and classified VAI. This CGMP inspection covered golimumab operations and found the TRP profile updated and acceptable.

OVERALL RECOMMENDATION:

There are no pending or ongoing compliance actions that prevent approval of this supplement. Please resubmit this TB-EER 15-30 days prior to the planned action date for a final compliance recommendation.

³

The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

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/s/

MAHESH R RAMANADHAM
12/19/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s005

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

BLA	125433
Submission Date:	09/18/2012
Proposed Brand Name	SIMPONI ARIA [®]
Submission Type	BLA
Generic Name	Golimumab
OCP Reviewer	Liang Zhao, Ph.D.
Team Leader (Acting)	Suresh Doddapaneni, Ph.D.
Pharmacometrics Reviewer	Liang Zhao, Ph.D.
Pharmacometrics Team Leader (Acting)	Atul Bhattaram, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Pulmonary, Allergy and Rheumatology Products
Sponsor	Jassen Biotech, Inc.
Formulation; Strength(s); Administration Route	50 mg/4 mL vial; Intravenous infusion
Approved Indication	• Moderately to severely active Rheumatoid Arthritis (RA) in adults, in combination with methotrexate • Active Psoriatic Arthritis (PsA) in adults, alone or in combination with methotrexate • Active Ankylosing Spondylitis in adults (AS)
Proposed Indication	Moderately to severely active Rheumatoid Arthritis (RA) in adults, in combination with methotrexate.
Approved Dosage Regimen	50 mg administered by subcutaneous injection once a month
Proposed Dosage Regimen	2 mg/kg intravenous infusion at weeks 0 and 4, then every 8 weeks

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1 Executive Summary

1.1 Recommendation

From a Clinical Pharmacology perspective, the application is acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

A relatively higher mean C_{max} and dosing-interval normalized AUC were observed in patients with RA following a single IV administration of 2 mg/kg SIMPONI ARIA than their corresponding values following a single SC administration of 100 mg SIMPONI. In addition, it is expected that the dosing interval normalized steady state AUC following every 8 week IV administration of 2mg/kg SIMPONI ARIA be more than the steady state AUC following monthly SC administration of 50 mg SIMPONI.

The systemic clearance of golimumab was estimated to be 6.9 ± 2.0 ml/day/kg in healthy subjects and 7.6 ± 2.0 ml/day/kg in patients with RA following a single IV administration of 2 mg/kg SIMPONI ARIA. Correspondingly, the mean terminal half-lives were estimated to be 12 ± 3 days in healthy subjects and 14 ± 4 days in RA patients. The mean volumes of distribution were estimated to be 115 ± 19 ml/kg in healthy subjects and 151 ± 61 ml/kg in RA patients. The volume of distribution of golimumab may indicate that golimumab is distributed primarily in the circulatory system with limited extravascular distribution.

Following the proposed IV regimen, serum concentrations reached steady state by Week 12. With concomitant use of MTX, treatment with 2 mg/kg golimumab every 8 weeks resulted in a mean steady-state trough serum concentration of 0.35 ± 0.38 µg/mL at Week 12, 0.31 ± 0.44 µg/mL at Week 20, and 0.42 ± 0.54 µg/mL at week 52. Based on the population pharmacokinetic (PK) analysis, the concomitant use of MTX reduced golimumab CL by 8.7% but the use of MTX did not demonstrate a statistically significant effect on golimumab CL ($p > 0.001$).

Patients who developed anti-golimumab antibodies generally had low trough steady-state serum concentrations of golimumab.

Golimumab exhibited approximately dose-proportional pharmacokinetics over the doses spanning from 0.1 to 10.0 mg/kg following a single IV dose.

No formal study of the effect of renal or hepatic impairment on the PK of golimumab was conducted.

Although subjects with higher body weight tended to have higher serum golimumab concentrations than subjects with lower body weight following IV infusion on a mg/kg (body weight) basis, based on population PK analysis, the difference in golimumab exposure following the recommended therapeutic dosing regimen across a range of body weights was not clinically relevant.

Following the proposed regimen, significant decreases from baseline were observed in TIMP-1, MMP-1, MMP-3, Resistin, IL-6, MIP-1b, VEGF, SAA, S100A12, and hsCRP in the golimumab group versus the PBO group at all time points tested. In addition, significant increase from baseline was observed in TRAP-5b in the golimumab group versus the PBO group at all time points tested.

The developed two-compartment population PK model, as validated by external data and sensitivity analysis, adequately described the time course of serum golimumab concentration following IV administration in subjects with active RA. Sponsor's statements made on clinically insignificant body weight, albumin, age, CRP level, and MTX comedication effects on drug clearance seem to be reasonable. However, Caveat should be given that, since MTX comedication may potentially reduce the incidence of immunogenicity, its effect on overall drug exposure can be underestimated.

Based on the final population PK model, patients who develop antibodies to golimumab was associated with a 33.3% increase in golimumab CL. Therefore, they may require a higher dose to achieve similar golimumab exposure compared to patients who are antibody negative. However, since only 40 subjects were antibody positive (n=40) and the associated large P value (p=0.0352), the effect of presence of antibodies to golimumab on CL remains statistically inconclusive.

The sponsor's rationale for dose justification is mainly based on exposure-response simulation predictions for different dosing regimens. It is in the reviewer's position that the simulation results to justify the 2 mg/kg q8w dose should be interpreted with caution when the simulated PK exposure is beyond the PK exposure range that has been clinically tested. Since the 4 mg/kg q8w dosing regimen will result in a PK exposure that has not been clinically tested, the magnitude of increase in efficacy response relative to the one associated with the 2 mg/kg q8w regimen may be associated with high uncertainty. Nonetheless, in the reviewer's assessment, additional efficacy increase from 2 mg/kg q8w to 4 mg/kg q8w dosing regimen is not likely to be significant given that the 2 mg/kg q8w regimen has demonstrated a better efficacy result than the 4 mg/kg q12w regimen based on the two Phase III study results. Overall, 2 mg/kg q8w is a reasonable dosing regimen.

2 Question-Based Review (QBR)

2.1 General Attributes

2.1.1. What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Chemistry and Physico-Chemical Properties: Golimumab is a human immunoglobulin G1 κ (IgG1 κ) monoclonal antibody that binds with high affinity and specificity to human tumor necrosis factor alpha (TNF α), thereby neutralizing the biological activity of TNF α .

It has molecular weight of 147k Daltons with a chemical formula of C₆₅₃₀H₁₀₀₆₈N₁₇₅₂O₂₀₂₆S₄₄.

Formulation: 50 mg/4 mL vial. The final vial product (FVP) for intravenous infusion (IV) drug product (DP) formulation is composed of 12.5 mg/mL golimumab, 9.5 mM L-histidine, 4.5% (w/v) sorbitol, and 0.015% (w/v) polysorbate 80 (PS 80), at pH 5.5. One presentation (50 mg/vial, nominal 4.0 mL fill volume) of FVP (IV) DP is manufactured.

2.1.2. What is the approved therapeutic indication, dosage and route of administration?

Indication:

Simponi® is indicated for the treatment of

- Moderately to severely active Rheumatoid Arthritis (RA) in adults, in combination with methotrexate
- Active Psoriatic Arthritis (PsA) in adults, alone or in combination with methotrexate
- Active Ankylosing Spondylitis in adults (AS)

Dosage and Route of Administration:

50 mg administered by subcutaneous (SC) injection once a month for all indications.

2.2 General Clinical Pharmacology

2.2.1. What are the clinical pharmacology and clinical trials used to support the proposed claims?

Table 1 shows the list of studies with IV dose that have been submitted during the original golimumab application (BLA125289) for its SC dosing regimen and the current golimumab application (BLA125433) for its IV dosing regimen. New clinical data available from the current BLA125433 application includes two phase III studies, CNTO148ART3001 and C0524T12.

Study CNTO148ART3001 was a safety, efficacy, and radiographic evaluation study testing the 2 mg/kg regimen, dosed at Weeks 0 and 4 and q8w thereafter, in subjects with moderately to severely active RA and an inadequate response to MTX, corticosteroids and/or nonsteroidal anti-inflammatory drugs (NSAIDs). Study CNTO148ART3001 is the single pivotal study with the proposed regimen. Study C0524T12 was a safety and efficacy (without radiographs) study testing 4 different dosing regimens (i.e., 2 mg/kg and 4 mg/kg golimumab dosed every 12 weeks with and without MTX) in RA subjects with an inadequate response to MTX, corticosteroids, NSAIDs, and/or anti-TNF α agents.

Table 1. Listing of Golimumab Clinical Studies with IV Component

Study ID/Subject Population/Phase	Location of CSR in eCTD	Dose Regimen ^a	Route of Administration ^b	Number of PK Subjects ^c	Sampling Scheme ^d
C0466T01/RA Phase 1	24-Week SC submission, BLA, Sequence 0000	IV: 0.1, 0.3, 1.0, 3.0, 6.0 or 10.0 mg/kg single dose	IV	26	Intensive
C0524T14/RA Phase 1	52-Week/104-Week SC submission, sBLA, Sequence 0069	IV: 2 mg/kg Days 1 and 85 SC: 100 mg q4w through Week 20	IV/SC ^e	16 ^e	Intensive
C0524T15/HS Phase 1	52-Week/104-Week SC submission, sBLA, Sequence 0069	IV: 100 mg single dose or SC: 100 mg single dose	IV/SC ^e	22 ^e	Intensive
C0524T12/RA Phase 3	Current	IV: 2 mg/kg and 4 mg/kg q12w	IV	642	Sparse
CNTO148ART3001/RA Phase 3	Current	IV: 2 mg/kg at Weeks 0, 4, and q8w thereafter	IV	463	Sparse

^a q12w = every 12 weeks, q8w = every 8 weeks

^b IV = intravenous

^c PK subjects (Non-compartmental analyses [NCA] for Phase 1, Population PK for Phase 3)

^d Intensive sampling schemes enable determination of the full PK profile using a non-compartmental analysis. Sparse sampling schemes require a model-based approach to characterize the pharmacokinetics adequately.

^e Although both IV and SC administrations were studied in C0524T14 and C0524T15, only IV data are presented in this document

Abbreviations: HS = healthy subjects; RA = subjects with active rheumatoid arthritis; PK = pharmacokinetics; BLA = biologics license

Studies C0524T14 and C0524T15 included both IV and SC administrations and were submitted under BLA125289, in which PK exposures can be directly compared within a study.

2.2.2. Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Serum golimumab concentrations were detected by a validated “sandwich” ECLIA on the (b) (4) platform in clinical studies C0524T12 and C0524T15. The validation parameters for the “sandwich” (b) (4) ECLIA method are shown in Table 2. Please refer to the corresponding product review for details.

Table 2. Validation Parameters for the “Sandwich” (b) (4) ECLIA Method

Validation Reports:	CP2006V-022, CP2006V-022-A1, CP2006V-022-A2, CP2006V-022-A3, CP2006V-022-A4, CP2006V-022-A5			
Assay Type	Sandwich ECLIA			
Reference Standard Lot Number	D05PJ7456			
Calibration Curve Fit	4-Parameter			
Standard Curve Range	15.63 to 1,000 ng/mL			
Standard Curve Accuracy and Precision	% Accuracy: 97.40% to 103.01% % CV (precision): 2.19% to 5.59%			
Lower Limit of Quantification	20 ng/mL (200 ng/mL at the MRD)			
Minimum Required Dilution	10-fold dilution in buffer (PBS, 2% BSA, 1% Tween 20)			
Quality Control Accuracy and Precision	<u>Controls (at MRD): 10, 50, 100 ng/mL</u> Inter-assay Accuracy: 86.33% to 98.73% Inter-assay Precision: 2.90% to 14.53% Intra-assay Accuracy: 98.52% to 109.59% Intra-assay Precision: 4.58% to 13.55%			
	<u>Controls: 10, 50, 100 ng/mL after dilution</u> Inter-assay Accuracy: 103.58% to 106.29% Inter-assay Precision: 1.32% to 8.72% Intra-assay Accuracy: 109.90% to 119.96% Intra-assay Precision: 4.44% to 11.92%			
	<u>Total Error:</u>			
	Control (ng/mL)	Inter-assay Accuracy (% RE)	Inter-assay Precision (% CV)	Total Error (% RE + % CV)
	750	-4.2%	7.0%	11.3%
	400	-5.5%	10.1%	15.6%
	50	1.9%	10.5%	12.4%
	20	14.9%	19.9%	34.9%
Dilutional Linearity	10,000-fold in PBS, 2% BSA, 1% Tween 20			
Specificity	Demonstrated with 3 IgG1 antibodies, 1 IgG4 antibody, and 1 IgG1 fusion protein that do not bind TNF α			
Method Reproducibility	Demonstrated with repeat analysis of incurred samples			
Stability	RT: 24 hours 4°C: 4 weeks -20°C: 8 weeks -70°C: 36 months			
Selectivity	Demonstrated with six individual human serum samples			
Abbreviations: BSA = bovine serum albumin; CV = coefficient of variance; IgG = immunoglobulin G; LLOQ = lower limit of quantification; MRD = minimum required dilution; PBS = phosphate buffered saline; RE = relative error; RT = room temperature; TNF α = tumor necrosis factor alpha				

The validated MSD ECLIA method, modified from the former validated ECLIA method due to (b) (4) acquisition, was used for PK analysis in clinical studies C0524T14 and CNT0148ART3001, and continues to be used in all studies. For MSD ELLIA, the (b) (4) ECLIA method was changed from a (b) (4) “sandwich” ECLIA to a (b) (4) “sandwich” ECLIA on the Meso Scale Discovery (MSD) platform. The validation parameters for the MSD ECLIA method are shown in Table 3. A comparison of the “sandwich” MSD ECLIA to the “sandwich” (b) (4) ECLIA showed that these two methods were comparable.

Table 3. Sandwich MSD ECLIA Validation Parameters

Assay Type	Sandwich ECLIA			
Reference Standard Lot Number	7DS1N			
Calibration Curve Fit	4-Parameter			
Standard Curve Range	7.81 ng/mL to 500 ng/mL			
Standard Curve Accuracy and Precision	Accuracy (% bias): -6.75% to 1.16% Precision (% CV): 15.24% to 1.34%			
Lower Limit of Quantification	7.81 ng/mL (39.05 ng/mL at the MRD)			
Minimum Required Dilution	5-fold dilution in buffer (PBS, 2%BSA, 1% Tween20)			
Quality Control Accuracy and Precision	Control (ng/mL)	Inter-Accuracy % bias	Inter-assay % CV	% Total Error
	ULOQ QC (500)	-6.79	4.06	10.85
	HQC (375)	-6.20	3.13	9.32
	MQC (100)	-1.79	3.91	5.69
	LQC (20)	-3.34	5.12	8.46
	LLOQ QC (7.81)	-19.51	4.28	23.79
Dilutional Linearity	12,500-fold in PBS, 2% BSA, 1% Tween 20			
Specificity	TNF α : golimumab molar ratios in excess of 1:1 demonstrated an impact on the accurate quantification of golimumab at the LLOQ of the assay			
Selectivity	Demonstrated with 9 of 10 individual healthy human serum samples. Demonstrated with 10 of 10 individual rheumatoid arthritis serum samples.			
Parallelism	Demonstrated using a pool of three incurred samples at 100-fold, 250-fold, and 500-fold dilutions in buffer			
Abbreviations: BSA = bovine serum albumin; CV = coefficient of variance; ECLIA = electrochemiluminescent immunoassay; HQC = high quality control; LLOQ = lower limit of quantification; LLOQ QC = lower limit of quantification quality control; LQC = low quality control; MQC = middle quality control; MRD = minimum required dilution; MSD = Meso Scale Discovery; PBS = phosphate buffered saline; TNF α = tumor necrosis factor alpha; ULOQ QC = upper limit of quantification quality control.				

Most part of the bioanalytical assays fulfilled the regulatory criterion (refer to the FDA guidance for industry “Bioanalytical Method Validation (Final-May 2001)) of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy. The accuracy and inter-day precision were acceptable for all the studies (<15% bias or %CV). Study samples were analyzed in runs containing calibrators and quality control samples, as recommended in the FDA guidance.

2.2.3. What are the PK characteristics of golimumab in patients?

Based on study C0524T14, a mean C_{max} of 44.4 ± 11.3 µg/ml was observed in patients with RA following a single IV administration of 2 mg/kg SIMPONI ARIA, as compared to a mean C_{max} of 5.07 ± 3.03 µg/ml following a single SC administration of 100 mg SIMPONI. After single dose, a mean AUC_{0-84d} of 276.8 ± 65.0 µg/ml was observed in patients with RA following a single IV administration of 2 mg/kg SIMPONI ARIA, as compared to a mean AUC_{0-28d} of 70.5 ± 41.0 µg/ml following a single SC administration of 100 mg SIMPONI. By deduction, the overall exposure as measured by AUC_{0-infinity} following a single dose SC administration of 50 mg should be less than half of the overall exposure following a single dose of IV administration of 2 mg/kg in RA patients. Therefore, the dosing interval normalized steady state AUC following monthly SC administration of 50 mg SIMPONI should be less than the steady state AUC following every 8 week IV administration of 2mg/kg SIMPONI ARIA.

The elimination pathways for golimumab have not been characterized. As exhibited in phase I studies, the systemic clearance of golimumab was estimated to be 6.9 ± 2.0 ml/day/kg in healthy subjects based on study C0524T15 and 7.6 ± 2.0 ml/day/kg in patients with RA based on study C0524T14 following a single IV administration of 2 mg/kg SIMPONI ARIA. Correspondingly, the mean terminal half-lives were estimated to be 12 ± 3 days in healthy subjects and 14 ± 4 days in RA patients. The mean volumes of distribution were estimated to be 115 ± 19 ml/kg in healthy subjects and 151 ± 61 ml/kg in RA patients. The volume of distribution of golimumab may indicate that golimumab is distributed primarily in the circulatory system with limited extravascular distribution.

Based on the phase III study CNTO148ART3001, serum concentrations reached steady state by Week 12 following 2 mg/kg SIMPONI ARIA IV infusion in RA patients according to the proposed dosing schedule of weeks 0, 4 and every 8 weeks thereafter. With concomitant use of MTX, treatment with 2 mg/kg golimumab every 8 weeks resulted in a mean steady-state trough serum concentration of 0.35 ± 0.38 µg/mL at Week 12, 0.31 ± 0.44 µg/mL at Week 20, and 0.42 ± 0.54 µg/mL at week 52. Based on the population PK analysis as appended, the concomitant use of MTX reduced golimumab CL by 8.7% but the use of MTX did not demonstrate a statistically significant effect on golimumab CL (p > 0.001).

Population PK analysis showed that covariates including concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of SIMPONI ARIA following SC administration.

Patients who developed anti-golimumab antibodies generally had low trough steady-state serum concentrations of golimumab.

Based on study C0466T01, which was a randomized, placebo-controlled, single ascending dose study in RA patients, golimumab exhibited approximately dose-proportional pharmacokinetics over the doses spanning from 0.1 to 10.0 mg/kg following a single IV dose.

No formal study of the effect of renal or hepatic impairment on the PK of golimumab was conducted.

Based on study CNTO148ART3001, subjects with higher body weight tended to have higher serum golimumab concentrations than subjects with lower body weight following IV infusion on a mg/kg (body weight) basis. At Week 12 and at Week 20, subjects in the highest weight quartile had median serum trough golimumab concentrations of 0.35 µg/mL and 0.29 µg/mL, respectively, compared to 0.27 µg/mL and 0.21 µg/mL, respectively, for subjects in the lowest weight quartile. At week 52, the subjects in the lowest and highest weight quartiles had similar median serum trough concentrations. Based on population PK analysis as appended, the difference in golimumab exposure following the recommended therapeutic dosing regimen across a range of body weights was not clinically relevant.

2.2.4. What are the PD characteristics of in patients?

The biomarker analyses were based on study results of CNTO148ART3001, where serum biomarker samples were analyzed for 26 proteins that were previously shown to be differentially expressed in subjects with RA and/or associated with the TNFα pathway

As highlighted in Table 4, significant decreases from baseline were observed in TIMP-1, MMP-1, MMP-3, Resistin, IL-6, MIP-1b, VEGF, SAA, S100A12, and hsCRP in the golimumab group versus the PBO group at all time points tested. In addition, significant increase from baseline was observed in TRAP-5b in the golimumab group versus the PBO group at all time points tested.

Table 4. Baseline versus Weeks 2, 4, and 14 Treatment Effects for Relative Change in Biomarker

Analyte	Week 2 Golimumab/Placebo			Week 4 Golimumab/Placebo			Week 14 Golimumab/Placebo		
	±Fold	% Diff	P-value	±Fold	% Diff	P-value	±Fold	% Diff	P-value
OPG	1.025204	2.410967	0.262734	0.989433	-1.04531	0.651034	1.032982	3.226353	0.222251
TRAP5b	0.894427	-12.3535	0.000131	0.901361	-11.1777	0.017107	0.871158	-15.8626	0.001595
TIMP-1	1.093977	8.552422	0.000467	1.090265	8.229818	0.000239	1.095741	8.807449	0.004172
MMP-1	1.271087	22.21182	4.93E-14	1.214553	18.42445	3.11E-11	1.260958	21.32343	5.54E-08
MMP-3	1.472764	33.42968	5.74E-27	1.47313	33.83402	4.42E-20	1.542325	37.70232	1.22E-14
Resistin	1.177844	15.90247	0.000513	1.058709	5.593163	0.043982	1.083716	8.006777	0.028321
TNF-R1	1.129956	11.59903	6.03E-09	1.045363	4.171238	0.059935	1.062748	5.885987	0.003626
HGF	1.138008	28.95367	0.012964	0.811186	-48.2063	0.179836	0.392021	-513.251	0.03675
Leptin	0.27126	-473.036	0.468852	0.325961	-359.36	0.804589	0.303268	-393.874	0.234115
BDNF	0.918654	-9.84468	0.105103	0.958613	-4.60373	0.562919	0.926634	-8.64901	0.021632
MPO	1.119679	12.94102	0.012719	0.973376	-3.11327	0.149952	0.970962	-3.64295	0.481258
RANTES	1.033488	4.317771	0.185993	1.08655	10.59896	0.144022	1.081698	10.12724	0.373313
VCAM-1	1.029971	3.178251	0.272183	0.995276	-0.50731	0.665901	0.993555	-0.72899	0.529201
tPAI-1	1.035398	3.547363	0.17625	1.081543	7.976239	0.139728	1.089462	8.821781	0.08888
EGF	3.621629	373.4461	0.043086	1.663846	84.74553	0.380133	0.980532	-2.99541	0.117702
IL-6	1.619161	50.10817	7.60E-10	1.145078	15.36028	3.03E-07	1.997557	82.59014	8.76E-10
MIP-1b	0.967825	-3.358	0.042788	1.183847	19.04612	0.00067	1.168715	18.08225	0.015702
VEGF	1.049923	4.752094	0.018358	1.055306	5.223899	0.016682	1.025236	2.426437	0.041187
Eotaxin	0.768759	-30.532	0.077139	0.913845	-9.89849	0.861026	0.937169	-7.74815	0.546097
RANK-L	30.74559	2797.033	0.102513	61.58972	5487.258	0.032491	42.95182	4120.111	0.032351
SAA	4.398299	179.6929	3.99E-30	2.876994	140.5373	4.70E-14	4.160073	208.2637	2.92E-18
ENA-78	1.345458	111.6294	0.173321	1.885309	225.1197	0.054373	1.458408	114.0234	0.177742
YKL-40	0.829924	-552.862	0.319498	1.913743	1265.562	0.82019	0.472797	-1538.49	0.015352
S100A12	2.824174	390.514	4.60E-22	6.056864	766.6587	2.57E-13	6.991744	664.2659	1.65E-12
(b) (4)	4.254589	134.9213	1.59E-46	2.733559	98.65383	2.30E-24	2.741365	88.0429	1.26E-29

Abbreviations: BDNF = brain-derived neurotrophic factor; CRP = C-reactive protein; EGF = epidermal growth factor; ENA-78 = epithelial-derived neutrophil-activating peptide 78; HGF = hepatocyte growth factor; IL-6 = interleukin 6; MIP-1b = macrophage inflammatory protein-1; MMP-1 = matrix metalloproteinase-1; MMP-3 = matrix metalloproteinase-3; MPO = myeloperoxidase; OPG = osteoprotegerin; RANK-L = receptor activator of nuclear factor kappa-B ligand; RANTES = regulated upon activation, normal T-cell expressed and secreted; S100A12 = S100 calcium binding protein A12; SAA = serum amyloid A protein; sCD40L = soluble CD40 ligand; TIMP = inhibitor of metalloproteinases 1; TNFR1 = tumor necrosis factor receptor 1; tPAI-1 = total plasminogen activator inhibitor 1; TRAP5b = abstract tartrate-resistant acid phosphatase; VCAM-1 = vascular cell adhesion molecule 1; VEGF = vascular endothelial growth factor; YKL-40 = chitinase-3-like protein 1.

a. Correlation coefficient and significance of correlation between log2 serum concentration and DAS at baseline or Week 14 was computed using Kendall correlation. The Kendall coefficient computed for censored data produced very similar results.

2.2.5. What are the key results from the population PK analysis?

The developed two-compartment population PK model adequately described the time course of serum golimumab concentration following IV administration in subjects with active RA. It has been validated by external data and sensitivity analysis. Sponsor's statements made on clinically insignificant body weight, albumin, age, CRP level, and MTX comedication effects on drug clearance seem to be reasonable. However, Caveat should be given that, since MTX comedication may potentially reduce the incidence of immunogenicity, its effect on overall drug exposure can be underestimated.

Based on the final confirmatory model, patients who develop antibodies to golimumab was associated with a 33.3% increase in golimumab CL. Therefore, they may require a higher dose to achieve similar golimumab exposure compared to patients who are antibody negative. However, since only 40 subjects were antibody positive (n=40) and the associated large P value (p=0.0352), the effect of presence of antibodies to golimumab on CL remains statistically inconclusive.

See the appended pharmacometrics report.

2.2.6. Is the proposed dosing regimen justified by the exposure-response for both efficacy and safety?

Sponsor also conducted an exposure-response (ER) analysis exploring the relationship between ACR responses (ACR 20/ACR 50/ACR 70) and golimumab systemic exposure in rheumatoid arthritis (RA) subjects that received concomitant MTX based on data through Week 24 from study CNTO148ART3001 and data through Week 48 from study C0524T12.

The sponsor's rationale for dose justification is mainly based on ER simulation predictions for different dosing regimens. It is in the reviewer's position that the simulation results to justify the 2 mg/kg q8w dose should be interpreted with caution when the simulated PK exposure is beyond the PK exposure range that has been clinically tested. Since the 4 mg/kg q8w dosing regimen will result in a PK exposure that has not been clinically tested, the magnitude of increase in efficacy response relative to the one associated with the 2 mg/kg q8w regimen may be associated with high uncertainty. Nonetheless, in the reviewer's assessment, additional efficacy increase from 2 mg/kg q8w to 4 mg/kg q8w dosing regimen is not likely to be significant given that the 2 mg/kg q8w regimen has demonstrated a better efficacy result than the 4 mg/kg q12w regimen based on the two Phase III study results. Overall, 2 mg/kg q8w is a reasonable dosing regimen.

See details in the appended pharmacometrics report.

2.3 Intrinsic Factors

2.3.1. What was the impact of demographic covariates on Canakinumab exposure?

See section 2.2.5 and the pharmacometrics report for details.

2.3.2. What were the immunogenicity findings for golimumab? What was the impact of immunogenicity on exposure and/or safety?

Antibodies to SIMPONI ARIA were detected in 40 out of 969 (4.1%) of SIMPONI ARIA-treated patients in the two Phase 3 IV studies through Week 24. Patients who received SIMPONI ARIA with concomitant MTX had a relative proportion of antibodies to SIMPONI ARIA than patients who received SIMPONI ARIA without MTX (approximately 8.9% versus 2.9%, respectively). Antibodies to SIMPONI ARIA were detected in 39 (4%) golimumab-treated patients following IV administration of TRADENAMESIMPONI ARIA in combination with MTX through approximately 1 year in the Phase 3 trials in RA. Of the patients with a positive antibody response to SIMPONI ARIA in the Phase 2 and 3 trials, most were determined to have neutralizing antibodies to golimumab as measured by a validated enzyme immunoassay method. The small number of patients positive for antibodies to SIMPONI ARIA limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures. The details of immunogenicity incidence are shown in Table 5.

The data above reflect the percentage of patients whose test results were considered positive for antibodies to SIMPONI ARIA in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SIMPONI ARIA with the incidence of antibodies to other products may be misleading.

Table 5. Incidence of immunogenicity of subjects with positive antibody to golimumab status through Week 52 by dose and methotrexate use; treated subjects in C0524T12 and CNTO148ART3001 by randomized treatment group

	Through Week 24			Through Week 48/52		
	Combined golimumab (with MTX)*	Combined golimumab (without MTX)*	Combined golimumab with and without MTX*	Combined golimumab (with MTX)	Combined golimumab (without MTX)	Combined golimumab with and without MTX
C0524T12						
n	257	256	513	370	256	626
Subjects with appropriate samples	245	248	493	362	251	613
Subjects positive for antibodies to golimumab at any time	5	22	27	13	30	43
% positive	2.0%	8.9%	5.5%	3.6%	12.0%	7.0%
CNTO148ART3001						
n	395	0	395	568	0	568
Subjects with appropriate samples	373	0	373	560	0	560
Subjects positive for antibodies to golimumab at any time	13	0	13	26	0	26
% positive	3.5%	N/A	3.5%	4.6%	N/A	4.6%
All subjects treated in the 2 Phase 3 IV studies						
n	652	256	908	938	256	1194
All RA subjects with appropriate samples	618	248	866	922	251	1173
Subjects positive for antibodies to golimumab at any time	18	22	40	39	30	69
% positive	2.9%	8.9%	4.6%	4.2%	12.0%	5.9%

*does not include subjects that were randomized to placebo and received 1 dose of golimumab

3 Labeling Recommendation

Below is the text added to the approved label from Clinical Pharmacology perspective. This reviewer suggested changes are denoted by strikethrough (for deletions) and underlined (additions) text. Refer to the sBLA action letter for the full text of the final labeling.

Absorption

Following a single IV administration of 2 mg/kg SIMPONI ARIA, a mean C_{max} of 44.4 ± 11.3 µg/ml was observed in patients with RA. Data directly comparing 2 mg/kg IV administration and 50 mg SC administration are not available.

Distribution

Following a single IV administration of 2 mg/kg SIMPONI ARIA, the mean volume of distribution was estimated to be 115 ± 19 ml/kg in healthy subjects, and 151 ± 61 ml/kg in patients with RA. The volume of distribution of golimumab may indicates that golimumab is distributed primarily in the circulatory system with limited extravascular distribution.

Elimination

The elimination pathways for golimumab have not been characterized. Following a single IV administration of 2 mg/kg SIMPONI ARIA, the systemic clearance of golimumab was estimated to be 6.9 ± 2.0 ml/day/kg in healthy subjects and 7.6 ± 2.0 ml/day/kg in patients with RA. The mean terminal half-life was estimated to be 12 ± 3 days in healthy subjects and the mean terminal half-life in RA patients was 14 ± 4 days. When 2 mg/kg SIMPONI ARIA was administered IV to patients with RA at weeks 0, 4 and every 8 weeks thereafter, serum concentrations reached steady state by Week 12. Following IV administration, (b) (4)

(b) (4) concomitant administration of methotrexate

decreases the clearance of SIMPONI ARIA by approximately 9% based on population PK analysis. In addition, concomitant administration of methotrexate decreases the SIMPONI ARIA clearance by reducing the development of anti-golimumab antibodies. With concomitant use of MTX, treatment with 2 mg/kg golimumab every 8 weeks resulted in a mean steady-state trough serum concentration of approximately 0.4 ± 0.4 µg/ml in patients with active RA despite MTX therapy.

Population PK analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of SIMPONI following SC administration.

Patients who developed anti-golimumab antibodies generally had low trough steady-state serum concentrations of golimumab.

No formal study of the effect of renal or hepatic impairment on the PK of golimumab was conducted.

Linearity

Golimumab exhibited approximately dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single IV dose.

Effect of weight on pharmacokinetics

Following IV administration, patients with higher body weight tended to have higher serum golimumab concentrations than patients with lower body weights when golimumab was administered on an mg/kg (body weight) basis. However, based on population PK analysis, there were no clinically relevant differences in golimumab exposure following IV administration of 2 mg/kg SIMPONI ARIA in patients across a range of different body weights.

4 Appendix: Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 What is the rationale behind the proposed golimumab dose/dosing regimen in rheumatoid arthritis (RA) patients following intravenous (IV) infusion?

The proposed dosing regimen in patients with RA is 2 mg/kg intravenous infusion at weeks 0 and 4, then every 8 weeks.

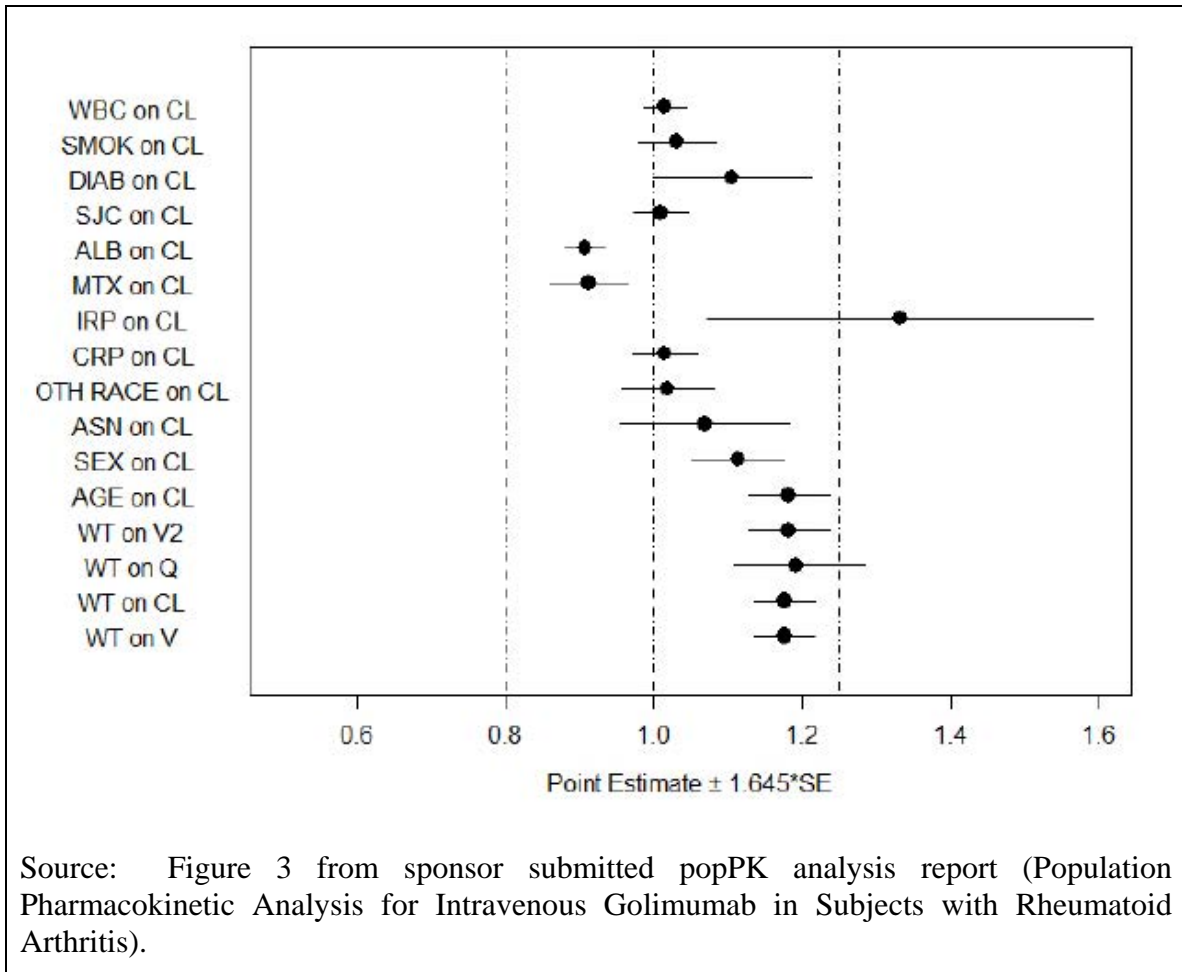
The dose justification for one of the phase III studies (study CNTO148ART3001) with the label recommended regimen was based on the results from two RA studies previously conducted with golimumab (i.e., C0524T12 (IV) and C0524T06 (SC)). Both a population PK model and an exposure-response model have been used to justify the dose regarding covariate information and efficacy.

The developed two-compartment population PK model adequately described the time course of serum golimumab concentration following IV administration in subjects with active RA. It has been validated by external data and sensitivity analysis. Sponsor's statements made on clinically insignificant body weight, albumin, age, CRP level, and methotrexate (MTX) comedication effects on drug clearance seem to be reasonable for the proposed IV regimen. However, Caveat should be given that, since MTX comedication may potentially reduce the incidence of immunogenicity that can increase golimumab clearance by 33%, the overall effect of MTX on overall drug exposure can be underestimated.

Based on the final confirmatory model, patients who develop antibodies to golimumab was associated with a 33.3% increase in golimumab CL. Therefore, they may require a higher dose to achieve similar golimumab exposure compared to patients who are antibody negative.

The covaraites effects on PK parameters are shown in Figure 1.

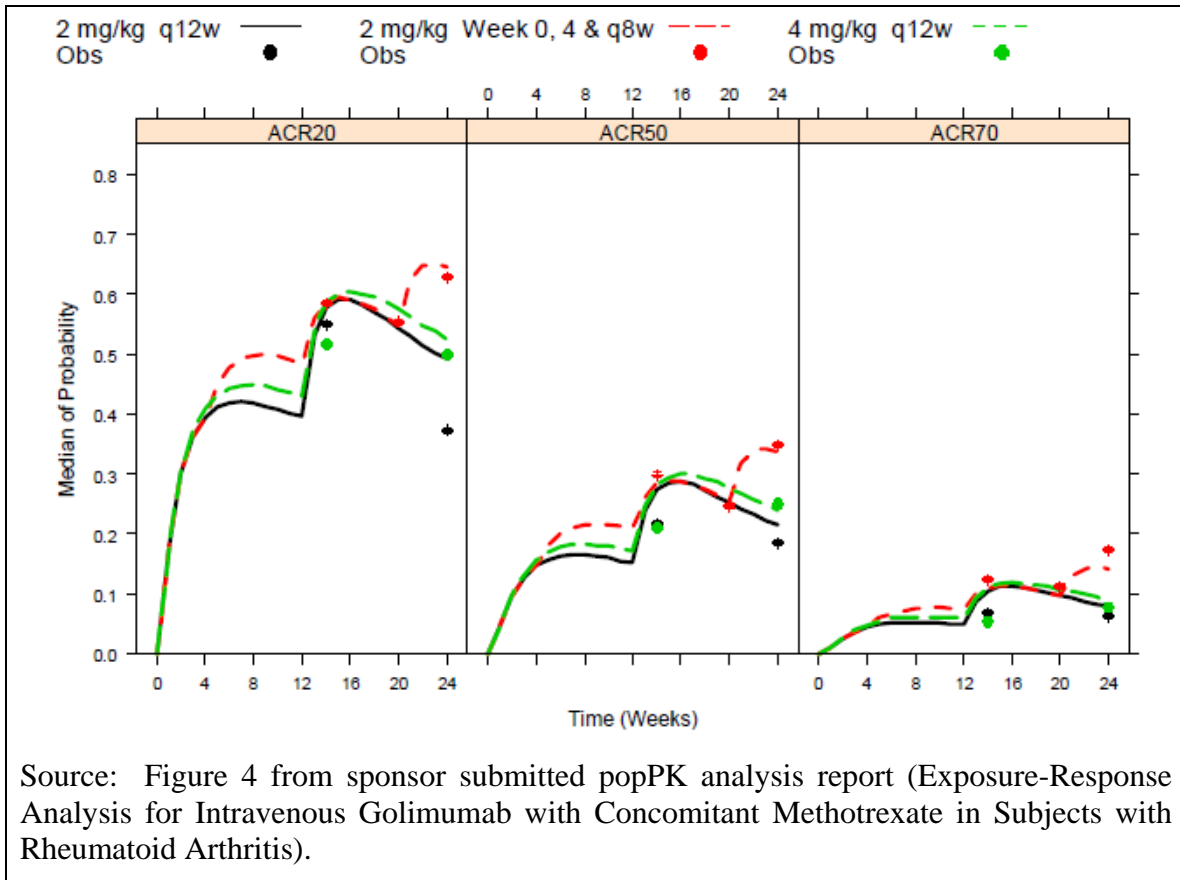
Figure 1 A Forest Plot to Illustrate Covariate Effects: 90% Confidence Intervals for the Ratios of Typical PK Parameters Between Subjects with the 75th and 25th Percentiles of the Continuous Covariate Values, or Between Subjects in Each Category for the Discrete Covariates.



Overall, the established population ER model for ACR responses in RA subjects following golimumab IV doses reasonably described data observed in the IV Phase 3 studies. However, it seems to over-predict the observed frequencies associated with the dosing regimen of 2 mg/kg q12w.

Although the simulated profiles are similar at Week 14, the observed and simulated probabilities for achieving ACR 20, ACR 50 and ACR 70 were consistently higher at Weeks 0, 4, 14, 20 and 24 and significantly higher at Week 24 for the 2 mg/kg q8w dosing regimen than the other two q12w dosing regimens. The reviewer agrees that q8w is an optimal dosing frequency than q12w from efficacy perspective.

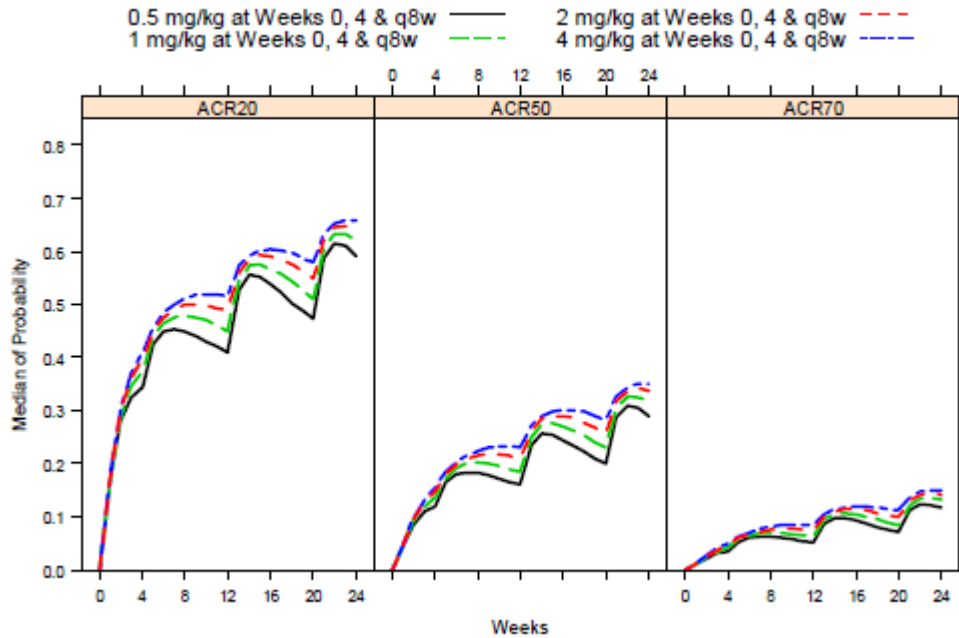
Figure 2 Comparison of Simulated Probability of Achieving ACR20, ACR50 and ACR70 between Dosing Regimens of Golimumab 2mg/kg Q12W, 2mg/kg Week 0, 4 & Q8W and 4mg/kg Q12w



The established population ER model is an empirical model to describe the exposure-response relationship in terms of achieving ACR 20, ACR 50, and ACR 70 responses for golimumab IV infusion. Therefore, the simulation results should be interpreted with caution when the simulated PK exposure is beyond the PK exposure range that has been clinically tested. Since the 4 mg/kg q8w dosing regimen will result in a PK exposure that has not been clinically tested, the magnitude of increase in efficacy response relative to the one associated with the 2 mg/kg q8w regimen as shown in Figure 3 may bear uncertainty.

In the reviewer's assessment, additional efficacy increase from 2 mg/kg q8w to 4 mg/kg q8w dosing regimen is not likely to be significant given that the 2 mg/kg q8w regimen has already demonstrated a better efficacy result than the 4 mg/kg q12w regimen based on the two Phase III study results. Overall, 2 mg/kg q8w is a reasonable dosing regimen.

Figure 3 Comparison of Simulated Probability of Achieving ACR 20, ACR 50 and ACR 70 between Dosing Regimens of Golimumab 0.5 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg at Weeks 0, 4 & q8w



Source: Figure 6 from sponsor submitted analysis report (Exposure-Response Analysis for Intravenous Golimumab with Concomitant Methotrexate in Subjects with Rheumatoid Arthritis).

For further information on effectiveness/safety of the tested doses please refer to the review by Dr. Rosemarie Neuner, Medical Officer, DPARP for further details.

1.2 Recommendations

Please see clinical pharmacology reviewer for proposed changes to labeling statements.

2 PERTINENT REGULATORY BACKGROUND

Golimumab ((b) (4)) (CNTO 148) is a human IgG1κ monoclonal antibody (mAb) that binds to the soluble and membrane bioactive forms of human tumor necrosis factor alpha (TNF α). Golimumab is approved as a subcutaneous (SC) injection in many countries under the trade name of SIMPONI for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).

The current IV program was conducted to fulfill the requirements to support this BLA filing for the IV route of administration for the RA indication as approved for the SC route of administration

2 mg/kg via IV infusion over 30 minutes at Weeks 0 and 4 then q 8 wks thereafter.

To investigate the pharmacokinetic characteristics and the exposure-efficacy and safety relationships of Golimumab in the RA population, the sponsor’s report describes the investigation and analyses results of the population pharmacokinetic analysis and population exposure-efficacy and safety analyses of golimumab in RA patients. The proposed labeling statements are derived based on population pharmacokinetic analysis.

3 RESULTS OF SPONSOR’S ANALYSIS

Population PK analysis

Data from two Phase 3 studies (C0524T12 and CNTO148ART3001) and one Phase 1 PK study (C0524T14) in subjects with active rheumatoid arthritis (RA) following IV administration of golimumab were used in the population PK analysis. The final PK dataset consist of 8461 golimumab serum concentrations collected from 1019 RA patients. The summary of data points from each study were summarized in Table 1.

Study Phase	Study ID	Patient Population	ROA	Dosing regimen	Patient #	PK samples
Phase I	C0524T14	RA	IV	2 mg/kg on Days 1 & 85	16	393
Phase III	C0524T12	RA despite MTX	IV	2, 4 mg/kg Q12W +/- MTX	540	3473
	CNTO148ART3001	RA despite MTX	IV	2 mg/kg on Weeks 0, 4, & Q8W thereafter	463	4550
Total					1019	8416

Source: From reviewer based on sponsor submitted popPK analysis report (Population Pharmacokinetic Analysis for Intravenous Golimumab in Subjects with Rheumatoid Arthritis)

The corresponding PK sampling scheme is shown in Table 2.

Table 2 Summary of Study Treatment Groups and PK Sampling Scheme Following Intravenous Administration of Golimumab in Studies C0524T14, C0524T12 and CNTO148ART3001.

Study	Number	Intravenous Golimumab Treatments	PK Sampling Scheme and Data Inclusion for Population PK Analysis
C0524T14		2 mg/kg at Days 1 and 85 (n=16)	Pre-dose 1 st dose: Days 1 (1 hr postinfusion), 2, 3, 4, 6, 8, 15, 22, 29, 36, 43, 50, 57, 71, 85 2 nd dose: Days 85 (1 hr postinfusion), 86, 88, 90, 92, 99, 113, 127, 141, 169 All IV data were included in the population PK analysis.*
C0524T12		2 mg/kg Q12W + MTX (n=129) 2 mg/kg Q12W (n=128) 4 mg/kg Q12W + MTX (n=128) 4 mg/kg Q12W (n=129) IV Placebo + MTX (n=129)	Pre-dose Weeks 0 (1 hr post infusion), 4, 8, 12 (preinfusion and 1 hr post infusion), 14, 16, 24 (preinfusion and 1 hr post infusion), 36 (preinfusion), 48 (preinfusion). 1 additional sample between Day 2 and Day 14 PK data through Week 24 were included in the population PK analysis
CNTO148ART 3001		2 mg/kg + MTX at Weeks 0, 4 Q8W thereafter (n=395) IV Placebo + MTX with opportunity to receive 2 mg/kg golimumab through early escape at Week 16 or cross-over at Week 24 (n=197)	Pre-dose Weeks 0 (1 hr post infusion), 2, 4 (preinfusion and 1 hr post infusion), 8, 12 (preinfusion and 1 hr post infusion), 14, 16, 20 (preinfusion and 1 hr post infusion), 36 (preinfusion and 1 hr post infusion), 52 (preinfusion and 1 hr post infusion), 76 (preinfusion and 1 hr post infusion), 100 (preinfusion and 1 hr post infusion) PK data through Week 20 were included in the population PK analysis
*data from the SC arm was not included			

Source: Table 1 from sponsor submitted popPK analysis report (Population Pharmacokinetic Analysis for Intravenous Golimumab in Subjects with Rheumatoid Arthritis)

The population PK model developed for the adult RA patients was used as a base model. This was a two-compartment model which was parameterized in terms of clearances and volumes of distribution. Due to the timing of phase III studies, the final model was developed through a two stage confirmatory procedure. There are a total of six distinct steps and two stages for this procedure as shown in Table 3. Model development at stage one was based on dataset of studies C0524T12 and C0524T14.

Table 3 Model Establishment.

Step	Stage	Description	Note:
1	1	Base Model Development	A 2-compartment model with IV infusion parameterized in terms of clearance (CL), central volume of distribution (V), inter-compartmental clearance (Q), and peripheral volume of distribution (V2) was best to describe the time course of golimumab serum concentration
2	1	Full Model Development	A full model was developed to include the potential covariate effects. Prior experiences in the population PK analysis for golimumab and clinical interest in various intrinsic or extrinsic factors were used to determine the inclusion of the covariates for each PK parameter
3	1	Final Model Development	A final parsimonious model was determined using a stepwise covariate selection procedure (forward selection and backward elimination)
4	2	Confirmatory Full-Model Approach	Dataset was simulated based on stage 1 base model and design/dosing/covariate information of Study CNTO148ART3001. If same based model would be derived from the simulated dataset, then the phase I full model would be used as the stage 2 full model for external data model validation. Based on satisfactory results, the full observed data would be used for final model determination
5	NA	External Model Evaluation: Stage 1 Final Model Predictive Performance for Study CNTO148ART3001	Simulated confidence band based on stage 1 final model and design structure and covariate information of CNTO148ART3001 was used for posterior predictive check
6	NA	Sensitivity analysis	For BQL concentrations values, effect of the matrix interference for PK assay, and outliers

Source: From reviewer based on sponsor submitted popPK analysis report (Population

Pharmacokinetic Analysis for Intravenous Golimumab in Subjects with Rheumatoid Arthritis)

First Order Conditional Estimation (FOCE) with interaction was used as the preferred method in case of rich data per subject, highly non-linear model or considerable between-patient variability.

Table 4 shows the continuous demographic data included in the pharmacokinetic analysis.

	C0524T12	C0524T14	CNT0148 ART3001	Total
Age (years)				
Mean± SD	49.6±11.6	57.3±9.92	51.6±12.3	50.6±12.0
Median	51	56.5	52	52
IQR	(42,58)	(51.3,63.3)	(45,60)	(44,59)
Weight (kg)				
Mean± SD	72.3±18.5	83.0±25.4	71.8±16.6	72.3±17.8
Median	69.9	75.3	70	70
IQR	(58.5,81.5)	(69.5,83.1)	(60,81.2)	(59.3,81.5)
C-Reactive Protein (mg/dL)				
Mean± SD	1.76±2.09	0.819±0.813	3.30±2.47	2.44±2.39
Median	0.9	0.5	2.58	1.72
IQR	(0.4,2.3)	(0.3,0.825)	(1.70,3.99)	(0.8,3.3)
Swollen Joint Counts				
Mean± SD	15.2±8.77	19.7±14.3	14.8±8.05	15.1±8.56
Median	13	15	12	13
IQR	(9,19)	(10,25.5)	(9,19)	(9,19)
Tender Joint Counts				
Mean± SD	26.8±15.4	23.5±19.6	26.1±13.6	26.4±14.7
Median	23	17	23	23
IQR	(15,37)	(10.5,25.8)	(15,34)	(15,36)
Albumin (g/dL)				
Mean± SD	4.15±0.343	4.00±0.292	3.70±0.352	3.94±0.411
Median	4.2	4.05	3.7	4
IQR	(3.9,4.4)	(3.88,4.2)	(3.5,3.9)	(3.7,4.2)
White Cell Counts (x10⁹/L)				
Mean± SD	7.93±2.47	7.20±2.60	8.79±2.63	8.31±2.58
Median	7.5	6.9	8.47	7.9
IQR	(6.2,9.2)	(5.9,7.6)	(6.94,10.3)	(6.5,9.88)
IQR – Interquartile range All values are based on data at baseline				

Source: Table 4 from sponsor submitted popPK analysis report (Population Pharmacokinetic Analysis for Intravenous Golimumab in Subjects with Rheumatoid Arthritis)

Table 5 shows the categorical demographic data included in the pharmacokinetic analysis.

Table 5 Summary of demographic data (categorical covariates) [N(%)].				
	C0524T12	C0524T14	CNT0148ART3001	Total
Sex, n (%)				
Male	105 (19.4)	4 (25.0)	80 (17.3)	189 (18.5)
Female	435 (80.6)	12 (75.0)	383 (82.7)	830 (81.5)
Race, n (%)				
Caucasian	378 (70)	15 (93.8)	380 (82.1)	773 (75.9)
Black	9 (1.67)	1 (6.25)	1 (0.216)	11 (1.08)
Asian	43 (7.96)	0 (0)	32 (6.91)	75 (7.36)
Other	110 (20.4)	0 (0)	50 (10.8)	160 (15.7)
IRP, n (%)				
Positive	27 (5)	0 (0)	13 (2.81)	40 (3.93)
Negative	513 (95)	16 (100)	450 (97.2)	979 (96.1)
MTX, n (%)				
No	256 (47.4)	5 (31.3)	0 (0)	261 (25.6)
Yes	284 (52.6)	11 (68.8)	463 (100)	758 (74.4)
Diabetes, n (%)				
No	500 (92.6)	0 (0)	439 (94.8)	939 (92.1)
Yes	40 (7.41)	0 (0)	23 (4.97)	63 (6.18)
Missing	0 (0)	16 (100)	1 (0.216)	17 (1.67)
Smoking, n (%)				
No	439 (81.3)	0 (0)	347 (74.9)	786 (77.1)
Yes	101 (18.7)	0 (0)	115 (24.8)	216 (21.2)
Missing	0 (0)	16 (100)	1 (0.216)	17 (1.67)
IRP - Subjects with positive immune response at any visit during the therapy was marked as 1.				
MTX – Coadministration of methotrexate				
DIAB – Status of diabetes				
SMOK – Smoking status				
All values are based on data at baseline except Immune Response (IRP)				

Source: Table 1 from sponsor submitted popPK analysis report (Population Pharmacokinetic Analysis for Intravenous Golimumab in Subjects with Rheumatoid

Arthritis)

Table 6 shows the summary of PK parameter estimates based on the final confirmatory full model.

Table 6 Summary of PK Parameter Estimates Based on the Final Confirmatory Full Model (Point Estimate +/- Standard Error

Parameter	Final Confirmatory Model*	p-value
V (L) (θ_1)	3.99 ± 0.0739	--
Weight (θ_9)	0.513 ± 0.0656	<0.0001
CL (L/day) (θ_2)	0.623 ± 0.024	-
Weight (θ_{10})	0.512 ± 0.067	<0.0001
Age (θ_{11})	-0.188 ± 0.0505	0.0002
Sex (θ_{12})	0.114 ± 0.0379	0.00263
Race-black**	NA	NA
Race -Asian (θ_{14})	0.0699 ± 0.0694	0.314
Race-other (θ_{15})	0.0193 ± 0.0373	0.605
C-reactive protein (θ_{16})	0.0105 ± 0.0188	0.577
Immune response (θ_{17})	0.333 ± 0.158	0.0352
Methotrexate coadministration (θ_{18})	-0.0869 ± 0.0323	0.00714
Albumin (θ_{19})	-0.769 ± 0.145	<0.0001
Swollen joint counts (θ_{20})	0.0126 ± 0.0297	0.671
Status of diabetes (θ_{22})	0.106 ± 0.0643	0.0993
Smoking status (θ_{23})	0.0319 ± 0.0323	0.323
White blood cell counts (θ_{24})	0.037 ± 0.0399	0.354
Q (θ_3)	0.229 ± 0.00725	--
Weight (θ_{25})	0.555 ± 0.143	0.0001
V2 (θ_4)	2.52 ± 0.0524	--
Weight (θ_{26})	0.528 ± 0.0879	<0.0001
Ω (Cov)		
V	0.362	
V-CL	0.258	
CL	0.404	
V2	0.324	
Proportional Residual Error (σ)	0.312	

*Dataset Used: All three studies

**Race-black was combined with Race-other due to a small n (n=10) which did not meet the criteria of n>20 to be tested using the confirmatory approach. ¹

$$CLi = \theta_2 \left(\frac{WT}{70}\right)^{\theta_{10}} \left(\frac{AGE}{35}\right)^{\theta_{11}} (1 + \theta_{12}SEX)(1 + \theta_{14}ASN)(1 + \theta_{15}OTH)$$
$$CLi = CLi \cdot (CRP)^{\theta_{16}}(1 + \theta_{17}IRP)(1 + \theta_{18}MTX) \left(\frac{ALB}{4.2}\right)^{\theta_{19}} \left(\frac{SJC + 1}{14}\right)^{\theta_{20}}$$
$$CLi = CLi \cdot (1 + \theta_{22}DIAB)(1 + \theta_{23}SMOK) \left(\frac{WBC}{7.5}\right)^{\theta_{24}}$$
$$Vi = \theta_1 \left(\frac{WT}{70}\right)^{\theta_9}$$
$$Qi = \theta_3 \left(\frac{WT}{70}\right)^{\theta_{25}}$$
$$V2i = \theta_4 \left(\frac{WT}{70}\right)^{\theta_{26}}$$

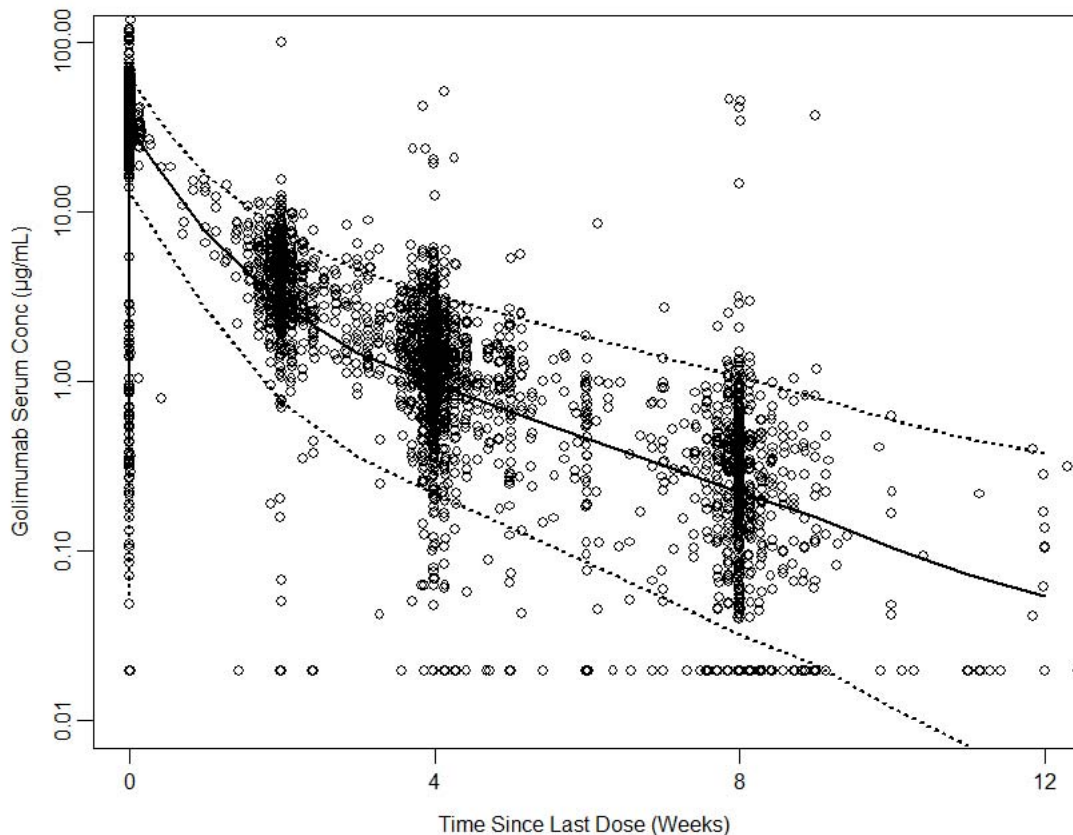
WT: body weight; AGE: age; ALB: albumin; SEX: Sex; ASN: race asian; OTH: race other; CRP: C-reactive protein; IRP: antibodies to golimumab; DIAB: diabetic comorbidity; SMOK: smoking status; WBC: white blood cell count.

Source: Table 11 from sponsor submitted popPK analysis report (Population Pharmacokinetic Analysis for Intravenous Golimumab in Subjects with Rheumatoid Arthritis)

The predictive performance of the Stage 1 final model was evaluated through an external posterior predictive check (PPC) on data from Study CNTO148ART3001. The associated predicted drug concentration profile including the median, the 5th, and the 95th percentiles was overlaid with the observed concentration to check the model performance (Figure 4). It showed that most of the observed concentrations fell into the predicted 90% confidence band, which indicated a valid final model had been developed in stage one of model building.

Based on the final model and the identified covariate structure, for a typical RA subject with a body weight of 70 kg, the estimated golimumab population typical values of CL, V, Q and V2 were 0.623 L/day, 3.99 L, 0.229 L/day, and 2.52 L, respectively. The estimated inter-individual variability for CL, V and V2 were 40.4%, 36.2% and 32.4%, respectively.

Figure 4 Results of External Model Evaluation: 90% Prediction Intervals for the Golimumab Serum Concentrations Over Time (Prediction Model – Stage 1 Final Model, Data – Observed from the Study CNTO148ART3001)



* BQL values were calculated as $\frac{1}{2}$ of the quantification limit for presentation purposes.

Source: Figure 2 from sponsor submitted popPK analysis report (Population Pharmacokinetic Analysis for Intravenous Golimumab in Subjects with Rheumatoid Arthritis).

Out of the identified covariates for golimumab clearance, which determines the overall drug exposure, body weight, albumin level, and age were confirmed as statistically significant ones ($P < 0.001$). The rest covariates were statistically insignificant ($P > 0.001$). Nonetheless, a forest plot (Figure 5) was drawn to illustrate the size of all of the covariates effects on the corresponding PK parameters. Table 7 reported the relative ratio of PK parameters corresponding to the 25th and 75th covariate values. It was shown that, although body weight demonstrated as the most influential covariate with a ratio of 1.18, the corresponding difference in PK exposure was not clinically meaningful. This finding was verified by further PK profile simulations as demonstrated by Figure 6, where no substantial differences in PK profile were shown in different weight categories as shown in Table 7.

Figure 5 A Forest Plot to Illustrate Covariate Effects: 90% Confidence Intervals for the Ratios of Typical PK Parameters Between Subjects with the 75th and 25th Percentiles of the Continuous Covariate Values, or Between Subjects in Each Category for the Discrete Covariates

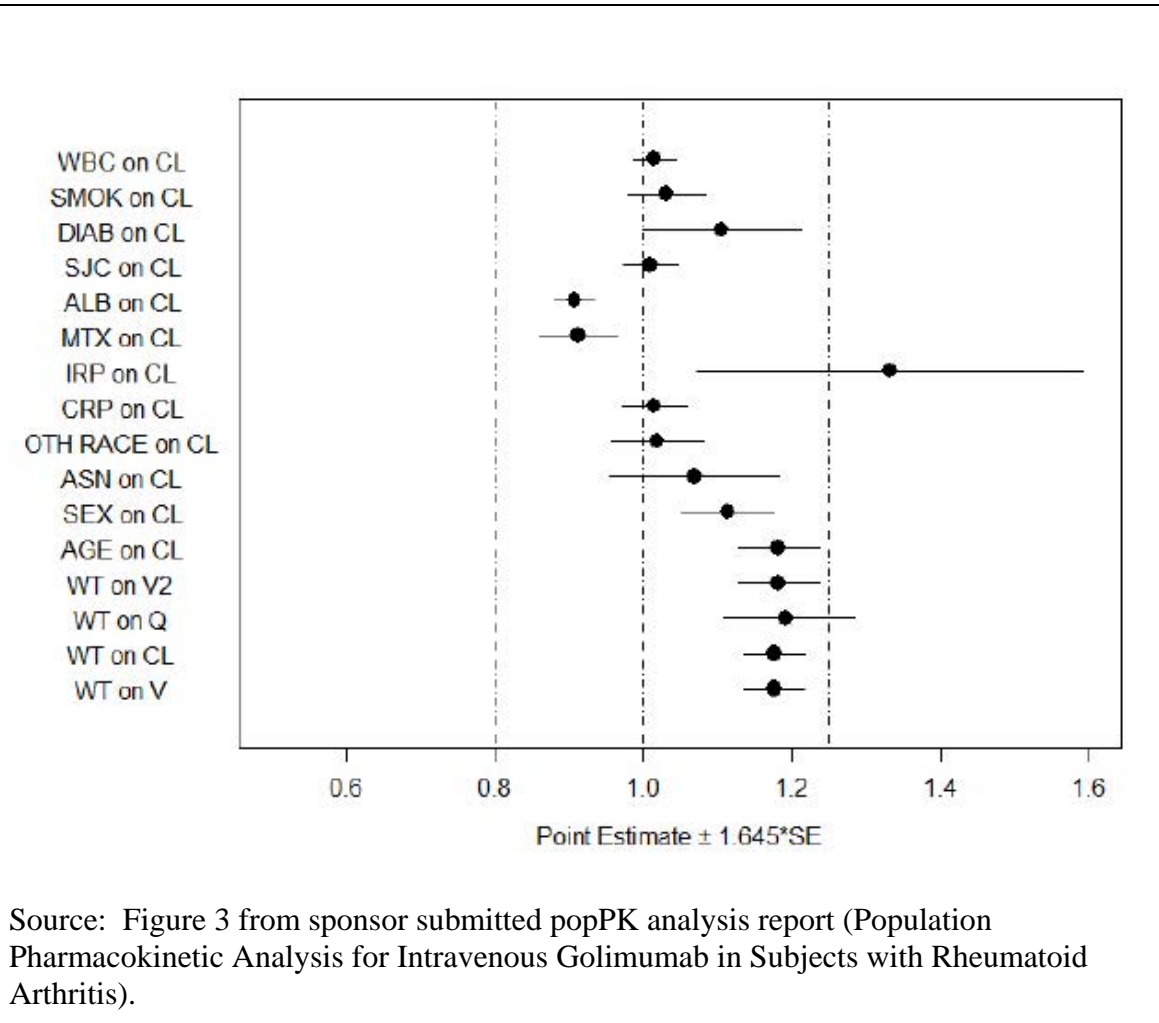
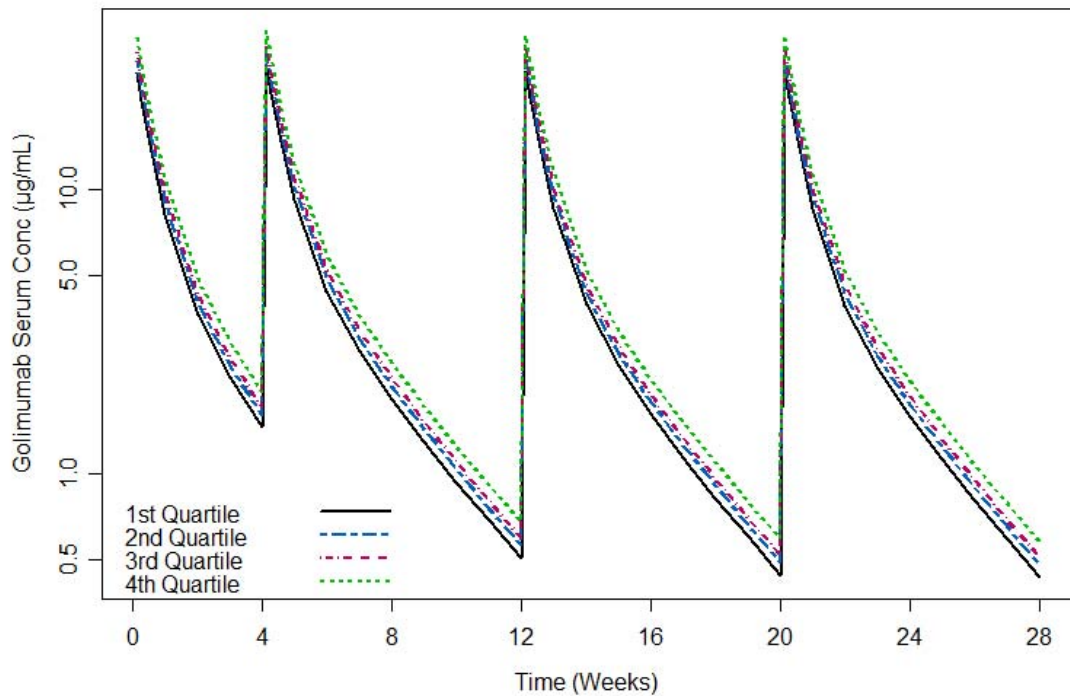


Table 7 Effects of continuous covariates on golimumab PK parameters.

Covariate Percentile	10th Pct	25th Pct	Median	75th Pct	90th Pct	Ratio of the PK parameter between the 25 th and 75 th covariate values
Weight (Kg)	53	59	70	82	96	
V (L)	3.46	3.65	3.99	4.33	4.69	1.19
CL (L/day)	0.540	0.571	0.623	0.676	0.732	1.18
Albumin (g/dL)	3.4	3.7	4.0	4.2	4.4	
CL (L/day)	0.733	0.687	0.647	0.623	0.601	0.907
Age (year)	33	44	52	59	65	
CL (L/day)	0.630	0.597	0.578	0.565	0.555	0.946

Source: Table 12 from sponsor submitted popPK analysis report (Population Pharmacokinetic Analysis for Intravenous Golimumab in Subjects with Rheumatoid Arthritis)

Figure 6 Simulated Mean Steady-state Golimumab Concentration vs. Time Profiles by Weight Following Administration of 2 mg/kg Golimumab on Weeks 0, 4, 12, 20. Median of 500 replicates is presented



Source: Figure 4 from sponsor submitted popPK analysis report (Population Pharmacokinetic Analysis for Intravenous Golimumab in Subjects with Rheumatoid Arthritis).

Sponsor also conducted an exposure-response (ER) analysis exploring the relationship between ACR responses (ACR 20/ACR 50/ACR 70) and golimumab systemic exposure in rheumatoid arthritis (RA) subjects that received concomitant MTX using data through Week 24 from study CNTO148ART3001 and data through Week 48 from study C0524T12. Table 8 summarizes the major design characteristics of these two studies from PK and efficacy perspectives. Table 9 summarizes number of subjects used in the analyses.

Table 8 Summary of Study Treatment Groups and PK Sampling and Efficacy Evaluation Scheme Following Intravenous Administration of Golimumab in Studies CNTO148ART3001 and C0524T12.

Study Number	Intravenous Golimumab Treatments	PK Sampling	Efficacy Evaluations
CNT0148ART3001	2 mg/kg + MTX at Weeks 0, 4 q8w thereafter (n=395) IV Placebo + MTX with opportunity to receive 2 mg/kg golimumab through early escape at Week 16 or cross-over at Week 24 (n=197)	Pre-dose Weeks 0 (1 hr post infusion), 2, 4 (preinfusion and 1 hr post infusion), 8, 12 (preinfusion and 1 hr post infusion), 14, 16, 20 (preinfusion and 1 hr post infusion) 1 additional sample between Week 14 and 20 other than the time of the Week 14, 16 or 20 visits. PK data through Week 20 were included in the population PK analysis	Weeks 0, 2, 4, 8, 12, 14, 16, 20, and 24
C0524T12	2 mg/kg q12w + MTX (n=129) 2 mg/kg q12w (n=128) 4 mg/kg q12w + MTX (n=128) 4 mg/kg q12w (n=129) IV Placebo + MTX (n=129)	Pre-dose Weeks 0 (1 hr post infusion), 4, 8, 12 (preinfusion and 1 hr post infusion), 14, 16 (preinfusion), 24 (preinfusion and 1 hr post infusion), 36 (preinfusion), 48 (preinfusion). 1 additional sample between Day 2 and Day 14 PK data through Week 24 were included in the population PK analysis	Weeks 0, 4, 8, 12, 14, 16, 20, 24, 36, 48

Source: Table 1 from sponsor submitted analysis report (Exposure-Response Analysis for Intravenous Golimumab with Concomitant Methotrexate in Subjects with Rheumatoid Arthritis).

Table 9 Number of Subjects and Observations in ER Analyses.

Treatment	Number of Subjects	Number of Observations
CNT0148ART3001		
2 mg/kg q8w + MTX	395	3086
Placebo + MTX → 2 mg/kg q8w + MTX	197	1407
C0524T12		
2 mg/kg q12w + MTX	129	1113
4 mg/kg q12w + MTX	126	1106
Placebo+MTX→4 mg/kg q12w + MTX	129	823
Total	976	7535

Source: Table 2 from sponsor submitted analysis report (Exposure-Response Analysis for Intravenous Golimumab with Concomitant Methotrexate in Subjects with Rheumatoid Arthritis).

As study objectives, this ER analysis were to develop an ER model to characterize the relationship between golimumab systemic exposure and ACR responses following intravenous (IV) administration of golimumab in subjects with active RA that received concomitant MTX. Dosing regimen simulations based on the established ER model were

used to support the proposed 2 mg/kg IV dose administered at Weeks 0, 4 and q8w thereafter + MTX for subjects with active RA.

The individual pharmacokinetic (PK) model parameters were fixed at their individual Bayesian estimates using the established population PK model as reviewed above. Individual drug exposures as simulated using the individual Bayesian estimates were then correlated with the ordered categorical ACR 20, ACR 50, and ACR 70 responses under an indirect response-logistic regression model and a latent variable indirect response model approach.

For the final model, the ACR variable was modeled using mixed-effect logistic regression:

$$\text{Logit}[\text{prob}(\text{ACR} \leq k)] = a_k + f_p(t) + f_d(t) + \eta$$

Here, $k = 1, 2, \text{ or } 3$ are ACR response outcomes; a_k is the parameter for the k^{th} ACR response. $f_p(t)$ is the placebo (MTX) effect; $f_d(t)$ is the drug (MTX+golimumab) effect.

$$f_p(t) = \log[1 - e^{-R_p t}]$$

$$f_d(t) = DE(1 - R(t))$$

$$\frac{dR(t)}{dt} = K_{in} \left(1 - \frac{C_p(t)}{EC_{50} + C_p(t)}\right) - K_{out} R(t)$$

DE is a parameter to determine the magnitude of drug effect. Given the fact that there should be no drug effect $f_d(t)$ at baseline, $R(0)$ is set to be 1. It was also assumed that $R(0)$ is at steady state at baseline. Therefore, $K_{in} - K_{out} R(t) = 0$ and it can be further deduced that $K_{in} = K_{out}$.

Since a_k values are relative terms, a_2 was set to be 0 for modeling convenience. The final parameter estimates are shown in Table 10.

Table 10 Number of Subjects and Observations in ER Analyses.

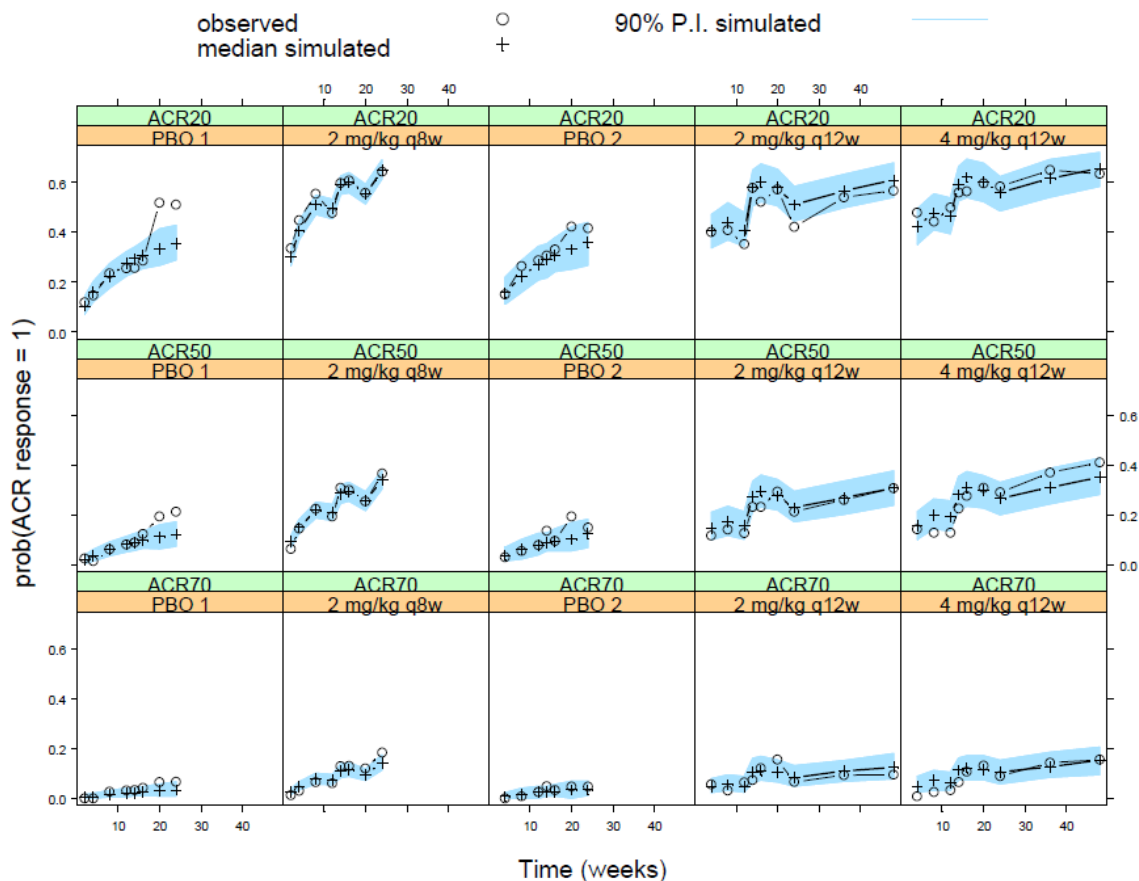
Parameter	α_1	α_3	R_p (1/day)	EC_{50} ($\mu\text{g/mL}$)	K_{out} (L/day)	DE	Var (η)
Estimate	-1.87	2.25	2.16×10^{-4}	0.132	0.155	2.38	5.13
(% RSE)	(3.6)	(2.6)	(16.7)	(23.8)	(25.4)	(7.8)	(6.5)

α_1, α_3 , intercepts; R_p , rate of placebo effect onset; EC_{50} , potency; K_{out} , disease amelioration rate; DE, drug effect; Var(η), variance of inter-subject variability η ; RSE, relative standard error.

Source: Table 3 from sponsor submitted analysis report (Exposure-Response Analysis for Intravenous Golimumab with Concomitant Methotrexate in Subjects with Rheumatoid Arthritis).

Visual predictive check was used as the major model diagnostics. Figure 7 demonstrated the medians and 90% confidence band of the simulated ACR response frequencies at scheduled observation times in overlay with the observed ACR response frequencies.

Figure 7 Median model predictions at planned observation times and 90% prediction intervals, in overlay with observed American College Rheumatology (ACR) response frequencies..



Source: Figure 2 from sponsor submitted analysis report (Exposure-Response Analysis for Intravenous Golimumab with Concomitant Methotrexate in Subjects with Rheumatoid Arthritis).

Simulations were performed for each of the dose regimens as described to evaluate the efficacy responses in terms of probabilities of achieving ACR 20, ACR 50 and ACR 70. Figure 8 and Table 11 showed response comparisons, both with observed and simulated frequencies, among 2 mg/kg q8w, 2 mg/kg q12w, and 4 mg/kg q12w dosing regimens. It was demonstrated that both the simulated and observed ACR responses following the 2 mg/kg q8w regimen are better or similar to those following the 4 mg/kg q12w regimen.

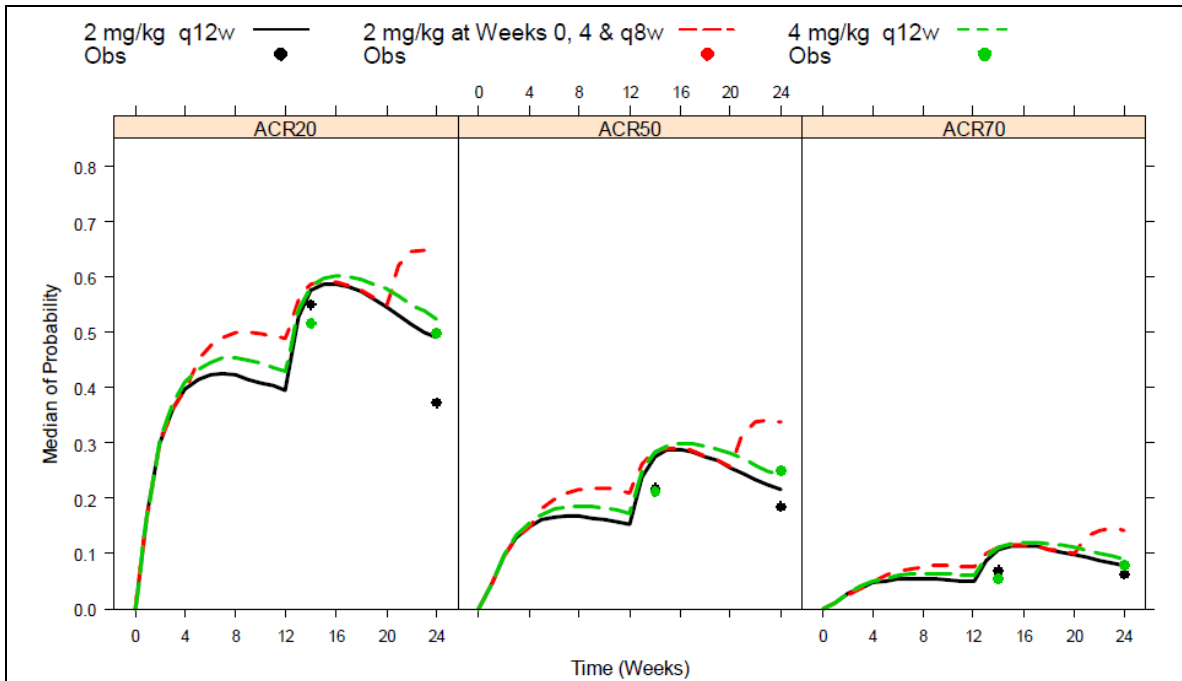
Subsequently, simulations were performed for the q8w dosing regimen with incremental doses of 0.5, 1, 2, and 4 mg/kg. Figure 9 showed that although responses increased with incremental doses, the 4 mg/kg q8w dosing regimen demonstrated limited additional benefit when compared to the 2 mg/kg q8w dosing regimen.

Table 11 Observed Probability of Achieving ACR 20, ACR 50 and ACR 70 and Simulated Values (Median) from the Exposure-Response Model.

Score Response	2 mg/kg at Weeks 0, 4 & q8w + MTX		2 mg/kg q12w + MTX		4 mg/kg q12w + MTX	
	Observed (n=395)	Simulated (n=400)	Observed (n=129)	Simulated (n=400)	Observed (n=128)	Simulated (n=400)
Week 14 Endpoint						
ACR 20	58.8%	58.8%	55.0%	57.5%	51.6%	58.3%
ACR 50	29.9%	28.5%	21.7%	27.5%	21.1%	28.3%
ACR 70	12.4%	11.0%	7.0%	10.8%	5.5%	11.0%
Week 20 Endpoint						
ACR 20	55.4%	55.0%	n/a	n/a	n/a	n/a
ACR 50	24.6%	25.8%	n/a	n/a	n/a	n/a
ACR 70	11.4%	10.0%	n/a	n/a	n/a	n/a
Week 24 Endpoint						
ACR 20	62.8%	64.3%	37.2%	49.0%	50.0%	52.3%
ACR 50	34.9%	33.8%	18.6%	21.5%	25.0%	24.0%
ACR 70	17.5%	14.3%	6.2%	7.8%	7.8%	9.0%

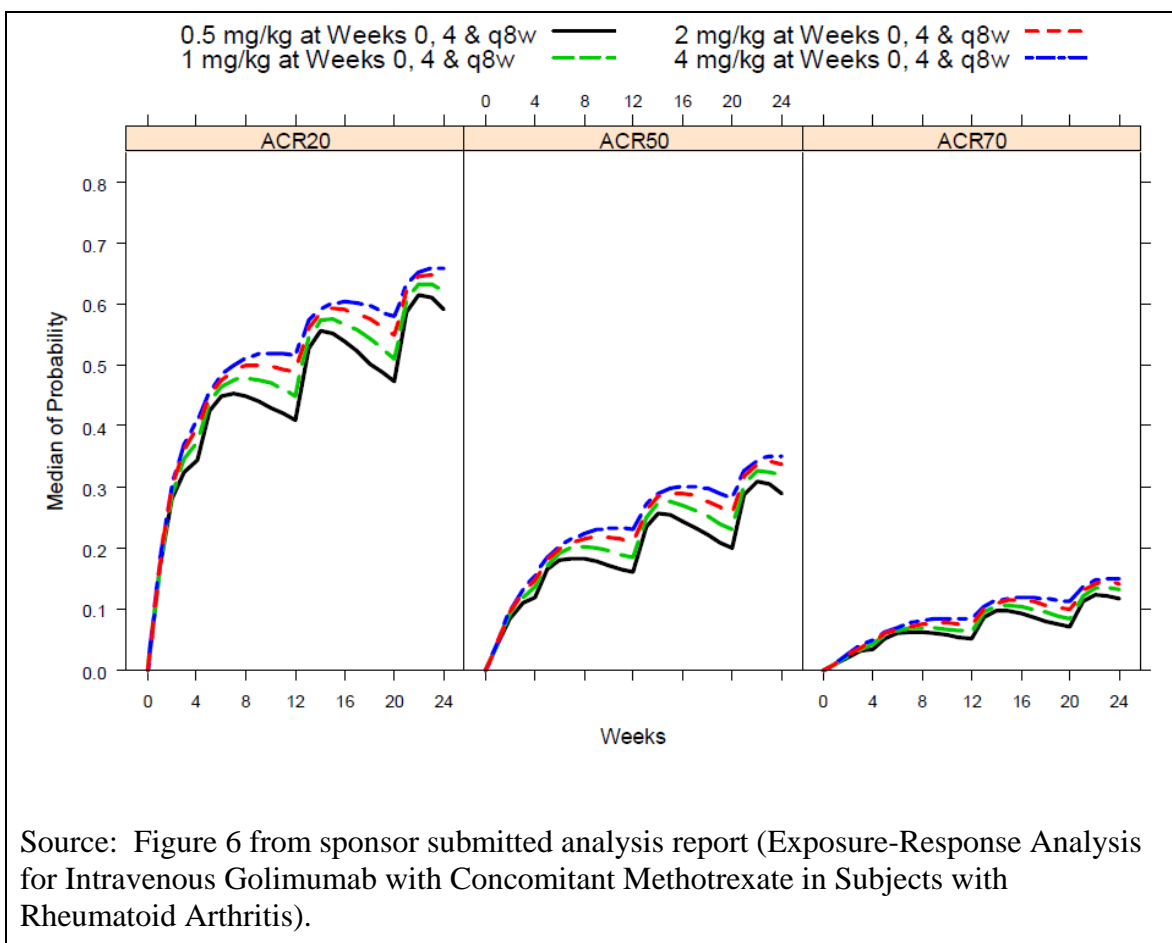
Source: Table 4 from sponsor submitted analysis report (Exposure-Response Analysis for Intravenous Golimumab with Concomitant Methotrexate in Subjects with Rheumatoid Arthritis).

Figure 8 Comparison of Simulated Probability of Achieving ACR 20, ACR 50 and ACR 70 between Dosing Regimens of Golimumab 2 mg/kg q12w, 2 mg/kg at Weeks 0, 4 & q8w and 4 mg/kg q12w



Source: Figure 4 from sponsor submitted popPK analysis report (Exposure-Response Analysis for Intravenous Golimumab with Concomitant Methotrexate in Subjects with Rheumatoid Arthritis).

Figure 9 Comparison of Simulated Probability of Achieving ACR 20, ACR 50 and ACR 70 between Dosing Regimens of Golimumab 0.5 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg at Weeks 0, 4 & q8w



Source: Figure 6 from sponsor submitted analysis report (Exposure-Response Analysis for Intravenous Golimumab with Concomitant Methotrexate in Subjects with Rheumatoid Arthritis).

Reviewer's comment: The reviewer was able to run the final population pharmacokinetic model and exposure-response model and confirm sponsor's estimates as reported.

The developed two-compartment population PK model adequately described the time course of serum golimumab concentration following IV administration in subjects with active RA. It has been validated by external data and sensitivity analysis. Sponsor's statements made on clinically insignificant body weight, albumin, age, CRP level, and MTX comedication effects on drug clearance and no dose adjustment based on these covariates seem to be reasonable. However, Caveat should be given that, since MTX comedication may potentially reduce the incidence of immunogenicity, its effects on overall drug exposure can be underestimated.

Based on the final confirmatory model, patients who develop antibodies to golimumab was associated with a 33.3% increase in golimumab CL. Therefore, they may require a higher dose to achieve similar golimumab exposure compared to patients who are antibody negative.

Overall, the established population ER model for ACR responses in RA subjects following golimumab IV doses reasonably described data observed in the IV Phase 3

studies. However, the model seems to over-predict the observed frequencies associated with the dosing regimen of 2 mg/kg q12w.

Based on Figure 8 and Table 11, although the simulated profiles are similar at Week 14, the observed and simulated probabilities for achieving ACR 20, ACR 50 and ACR 70 were consistently higher at Weeks 0, 4, 14, 20 and 24 and significantly higher at Week 24 for the 2 mg/kg q8w dosing regimen than the other two q12w dosing regimens. The reviewer agrees that q8w is an optimal dosing frequency than q12w from efficacy perspective.

The established population ER model is an empirical model to describe the exposure-response relationship in terms of achieving ACR 20, ACR 50, and ACR 70 responses for golimumab IV infusion. Therefore, the simulation results should be interpreted with caution when the simulated PK exposure is beyond the PK exposure range that has been clinically tested. Since the 4 mg/kg q8w dosing regimen will result in a PK exposure that has not been clinically tested, the magnitude of increase in efficacy response relative to the one associated with the 2 mg/kg q8w regimen may bear more uncertainty.

In the reviewer's assessment, additional efficacy increase from 2 mg/kg q8w to 4 mg/kg q8w dosing regimen is not likely to be significant given that the 2 mg/kg q8w regimen has already demonstrated a better efficacy result than the 4 mg/kg q12w regimen based on Phase III study results. Taking all considerations into account, 2 mg/kg is a reasonable dose associated with q8w dosing frequency.

Proposed labeling statements

See clinical pharmacology review.

Table 12. Analysis Data Sets

Study Number	Name	Link to EDR
pop-pk-iv-ra.pdf	Population pharmacokinetic analysis for intravenous golimumab in subjects with rheumatoid arthritis	\\cber-fs3\m\ectd_submissions\stn125433\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-ra-iv\pop-pk-iv-ra.pdf
exposure-resp-report-ra.pdf	Exposure-response analysis for intravenous golimumab with concomitant methotrexate in subjects with rheumatoid arthritis	\\cber-fs3\m\ectd_submissions\stn125433\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\exposure-response\exposure-resp-report-ra.pdf

4 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
POPPKIV mod	Population pharmacokinetic model (Final)	\Golimumab_BLA_125433_LZ\PPK Analyses\Final Model
Fit.tab	Output of final population pharmacokinetic model	\Golimumab_BLA_125433_LZ\PPK Analyses\Final Model
POPPKIV.lst	Parameter estimates from final population pharmacokinetic model	\Golimumab_BLA_125433_LZ\PPK Analyses\Final Model
PKPD mod	Final model for exposure-response analysis	\Golimumab_BLA_125433_LZ\ER Analyses\Final Model
Exp.eta	Output of exposure response model	\Golimumab_BLA_125433_LZ\ER Analyses\Final Model
PKPD.lst	Parameter estimates from exposure-response model	\Golimumab_BLA_125433_LZ\ER Analyses\Final Model

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

/s/

LIANG ZHAO
06/14/2013

VENKATESH A BHATTARAM
06/17/2013

SURESH DODDAPANENI
06/17/2013

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125433	Brand Name	TRADENAME
OCP Division (I, II, III, IV, V)	II	Generic Name	Golimumab
Medical Division	570	Drug Class	Anti-TNFalpha
OCP Reviewer	Liang Zhao, Ph.D.	Indication(s)	RA
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	50 mg/4 mL vial
Pharmacometrics Reviewer	TBD	Dosing Regimen	2 mg/kg intravenous infusion at weeks 0, 4, and every 8 weeks
Date of Submission	September 18 th , 2012	Route of Administration	Intravenous infusion
Estimated Due Date of OCP Review	June 10 th , 2013	Sponsor	Jassen Biotech, Inc.
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	July 19 th 2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X			Referred to 3 phase I studies with the SC BLA submission (BLA#: 125289)
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	X	2	2	PopPK analysis and exposure-response analysis
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

___ Yes ___

This BLA submission (BLA125433) is fileable from a Clinical Pharmacology standpoint. Submission is supported by Phase III (efficacy and safety) trials. Please refer to the attached filing meeting slides for details.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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Bottomline Assessment

- **Fileable from Clin Pharm perspective**
 - Relevant datasets are included in submission
- **Mid-Cycle Deliverables:**
 - Evaluations of potential factors leading to PK variability
 - Evaluation of exposure-response analysis
 - Preliminary assessment of labeling language
 - DDI language
 - Immunogenicity
 - MOA

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Background

- Human monoclonal antibody that binds to both the soluble and transmembrane human TNF α
- Currently approved for the treatment of RA, PsA, AS
- Approved dosing regimen: 50 mg SC once a month, monotherapy or in combination with DMARDS
- Proposed dosing regimen: 2 mg/kg IV infusion at weeks 0 and 4, then every 8 weeks
- Separate BLA:
 - First BLA #: 125289 for SC
 - Current BLA #: 125433 for IV

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Summary of Prior PK in RA Patients

- Bioavailability in HV: 53%
- Tmax in RA population: 2-6 days
- Dose-proportional in RA patients (0.1-10 mg/kg IV)
- T1/2: 2 weeks in HV, patients with RA, PsA, or AS
- Time to reach SS with QM dosing: week 12
- Co-treatment with MTX
 - increases trough concentrations at SS
 - Decreases ADA from 7% to 2%
- Renal/hepatic impairment
 - No formal study of the effect of renal or hepatic impairment on the PK of golimumab was conducted.
- PopPK results regarding effects of important covariates
 - CL/F has no correlation with comed (ie, NSAIDS, corticosteroids, or sulfasalazine), gender for RA and PsA, age, and race
 - CL/F increase with increasing BW, (no meaningful observed clinical difference)
- IM+ patients generally had lower steady-state serum trough concentrations

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Clinical pharmacology studies in submission

- **Clinical pharmacology data available from**
 - **Three Phase I studies (i.e., C0466T01, C0524T14, and C0524T15, from SC submission BLA125289)**
 - C0466T01: FIH
 - C0524T14 and C0524T15: PK studies
 - **Two Phase III studies (i.e., C0524T12 and CNTO148ART3001, new information for this submission)**

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Summary of Clinical Pharmacology Related Studies

Study ID/Subject Population/Phase	Location of CSR in eCTD	Dose Regimen ^a	Route of Administration ^b	Number of PK Subjects ^c	Sampling Scheme ^d
C0466T01/RA Phase 1	24-Week SC submission, BLA, Sequence 0000	IV: 0.1, 0.3, 1.0, 3.0, 6.0 or 10.0 mg/kg single dose	IV	26	Intensive
C0524T14/RA Phase 1	52-Week/104-Week SC submission, sBLA, Sequence 0069	IV: 2 mg/kg Days 1 and 85 SC: 100 mg q4w through Week 20	IV/SC ^e	16 ^e	Intensive
C0524T15/HS Phase 1	52-Week/104-Week SC submission, sBLA, Sequence 0069	IV: 100 mg single dose or SC: 100 mg single dose	IV/SC ^e	22 ^e	Intensive
C0524T12/RA Phase 3	Current	IV: 2 mg/kg and 4 mg/kg q12w	IV	642	Sparse
CNT0148ART30 01/RA Phase 3	Current	IV: 2 mg/kg at Weeks 0, 4, and q8w thereafter	IV	463	Sparse

^a q12w = every 12 weeks, q8w = every 8 weeks

^b IV = intravenous

^c PK subjects (Non-compartmental analyses [NCA] for Phase 1, Population PK for Phase 3)

^d Intensive sampling schemes enable determination of the full PK profile using a non-compartmental analysis. Sparse sampling schemes require a model-based approach to characterize the pharmacokinetics adequately.

^e Although both IV and SC administrations were studied in C0524T14 and C0524T15, only IV data are presented in this document

Abbreviations: HS = healthy subjects; RA = subjects with active rheumatoid arthritis; PK = pharmacokinetics; BLA = biologics license

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Bioassay

- PK: enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescent immunoassays (ECLIA)
 - Studies using ELISA: C0466T01
 - Studies using MSD ECLIA: C0524T14, C0524T12 (LTE), CNT0148ART3001
 - Studies using ^{(b) (4)} ECLIA: C0524T12 (through week 48),
 - LOQs
 - ELISA: 0.078 mcg/mL in a sample with 1:10 dilution
 - ^{(b) (4)} ECLIA: 0.2 mcg/mL in a sample with 1:10 dilution
 - MSD ECLIA: 0.039 mcg/mL in a sample with 1:5 dilution
 - Assays are the same as used for SC application (BLA125289)
- IM: A validated enzyme immunoassay (EIA) method

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PopPK analysis

- **Data derived from RA subjects after IV administration:**
 - Phase 1 study C0524T14: intensive PK sampling
 - Two Phase III studies C0524T12 and CNTO148ART3001: sparse sampling
 - why not to include studies from C0466T01 and C0524T15?
 - Drug source: C0466T01 was from an earlier cell line (C0466D)
 - Formulation: C0466T01 used a different formulation
 - Assay:
 - ELISA for C0466T01; ECLIA for in C0524T14, C0524T12, and CNTO148ART3001;
 - Population: C0524T15 in healthy subjects
 - Study design: the available covariate information from C0466T01 and C0524T15 were limited.
- **Demographics evaluated:**
 - Intrinsic factors: weight, age, gender, race, immune response (IR, ie, antibodies to golimumab), albumin, CRP, baseline swollen joint count, baseline tender joint count, diabetes status and white blood cell count (WBC)
 - Extrinsic factors: Smoking status and the use of concomitant MTX

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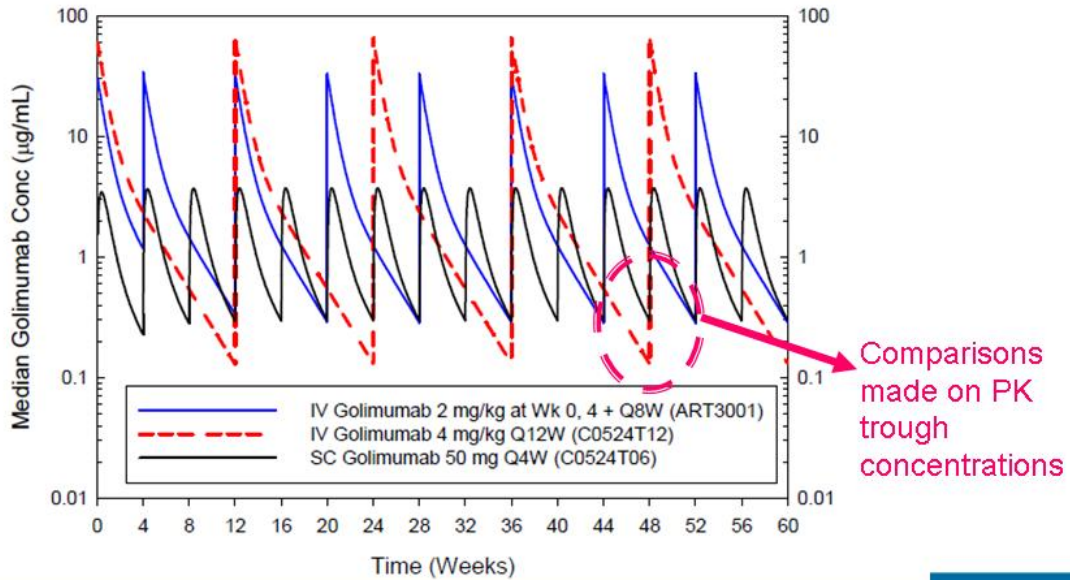
Pop PK Results

- Population PK analysis showed that body weight was a significant covariate on golimumab PK
 - When administered on a mg/kg (body weight) basis, higher concentrations with higher body weight
 - No substantial differences in golimumab PK profiles for subjects across different ranges of body weights
 - Consistent treatment benefit was seen for all subjects CSR, Section 5.1.3 and Attachment 2.4).
- Covariate analysis did NOT warrant dose adjustment based on
 - albumin level, CRP level, or concomitant use of MTX

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Sponsor's PK rationale for the proposed dosing regimen

Figure 7: Median Serum Golimumab Concentration-Time Profiles Following IV or SC Administration of Golimumab



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Exposure-response analysis

- Explored the relationship between ACR responses (ACR 20/ACR 50/ACR 70) and golimumab exposure
- Used data through Week 24 from studies CNT0148ART3001 and C0524T12
- Developed an indirect drug response model to simultaneously fit ACR 20/ACR 50/ACR 70 response rates through a latent variable approach

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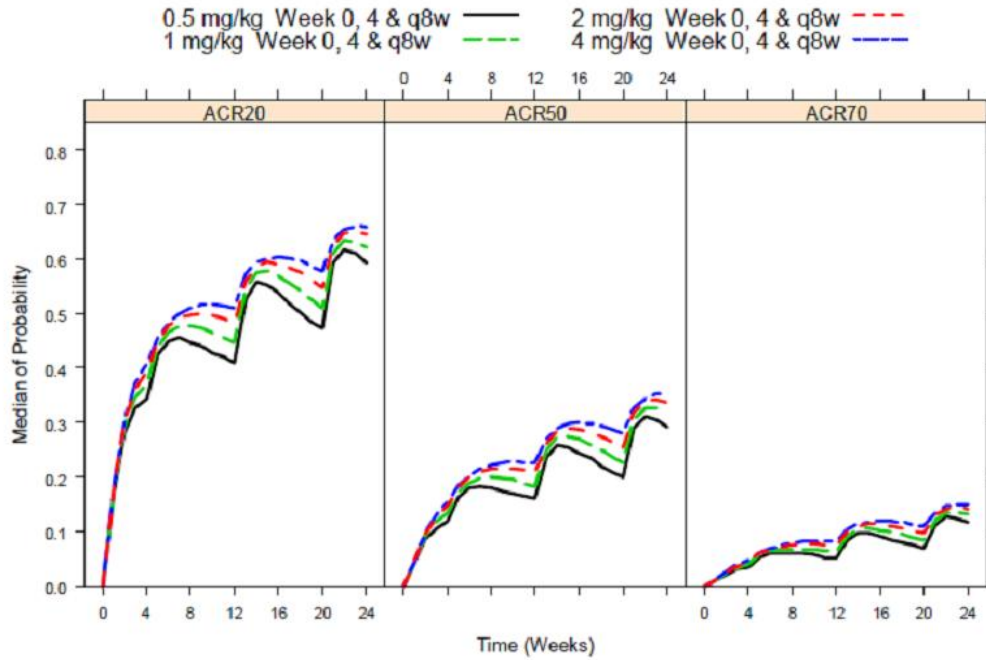
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Major Exposure-Response Modeling & Simulation Conclusions From Sponsor

- When ACR responses for IV golimumab 0.5 to 4 mg/kg given at Weeks 0, 4, and q8w + MTX were simulated, the 2 mg/kg dose level provided the desired ACR responses and increasing the dose to 4 mg/kg did not substantially increase ACR responses as compared with the 2 mg/kg at Weeks 0, 4, and q8w + MTX dosing regimen
- The proposed dosing regimen of golimumab 2 mg/kg administered IV at Weeks 0, 4, and q8w + MTX is well suited to achieve the desired ACR responses

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Figure 6: Comparison of Simulated Probability of Achieving ACR20, ACR50 and ACR70 between Dosing Regimens of Golimumab 0.5mg/kg, 1mg/kg, 2mg/kg and 4mg/kg at Week 0, 4 & Q8W



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Immunogenicity

- The combined antibody to golimumab incidence across all subjects treated in the two Phase 3 IV studies was 4.6% (26/560) and 7.0% (43/613) through weeks 48 and 52, respectively
- Through week 52, for subjects who did not receive MTX (golimumab monotherapy) the antibody to golimumab incidence was 12% (30/251) while the incidence was 4.2% (39/922) for subjects who were treated with golimumab + MTX
- For those subjects who were positive for antibodies to golimumab in CNT0148ART3001, 100% were positive for neutralizing antibodies
- IM+ → lower PK concentration

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/s/

LIANG ZHAO
11/07/2012

SURESH DODDAPANENI
11/08/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 28, 2013
From	Susan Limb, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 125433, SN00
Supplement#	
Applicant	Janssen Biotech, Inc.
Date of Submission	September 18, 2012
PDUFA Goal Date	July 19, 2013
Proprietary Name / Established (USAN) names	Simponi Aria/golimumab
Dosage forms / Strength	2 mg/kg intravenous infusion
Proposed Indication(s)	1. Rheumatoid arthritis in adults
Recommended:	<i>Approval</i>

1. Introduction

Janssen Biotech, Inc., submitted a new Biologics Licensing Application (BLA 125433) for golimumab intravenous (IV) infusion on September 18, 2012. The proposed indication is the treatment of moderately to severely active rheumatoid arthritis (RA) in adults, in combination with methotrexate. Golimumab is a tumor necrosis factor (TNF) inhibitor which is already marketed as a subcutaneous (SC) formulation for the same indication under the tradename, Simponi®. Golimumab IV is proposed as an alternative formulation with less frequent dosing and data to support a radiographic benefit, which golimumab SC does not have. The proposed tradename for golimumab IV is Simponi Aria.

This memorandum provides an overview of the regulatory background, development program, and risk-benefit assessment, addressing the adequacy of the efficacy and safety assessments.

2. Background

Rheumatoid arthritis is an autoimmune condition characterized by inflammatory polyarthritis and multiple extraarticular manifestations. Treatments for RA include non-steroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs). NSAIDs and COX-2 inhibitors are reserved primarily for symptomatic pain relief in milder disease. DMARDs are used for moderate to severe disease, given their ability to alter disease progression and reduce joint damage. Corticosteroids also have anti-inflammatory, disease-modifying effects but due to the undesirable effects associated with higher doses and chronic use, corticosteroids are currently used most often as a bridging treatment until other DMARDs take effect or as an adjunctive therapy in patients with poorly controlled severe disease.

DMARDs include both small molecule and biologic products that act on a variety of inflammatory pathways. TNF- α inhibitors are a well-established class of DMARDs, summarized in Table 1. While these products all work to inhibit TNF- α -mediated inflammation, the mechanisms of action and approved indications differ slightly among the products. In terms of secondary claims for RA, golimumab SC is notable for its failure to obtain secondary claims for major clinical response and radiographic response. As a class, the labeling for TNF inhibitors includes a boxed warning for serious infections and malignancy as well as medication guides discussing these risks.

Table 1 TNF-α inhibitors		
Product (tradename) Year approved	Indications Secondary RA claims¹	Dose and route of administration
Etanercept (Enbrel) 1998	Rheumatoid arthritis (RA) • <i>Clinical response</i> • <i>Major clinical response</i> • <i>Physical function response</i> • <i>Radiographic response</i> Polyarticular juvenile idiopathic arthritis (JIA) Psoriatic arthritis (PsA) Ankylosing spondylitis (AS) Plaque psoriasis (PsO)	<u>RA, PsA, AS</u> • 50 mg SC Qwk $\pm$ MTX <u>AS</u> • 50 mg SC Qwk <u>PsO</u> • 50 mg SC twice weekly x 3 mos, then 50 mg SC Qwk <u>JIA</u> • 0.8 mg/kg SC Qwk (max 50mg)
Infliximab (Remicade) 1999	Rheumatoid arthritis • <i>Clinical response</i> • <i>Major clinical response</i> • <i>Physical function response</i> • <i>Radiographic response</i> Psoriatic arthritis Ankylosing spondylitis Plaque psoriasis Crohn's disease (CD) and pediatric CD Ulcerative colitis (UC) and pediatric UC	<u>RA</u> • 3 mg/kg IV + MTX at 0, 2, and 6 weeks then Q8wk (may increase to 10 mg/kg or Q4wk) <u>AS</u> • 5 mg/kg IV at 0, 2, and 6 weeks and then Q6wk <u>PsO, PsA, CD, UC</u> • 5 mg/kg IV at 0, 2, and 6 weeks and then Q8wk
Adalimumab (Humira) 2005	Rheumatoid arthritis • <i>Clinical response</i> • <i>Major clinical response</i> • <i>Physical function response</i> • <i>Radiographic response</i> Polyarticular juvenile idiopathic arthritis Psoriatic arthritis Ankylosing spondylitis Plaque psoriasis Crohn's disease Ulcerative colitis	<u>RA, PsA, AS</u> • 40 mg SC Qowk (may increase to Qwk) <u>JIA</u> • 15 kg to <30 kg: 20 mg SC Qowk • $\geq$30 kg: 40 mg SC Qowk <u>PsO</u> • 80 mg SC initial dose, then 40 mg Qowk <u>CD, UC</u> • 160 mg SC initial dose, 80 mg 2nd dose 2 wks later, then 40 mg Qowk
Golimumab (Simponi) 2009	Rheumatoid arthritis • <i>Clinical response</i> • <i>Physical function response</i> Psoriatic arthritis Ankylosing spondylitis	<u>RA, PsA, AS</u> • 50 mg SC Qmonth
Certolizumab pegol	Rheumatoid arthritis	<u>RA</u>

(Cimzia) 2009	• <i>Clinical response</i> • <i>Major clinical response</i> • <i>Physical function response</i> • <i>Radiographic response</i> Crohn's disease	• 400 mg SC Q2wk x 3, then 200 mg Q4wk (may increase to 400 mg) <u>CD</u> • 400 mg SC Q2wk x 3, then 400 mg Q4wk

¹ Clinical response = ACR20, 50, and 70 response over time (>3 months); Major clinical response = ACR70 response maintained continuously over ≥ 6 months; Physical function response = Health assessment questionnaire (HAQ) over ≥ 6 months; Radiographic response = change in Total Sharp Score (TSS) on joint radiograph over 6 or 12 months (may include erosion score [ES] and joint space narrowing [JSN] components)

² RA=rheumatoid arthritis; JIA=Polyarticular juvenile idiopathic arthritis; PsA=psoriatic arthritis; AS=ankylosing spondylitis; PsO=plaque psoriasis

Regulatory history

The following timeline summarizes highlights of the regulatory history for golimumab IV and major interactions between FDA and the Applicant.

- **May 10, 2006**, Pre-IND/pre-phase 3 meeting written responses (IND 9925):
 - The Division of Anesthesia, Analgesics, and Rheumatology Products (DAARP) recommended PK evaluation of multiple IV dosing prior to Phase 3. DAARP also stated that the overall efficacy profile of golimumab IV should be comparable to golimumab SC. DAARP agreed in principle that a single positive phase 3 IV trial in conjunction with data available for the SC formulation may be sufficient to support approval of the RA indication and extrapolation of psoriatic arthritis and ankylosing spondylitis indications.
- **April 24, 2009**, golimumab SC (BLA 125289) approved for the treatment of RA, psoriatic arthritis, and ankylosing spondylitis.
- **May 18, 2009**, End-of-Phase 2 meeting:
 - DAARP stated that the estimated pharmacokinetic differences between the IV and SC formulation of golimumab may limit the extrapolation of data from the SC program in support of the new IV product. In particular, DAARP noted that the proposed IV formulation of 4 mg/kg appeared to have a higher C_{max} and AUC, raising concerns about a possible dose-related increase in malignancy. The proposed size and duration of the pivotal trial 3001 was deemed reasonable for assessing this concern given that the signal was first identified in an asthma trial of comparable size (Study 3, n=309), but DAARP cautioned that the adequacy of the safety database would be a review issue. DAARP advised inclusion of SC golimumab as an active control in the pivotal trial to facilitate a head-to-head comparison of the IV and SC products.
- **September 9, 2011**, Complete Response for golimumab SC (sBLA 125289, S^{(b) (4)}) for [REDACTED]^{(b) (4)}
- **September 23, 2011**, Pre-BLA meeting:
 - The Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP) noted that given the PK differences and the absence of a direct comparison to the SC formulation, the golimumab IV program would be viewed as a standalone program with a requirement for independent substantiation of efficacy. DPAAP stated that replicate trials were typically required but stated that robust radiographic results might also be considered as independent substantiation. The Applicant stated that the safety database would include 550

patients exposed for 24 weeks and approximately 350 patients exposed for 1 year to the proposed 2 mg/kg dosing regimen.

- September 18, 2012, golimumab IV new BLA submission (BLA 125433)

3. CMC/Device

The recommended action from a CMC/device perspective is Approval. There are no outstanding product issues at the time of this review.

- General product quality considerations
Golimumab is a human IgG monoclonal antibody that binds TNF α . The IV formulation is composed of 12.5 mg/ml golimumab, L-histidine, sorbitol, polysorbate 80 and is packaged in a 50 mg/vial (nominal 4 ml fill volume). The golimumab antibody is produced from the same manufacturing process used for the approved SC product. The container closure system is a 4 ml Type 1 (b) (4) glass vial with a (b) (4) stopper and (b) (4) seal. Stability data support a shelf life of (b) (4) months when stored at 2-8°C and protected from light. The proposed route of administration and dosing is golimumab 2mg/kg IV given as a 30-minute IV infusion at Weeks 0 and 4 then every 8 weeks.
- Facilities review/inspection
The drug substance is manufactured at Janssen Biologics, BV (Leiden, The Netherlands) or Janssen Biologics Ltd., Cork Ireland. The final vial product for IV infusion is manufactured by Cilag AG (Schaffhausen, Switzerland). Facilities and equipment for drug substance were reviewed and inspected previously for the sc golimumab product and found to be acceptable. Cilag AG is a multi-product facility approved for other monoclonal antibody products; the site inspection for this product was waived due to multiple previous inspections.
- Other notable issues (resolved or outstanding)
No other issues.

4. Nonclinical Pharmacology/Toxicology

The recommended action from a nonclinical perspective is Approval. There are no outstanding nonclinical issues.

No new nonclinical pharmacology/toxicology information was included in the application. With the proposed IV dosing regimen, there is an approximate 2-fold increase in AUC and 26-fold increase in C_{max} as compared to the approved SC product. Nonclinical data in support of IV golimumab was previously submitted and reviewed under BLA 125289 for the SC product.

5. Clinical Pharmacology/Biopharmaceutics

The recommended action from a clinical pharmacology perspective is Approval. There are no outstanding issues from a clinical pharmacology perspective.

The application includes clinical pharmacology data for golimumab IV from the trials summarized in Table 2. Other clinical pharmacology data to support the golimumab SC product was previously reviewed and is summarized in the current package insert for SC product.

Trial	Design	Doses
C0524T14	Phase 1, OL, R trial in RA patients	2 mg/kg/ IV at Days 1 and 85 100 mg SC Q4wk through Week 20
C0524T15	Phase 1, OL, R trial in healthy volunteers	100 mg IV single dose 100 mg SC single dose
C0524T12	Phase 2, 48-week, MC, R, DB, PC trial in RA patients ± MTX	2 mg/kg IV Q12wk 4 mg/kg IV Q12wk
CNT0148ART3001	Phase 3 52-week, MC, R, DB, PC trial in RA patients with concomitant MTX	2 mg/kg IV at Wk 0, 4, and Q8wk

OL=open-label, MC=multi-center, R=randomized, DB=double-blind, PC=placebo-controlled, MTX=methotrexate

Following the proposed IV regimen, serum concentrations reach steady state by week 12. With concomitant use of MTX, treatment with 2 mg/kg golimumab every 8 weeks resulted in a mean steady-state trough serum concentration of 0.35 ± 0.38 µg/mL at Week 12, 0.31 ± 0.44 µg/mL at Week 20, and 0.42 ± 0.54 µg/mL at week 52. Dose-proportional pharmacokinetics over doses spanning 0.1 to 10.0 mg/kg following a single IV dose was observed. Although subjects with higher body weight tend to have higher serum golimumab concentrations than lower-weight subjects, the difference in golimumab exposure following the recommended dosing does not appear to be clinically significant based on population PK analysis. No formal study of hepatic or renal impairment was conducted. Patients who developed anti-golimumab antibodies tended to have lower serum trough values with a 33% increase in golimumab clearance.

The golimumab IV development program did not include a direct comparison of pharmacokinetics between the to-be-marketed 2mg/kg IV dose and the approved SC dose. Cross-study comparisons indicate a relatively higher mean C_{max} and an AUC that is approximately 2- to 3-fold higher with golimumab IV compared to golimumab SC.

Dose selection

Dose selection for golimumab IV is based on previous information available for the SC formulation as well as the results of Trial 12. The Applicant initially conducted Trial 12, a 48-week, randomized, double-blind, placebo-controlled trial in 643 patients with RA with or without concomitant methotrexate. Patients were randomized to golimumab IV 2 mg/kg, 4 mg/kg, or placebo administered every 12 weeks. Trial 12 did not meet its primary endpoint, ACR50 response at Week 14. The to-be-marketed dosing regimen, 2 mg/kg administered

every 8 weeks, was not included in Trial 12. The Applicant concluded that the failure of the trial was attributable to low systemic drug concentrations observed in the latter part of the 12-week dosing interval.

Based on the results of Trial 12 and pharmacokinetic simulation, the Applicant selected a nominal IV dose and dosing frequency to achieve serum trough values that are similar to trough values achieved with the SC formulation. The selected doses, 2 mg/kg IV administered at Week 0 and Week 4 following by administration every 8 weeks thereafter was subsequently evaluated in the confirmatory trial, Trial 3001.

6. Clinical Microbiology

The application is recommended for approval from a microbial control, CMC sterility assurance, and microbiology product quality perspective.

7. Clinical/Statistical- Efficacy

Clinical development program

The clinical development program for golimumab IV is based primarily on Trial 3001 (Table 3). While information from golimumab SC provided insight into the approximate nominal dose range and general safety profile for the molecular entity, the clinical program did not include a direct pharmacokinetic link or clinical head-to-head comparison of the IV and SC formulations.

Trial	Design	N	Doses	Efficacy variables	Study sites (% US enrollment)
3001 Sep 2009 - ongoing	112-wk R, DB, PC trial in RA patients on MTX	592	Golimumab IV 2 mg/kg Q8wk Placebo	ACR20 DAS28 HAQ-DI ACR50 vdH-S	S. America, Australia, E. Europe, Malaysia, Mexico, New Zealand, US (4%)

R=randomized, DB=double-blind, PC=placebo-controlled, MTX=methotrexate, OLE=open-label extension

Trial 3001 was a randomized, double-blind, placebo-controlled trial in patients with moderate to severely active RA on methotrexate (Table 3). To be eligible, patients were required to have moderate to severely active RA despite MTX therapy, defined as ≥ 6 tender and ≥ 6 swollen joints at screening and at baseline. Patients were also required to have CRP ≥ 1.0 mg/dl and be rheumatoid factor- or anti-cyclic citrullinated peptide-positive.

Following screening, patients were randomized 2:1 to golimumab IV 2 mg/kg (+ background MTX 15 to 25 mg/week) or placebo (+ background MTX 15 to 25 mg/week). Patients were stratified based upon screening CRP of < 1.5 or ≥ 1.5 mg/dl and site. Study drug was administered at Weeks 0 and 4 and then Q8wks by IV infusion over 30 minutes. Patients in the placebo arm were eligible to enter early escape at Week 16 and switched to golimumab IV

if <10% improvement in tender and swollen joint count was noted. Patients remaining on placebo were switched to golimumab IV at Week 24. Treatment was to be continued through Week 100 for all patients, followed by an additional 12-week follow-up period. The study report in the original BLA submission included data through 52 weeks. Additional safety data through August 15, 2012, were included in the 120-day safety update dated January 17, 2013.

The primary efficacy endpoint was ACR20 response at Week 14. Other efficacy endpoints were Disease Activity Index Score (DAS28) response at Week 14, change from baseline in HAQ-DI at Week 14, ACR50 response at Week 24, and change from baseline in van der Heijde (vdH-S) score at Week 24. Safety parameters included adverse events, physical exams, laboratory parameters, and anti-golimumab antibody titers. In general, the study design and assessed endpoints were similar to those used in efficacy and safety trials conducted for other TNF-inhibitors in RA.

Patient disposition, demographics, and baseline disease characteristics

A total of 395 patients were randomized to golimumab IV and 197 patients to placebo. At Week 16, 68 (35%) of the placebo patients met early escape criteria and were switched to golimumab IV. Seventeen (4%) of golimumab IV patients also met early escape criteria at Week 16 but were maintained on golimumab IV. Through Week 24, the most common reason cited for early discontinuation of treatment was adverse event, which is slightly higher for patients initially randomized to golimumab compared to placebo (2% versus 1%). Overall, premature discontinuations were infrequent and otherwise balanced across treatment groups.

Baseline demographic features were similar between the two treatment groups. The mean age was 52 years, 85% were female, and 80% were reported as Caucasian. The mean duration of RA disease was 7 years and approximately half the patients reported DMARD use prior to enrollment. The majority of patients (68%) were on methotrexate 15 mg Qweek, with the remainder taking higher doses up to 25 mg Qweek.

Efficacy

Primary efficacy endpoint: ACR20 at Week 14

The ACR20 response rate at Week 14 was assessed as the primary endpoint in Trial 3001. A higher response rate was observed for patients treated with golimumab IV compared to placebo. A sensitivity analysis imputing missing data as non-responders produced a similar result. Results for the individual ACR components (number of swollen joints, number of tender joints, patient's assessment of pain, and patient's global assessment of disease activity) were also supportive of efficacy.

Table 4 Primary efficacy endpoint: ACR20 response at Week 14 (Trial 3001)				
	Primary Analysis		Sensitivity Analysis with Missing as Non-Responders	
	Placebo N=197	Golimumab IV N=395	Placebo N=197	Golimumab IV N=395
ACR20 Response	49 (25%)	231 (58%)	48 (24%)	226 (57%)
Difference between treatment groups	34% [95% CI (26, 41)] (p<0.001)		33% (p<0.001)	

Source: FDA Biostatistics Review, Week 24 CSR (Table 18, Attachment 3.6), and submission dated June 27, 2013

ACR20 response at Week 24 was similarly supportive (32% placebo versus 63% golimumab IV; treatment difference of 31% [95% CI (23, 39)]).

Secondary efficacy endpoints

Secondary efficacy variables assessed included ACR50 and ACR70 responses, disease activity as measured by DAS28-CRP, physical function as measured by HAQ-DI, and radiographic progression as measured by van der Heijde-Modified Sharp score (vDH-S score). Overall, the results for these various endpoints were supportive for the efficacy of golimumab IV compared to placebo (Table 5).

Table 5 Secondary efficacy endpoints (Trial 3001)			
	Placebo N=197	Golimumab IV N=395	Difference between treatment groups [95% CI]^a
ACR50 response (%)			
<i>At Week 14</i>	17 (9%)	118 (30%)	21% [15, 27]
<i>At Week 24</i>	26 (13%)	138 (35%)	22% [15, 28]
ACR70 response (%)			
<i>At Week 14</i>	6 (3%)	49 (12%)	9% [5, 13]
<i>At Week 24</i>	8 (4%)	69 (18%)	14% [9, 18]
DAS28 <2.6 at Week 14 (%)	9 (5%)	61 (15%)	10% [6, 16]
HAQ-DI at Week 14 (SD)	0.2 (0.6)	0.5 (0.6)	0.3 [0.2, 0.4]
Mean change in vDH-S score at Week 24 (SD)	1.1 (3.2)	0.03 (1.9)	1.06 (p<0.001)*
<i>Change in erosion score</i>	0.5 (2.1)	0.1 (1.1)	
<i>Change in joint space narrowing score</i>	0.6 (1.7)	0.1 (1.3)	
Proportion with no progression in vDH-S score at Week 24	113 (57%)	279 (71%)	13% [5, 22]

Source: FDA Biostatistics Review, Week 24 CSR (Tables 20 and 21, Attachments 3.14, 3.17, 3.26), Week 52 CSR (Tables 4 and 9), and submission dated June 27, 2013

* P-value based on transformed data. FDA Biostatistics Review.

The radiographic progression endpoint is of particular interest, given the lack of benefit for this particular endpoint observed with golimumab SC and the relative difficulty in demonstrating a statistically significant benefit over standard-of-care methotrexate. Previously, the Division had informed the Applicant at the September 23, 2011, pre-BLA meeting that a robust result for the radiographic endpoint could be viewed as independent substantiation of efficacy in addition to a positive outcome for the primary endpoint based on ACR20 response. For this reason, the statistical review examined several sensitivity analyses,

excluding outliers as well as different imputation strategies for missing data. The results of these additional analyses supported the pre-specified analysis and the robustness of the radiographic benefit.

Efficacy summary

Data from Trial 3001 provide adequate support for the efficacy of golimumab 2 mg/kg IV administered every 8 weeks in the treatment of moderately to severely active rheumatoid arthritis (RA) in adults, in combination with methotrexate. The clinical review and biostatistics reviews conclude that the trial supports the efficacy of golimumab IV for clinical response, physical function response, and radiographic response. This CDTL memorandum concurs with these conclusions.

8. Safety

Exposure and discontinuations

The safety database for golimumab IV is based primarily on Trial 3001 (Table 6). Additional support for the product is obtained from the dose-ranging Trial 12 and from the SC development program, but these data are considered secondary due to the lower systemic exposures with the other IV doses evaluated and the SC formulation.

Table 6 Trial 3001: Exposure to golimumab 2 mg/kg IV dosed every 8 weeks at 52 weeks					
	Placebo	Placebo → golimumab IV at Wk 16	Placebo → golimumab IV at Wk 24	Golimumab IV	Any golimumab IV
Number of patients	197	68	121	395	584
Mean duration (wks)	21	36	27	50	44
Mean #doses	4	5	4	7	6

More patients who were randomized to golimumab IV discontinued treatment early due to an adverse event (AE) than placebo patients (4% vs. 1%), with infections cited as the most common AE during the 24-week controlled period. Of note, the protocol stipulated that patients who developed more serious infections were to be withdrawn from treatment. A similar rate of treatment discontinuation was observed over the duration of the 52-week treatment period.

Deaths

There were 6 deaths reported in Trial 3001 as of the 120-day safety update, 1 case in the placebo group, 2 cases in patients who crossed over to golimumab at Week 24, and 3 cases in the patients randomized to golimumab IV. The placebo patient died due to stroke in the setting of hypertensive crisis. The causes of death cited for patients who crossed from placebo to golimumab IV at Week 24 were sudden death (died while swimming) and cardiopulmonary arrest in the setting of *C. difficile* colitis. The remaining cases of death were myocardial infarction, acute abdominal syndrome in the setting of tuberculosis, and septic shock secondary to pyogenic lung abscess (history of latent TB). The nature of these deaths appears consistent with the increased risk of cardiovascular disease associated with RA as well as the known risk

of serious infections associated with TNF inhibition. The frequency of death was not higher than the frequencies observed in other development programs for a similar RA patient population.

Malignancy

While an increased risk of malignancy, particularly lymphoma, is associated with the use of TNF inhibitors in RA, earlier studies with golimumab IV raised the possibility of a dose-related increase. In the dose-ranging Trial 12, the incidence of all malignancies per 100 subject-years of follow-up was 0.71 (0.09, 2.56) for the 2 mg/kg arm Q12wks and 0.83 (0.23, 2.13) for the 4 mg/kg Q12 weeks arm.

In Trial 3001, one case of breast cancer with no metastases was reported in a 53-year-old woman randomized to golimumab IV on Study Day 164 versus no cases of malignancy in the placebo arm through Week 24. In the follow-up period, 3 additional cases of malignancy were reported: basal cell carcinoma in a 55-year-old female at Day 187; cervix carcinoma, and chronic lymphocytic leukemia. The incidence of all malignancies in the golimumab IV group was 0.56 (95% CI 0.01, 3.11), compared to 0 (95% CI 0.00, 3.79) in placebo.

Serious infections

An imbalance in serious infections was observed in Trial 3001. The reported cases included a range of infections, including intrabdominal abscesses, bacteremia, and complications of interstitial lung disease. Through Week 24, there were no cases reported in the placebo arm and 4 cases (0.9%) reported in the golimumab arm. When adjusted in terms of exposure, the incidence through the last IV dose per 100 subject-years was 4.07 (95% CI 2.90, 5.57). For context, the reported incidence of serious infections for golimumab 50 mg SC in an RA patient population was 3.4 cases per 100 subject-years and 5.0 cases per 100 subject-years for golimumab 100 mg SC (Medical Officer Review dated June 24, 2009, BLA 125289). While cross-study comparisons have limitations, the available information suggests that the risk of serious infection associated with golimumab IV is of similar magnitude to the risk associated with other TNF inhibitors, including golimumab SC. The golimumab SC label reports a variety of infections as well, including sepsis, pneumonia, abscess, tuberculosis, invasive fungal infections, and hepatitis B infection.

Common adverse events

In general, the rate of adverse events was slightly higher in patients randomized to golimumab IV compared to placebo during the 24-week controlled period (56% vs. 49%) in Trial 3001. Table 7 summarizes adverse events that occurred at a frequency >1% and greater than in placebo through Week 24. The most commonly reported AEs included headache, hypertension, nasopharyngitis, bronchitis, and pyrexia.

Table 7 Trial 3001: Adverse events associated with golimumab IV occurring at a frequency >1% and greater than in placebo through Week 24				
MedDRA Preferred Term	Treatment Group Assigned at Randomization		Placebo →	Golimumab Combined N=463
	Placebo N=197	Golimumab IV N=395	Golimumab IV (Early Escape) N=68	
Total number of patients with ≥1 AE N (%)	97 (49)	226 (56)	19 (28)	245 (53)
Headache	5 (2.5)	19 (4.8)	3 (4.4)	22 (4.8)
Hypertension	4 (2.0)	14 (3.5)	1 (1.5)	15 (3.2)
Nasopharyngitis	5 (2.5)	10 (2.5)	2 (2.9)	12 (2.6)
Bronchitis	2 (1.0)	11 (2.8)	0	11 (2.4)
Pyrexia	0	9 (2.3)	1 (1.5)	10 (2.2)
Pharyngitis	2 (1.0)	9 (2.3)	0	9 (1.9)
Aspartate Aminotransferase Increased	3 (1.5)	7 (1.8)	1 (1.5)	8 (1.7)
Diarrhea	2 (1.0)	8 (2.0)	0	8 (1.7)
Rash	1 (0.5)	8 (2.0)	0	8 (1.7)
Respiratory Tract Infection	0	7 (1.8)	1 (1.5)	8 (1.7)
Influenza	4 (2.0)	5 (1.3)	2 (2.9)	7 (1.5)
Sinusitis	3 (1.5)	7 (1.8)	0	7 (1.5)
Pruritus	1 (0.5)	6 (1.5)	0	6 (1.3)
Cough	0	5 (1.3)	0	5 (1.1)
Cystitis	0	5 (1.3)	0	5 (1.1)
Gastroenteritis	1 (0.5)	5 (1.3)	0	5 (1.1)

Source: 24-week CSR, Attachment 4.3

Other adverse events of interest

The Applicant assessed the formation of anti-drug antibodies (ADA) throughout the conduct of Trial 3001. Approximately 4% of patients who received at least one dose of golimumab IV developed anti-golimumab antibodies. ADA formation was not associated with increased AEs, including hypersensitivity events, or decreased efficacy, although the number of positive patients was fairly low, limiting the ability to draw conclusions from the information. Based on PK measurements, ADA formation does appear to be associated with decreased exposure, but there are no data at this time to support the need for dose adjustment in such situations.

Infusion reactions, defined as any AE occurring during or within 1 hour of infusion, were reported in 4% of patients receiving golimumab IV during the 24-week treatment period, compared to 0.5% in placebo. The infusion reactions encompassed a range of symptoms and signs, including rash, flushing, headache, hypertension or hypotension, bradycardia, and vertigo. The reactions did not result in discontinuation, nor were they associated with positive ADA titers. A review of the individual line listings did not suggest any unidentified cases of anaphylaxis among the reported infusion reactions.

Safety summary

The safety for golimumab is based primarily on Trial 3001. No direct head-to-head comparison is available to compare the relative safety of the proposed IV product to the approved SC product, and differences in safety cannot be ruled out given the higher exposure associated with the proposed IV product. That being said, the clinical review has concluded that the safety profile observed for golimumab IV appears generally consistent with the profile observed for TNF-inhibitors as a drug class. The major safety issues include an increased risk

of malignancy and serious infections. No new safety signals were identified. This memorandum concurs with these conclusions.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, since golimumab is an established pharmaceutical entity, and no new indications or claims were proposed.

10. Pediatrics

Under the Pediatric Research Equity Act, the Applicant is required to conduct a trial that will evaluate the safety, efficacy, PK/PD and immunogenicity of IV golimumab in pediatric patients between the ages 2 to 17 years and 11 months with active Juvenile idiopathic arthritis (JIA) despite standard therapy with methotrexate. The Applicant has agreed to the PREA PMR and has provided the following timeline for this partial deferral:

Final Protocol Submission: 12/13/2013

Trial Initiation: (b) (4)

Study/Trial Completion: (b) (4)

Final Report Submission: (b) (4)

The proposed trial design is a 52-week, randomized, withdrawal controlled Phase 3 trial in children ages 2 to 17 years and 11 months old with active JIA despite standard therapy with methotrexate (MTX). Patients who complete the trial will have the option to enroll in an open-label extension. The proposed dose for evaluation is a golimumab IV body surface area (BSA)-adjusted dosing regimen (80 mg/m²) at Weeks 0, 4, and every 8 weeks thereafter. The proposed dose is based on the adult golimumab IV dosing frequency, the available experience with golimumab SC in JIA, and the negative results previously obtained with infliximab (a related chimeric TNF-inhibitor) in JRA. The Applicant had concluded from the failed infliximab pediatric program that extrapolation from an adult IV dose on mg/kg basis may result in subtherapeutic doses in younger patients with low body weights.

A study of patients under the age of 2 years will be waived, as there are so few patients in this age range with pediatric JIA to make studying this population impractical.

The Applicant originally requested a waiver for all pediatric studies, stating that study of the IV formulation was not warranted given an ongoing pediatric trial with the SC formulation. The Division disagreed with this rationale, noting that golimumab IV was associated with different systemic exposure and appeared to have a different efficacy profile. The Applicant subsequently submitted a revised pediatric plan on December 12, 2012, outlining the proposed randomized withdrawal trial in patients 2 to 17 years of age and a request for partial waiver in patients <2 years of age. Given the uncertainty surrounding the proposed dose selection, the Division found the Applicant's proposed randomized, withdrawal design to be reasonable for obtaining clinical efficacy and safety data to confirm the proposed pediatric dosing regimen.

The plan for partial deferral in patients 2 to 17 years of age and partial waiver for patients <2 years was discussed and agreed upon at the May 1, 2013, meeting of the Pediatric Review Committee (PeRC).

11. Other Relevant Regulatory Issues

The Applicant certified that Trials 12 and 3001 were conducted in compliance with the following: Good Clinical Practice standards as outlined in the Declaration of Helsinki or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, with the institutional review board regulations as per 21 CFR (56), and the informed consent regulation as per 21 CFR (50). The required financial disclosures were provided.

The Division of Scientific Investigation (DSI) inspected a study site in Poland and one site in the US that participated in the pivotal Phase 3 trial 3001. Both sites were chosen based on high study enrollment (20 subjects and 15 subjects, respectively). The DSI review concluded that the data generated by these sites appeared to be reliable to support this application.

12. Labeling

Final labeling and review the of medication guide remain pending at the time of this memorandum. High-level issues pertaining to the label are noted as follows:

- The proposed tradename, Simponi Aria, has been found acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP).
- Simponi Aria will have a label separate from the currently approved SC formulation, Simponi.
- Warnings and Precautions statements consistent with the TNF-inhibitor class of drugs will be included.
- Clinical trial data from Trial 3001 will be featured in Section 6, Adverse Reactions and Section 14, Clinical Studies. Pooled data or other data from the SC registration trials will not be included.
- Medication Guide will follow a similar format as the guides for other TNF-inhibitor products and will feature the safety risks outlined in the Warnings and Precautions section of the package insert.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended action is Approval.

- Risk Benefit Assessment

The efficacy of golimumab IV 2 mg/kg dosed at Week 0 and Week 4 then every 8 weeks thereafter is supported by statistically significant results from Trial 3001 for the proposed indication, the treatment of moderately to severely active rheumatoid arthritis (RA) in adults, in combination with methotrexate. Clinical trial data show that golimumab IV is associated with certain safety concerns, including an increased risk of serious infections and malignancy. These safety concerns are consistent with the concerns associated with other TNF-inhibitors in the same drug class. Overall, the risk-benefit favors approval of golimumab IV for the proposed indication, accompanied by appropriate labeling and a medication guide that details the potential for these risks.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk evaluation and management strategies are recommended.

- Recommendation for other Postmarketing Requirements and Commitments

Under the Pediatric Research Equity Act, the Applicant is required to conduct a trial that will evaluate the safety, efficacy, PK/PD and immunogenicity of IV golimumab in pediatric patients between the ages 2 to 17 years and 11 months with active Juvenile Idiopathic Arthritis (JIA) despite standard therapy with methotrexate.

- Recommended Comments to Applicant

The following comment regarding the PREA PMR will be conveyed to the Applicant:

Conduct a trial to evaluate the safety, efficacy, PK/PD, and immunogenicity of IV golimumab in pediatric patients between the ages 2 to 17 years and 11 months with active Juvenile Idiopathic Arthritis (JIA) despite standard therapy with methotrexate.

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

/s/

SUSAN L LIMB
06/27/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SIMPONI[®] ARIA[™] safely and effectively. See full prescribing information for SIMPONI ARIA.

SIMPONI ARIA

(golimumab) injection, for intravenous use

Initial U.S. Approval: 2009

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal (such as histoplasmosis), and other opportunistic infections have occurred in patients receiving SIMPONI ARIA (5.1).
- Discontinue SIMPONI ARIA if a patient develops a serious infection or sepsis (5.1).
- Perform test for latent TB; if positive, start treatment for TB prior to starting SIMPONI ARIA (5.1).
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1).
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI ARIA is a member (5.2).

INDICATIONS AND USAGE

SIMPONI ARIA is a tumor necrosis factor (TNF) blocker indicated for the treatment of adult patients with moderately to severely active Rheumatoid Arthritis (RA) in combination with methotrexate (1.1)

DOSAGE AND ADMINISTRATION

- 2 mg/kg intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks (2.1)
- Dilution of supplied SIMPONI ARIA solution with 0.9% w/v sodium chloride is required prior to administration (2.3)

DOSAGE FORMS AND STRENGTHS

- Injection: 50 mg/4 mL (12.5 mg/mL) in a single use vial (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

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2 DOSAGE AND ADMINISTRATION

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14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Serious infections – Do not start SIMPONI ARIA during an active infection. If an infection develops, monitor carefully, and stop SIMPONI ARIA if infection becomes serious (5.1).
- Invasive fungal infections – For patients who develop a systemic illness on SIMPONI ARIA, consider empiric antifungal therapy for those who reside in or travel to regions where mycoses are endemic (5.1).
- Hepatitis B reactivation – Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop SIMPONI ARIA and begin antiviral therapy (5.1).
- Malignancies – More cases of lymphoma have been observed among patients receiving TNF-blockers compared with patients in the control groups. Cases of other malignancies have been observed among patients receiving TNF-blockers (5.2).
- Heart failure – Worsening, or new onset, may occur. Stop SIMPONI ARIA if new or worsening symptoms occur (5.3).
- Demyelinating disease, exacerbation or new onset, may occur (5.4).
- Hypersensitivity reactions: Serious systemic hypersensitivity reactions including anaphylaxis may occur (5.10).

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 3\%$) are: upper respiratory tract infection, viral infection, bronchitis, hypertension, and rash (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Biologics, including abatacept and anakinra: Increased risk of serious infection (5.1, 5.5, 5.6, 5.7, 7.2)
- Live vaccines should not be given with SIMPONI ARIA (5.9, 7.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2013

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with SIMPONI ARIA are at increased risk for developing serious infections that may lead to hospitalization or death [see *Warnings and Precautions (5.1)*]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue SIMPONI ARIA if a patient develops a serious infection.

Reported infections with TNF-blockers, of which SIMPONI ARIA is a member, include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Test patients for latent tuberculosis before SIMPONI ARIA use and during therapy. Initiate treatment for latent tuberculosis prior to SIMPONI ARIA use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.

Consider the risks and benefits of treatment with SIMPONI ARIA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with SIMPONI ARIA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy [see *Warnings and Precautions (5.1)*].

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI ARIA is a member [see *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

SIMPONI ARIA, in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis.

2 DOSAGE AND ADMINISTRATION

2.1 Rheumatoid Arthritis

The SIMPONI ARIA dosage regimen is 2 mg per kg given as an intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter.

SIMPONI ARIA should be given in combination with methotrexate. Other non-biologic DMARDs, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with SIMPONI ARIA.

The efficacy and safety of switching between intravenous and subcutaneous formulations and routes of administration have not been established.

2.2 Evaluation for Tuberculosis and Hepatitis B Prior to Dosage

Prior to initiating SIMPONI ARIA and periodically during therapy, evaluate patients for active tuberculosis and test for latent infection [*see Warnings and Precautions (5.1)*]. Prior to initiating SIMPONI ARIA, test patients for hepatitis B viral infection [*see Warnings and Precautions (5.1)*].

2.3 Important Administration Instructions

SIMPONI ARIA solution for intravenous infusion should be diluted by a healthcare professional using aseptic technique as follows:

1. Calculate the dosage and the number of SIMPONI ARIA vials needed based on the recommended dosage of 2 mg/kg and the patient's weight. Each 4 mL vial of SIMPONI ARIA contains 50 mg of golimumab.
2. Check that the solution in each vial is colorless to light yellow and opalescent. The solution may develop a few fine translucent particles, as golimumab is a protein. Do not use if opaque particles, discoloration or other foreign particles are present.
3. Dilute the total volume of the SIMPONI ARIA solution with 0.9% w/v sodium chloride for infusion to a final volume of 100 mL. For example, this can be accomplished by withdrawing a volume of the 0.9% w/v sodium chloride solution from the 100-mL infusion bag or bottle equal to the total volume of SIMPONI ARIA. Slowly add the total volume of SIMPONI ARIA solution to the 100-mL infusion bag or bottle. Gently mix. Discard any unused solution remaining in the vials.
4. Prior to infusion, visually inspect the diluted SIMPONI ARIA solution for particulate matter or discoloration. Do not use if these exist.
5. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.22 micrometer or less).

6. Do not infuse SIMPONI ARIA concomitantly in the same intravenous line with other agents. No physical biochemical compatibility studies have been conducted to evaluate the use of SIMPONI ARIA with other intravenous agents in the same intravenous line.
7. Infuse the diluted solution over 30 minutes.
8. Once diluted, the infusion solution can be stored for 4 hours at room temperature.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg of golimumab per 4 mL of solution (12.5 mg of golimumab per mL) in each vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with SIMPONI ARIA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease. The concomitant use of a TNF-blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMPONI ARIA and these biologic products is not recommended [*see Warnings and Precautions (5.5, 5.6) and Drug Interactions (7.2)*].

Treatment with SIMPONI ARIA should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating SIMPONI ARIA in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with SIMPONI ARIA. Discontinue SIMPONI ARIA if a patient develops a serious infection, an opportunistic infection, or sepsis. For patients who develop a new infection during treatment with SIMPONI ARIA, perform a prompt and complete diagnostic workup

appropriate for an immunocompromised patient and initiate appropriate antimicrobial therapy and closely monitor them.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF-blockers, including patients who have previously received treatment for latent or active tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating SIMPONI ARIA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF-blockers has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating SIMPONI ARIA, assess if treatment for latent tuberculosis is needed; An induration of 5 mm or greater is a positive tuberculin skin test, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of SIMPONI ARIA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Consider tuberculosis in the differential diagnosis in patients who develop a new infection during SIMPONI ARIA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Consider appropriate empiric antifungal therapy and take into account both the risk for severe fungal infection and the risks of antifungal therapy while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Hepatitis B Virus Reactivation

The use of TNF-blockers, of which SIMPONI ARIA is a member, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e., surface antigen positive). In some instances, HBV reactivation occurring in conjunction with

TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants.

All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMPONI ARIA, to patients who are carriers of HBV. Adequate data are not available on whether anti-viral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF-blockers. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

In patients who develop HBV reactivation, TNF-blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF-blockers after HBV reactivation has been controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF-blockers in this situation and monitor patients closely.

5.2 Malignancies

Malignancies in Pediatric Patients

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy $\leq$ 18 years of age), of which SIMPONI ARIA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression, and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports. Use of SIMPONI ARIA in patients under 18 years of age has not been established.

Malignancies in Adult Patients

The risks and benefits of TNF-blocker treatment including SIMPONI ARIA should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF-blocker in patients who develop a malignancy.

In the controlled portions of clinical trials of TNF-blockers including the subcutaneous formulation of golimumab more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with patients in the control groups. Patients with RA and other chronic inflammatory diseases, particularly patients with highly active disease and/or

chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Melanoma has been reported in patients treated with TNF-blocking agents, including the subcutaneous formulation of golimumab. Merkel cell carcinoma has been reported in patients treated with TNF-blocking agents. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

In controlled trials of other TNF-blockers in patients at higher risk for malignancies (e.g., patients with COPD, patients with Wegener's granulomatosis treated with concomitant cyclophosphamide) a greater portion of malignancies occurred in the TNF-blocker group compared to the controlled group. In an exploratory clinical trial evaluating the use of the subcutaneous formulation of golimumab in patients with severe persistent asthma, more patients treated with golimumab reported malignancies compared with control patients. The significance of this finding is unknown.

During the controlled portion of the Phase 3 trial in RA for SIMPONI ARIA, the incidence of malignancies other than lymphoma and NMSC per 100-patient-years of follow-up was 0.56 (95% CI: 0.01, 3.11) in the SIMPONI ARIA group compared with an incidence of 0 (95% CI: 0.00, 3.79) in the placebo group.

5.3 Congestive Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blockers, including SIMPONI ARIA. In several exploratory trials of other TNF-blockers in the treatment of CHF, there were greater proportions of TNF-blocker treated patients who had CHF exacerbations requiring hospitalization or increased mortality. SIMPONI ARIA has not been studied in patients with a history of CHF and SIMPONI ARIA should be used with caution in patients with CHF. If a decision is made to administer SIMPONI ARIA to RA patients with CHF, these patients should be closely monitored during therapy, and SIMPONI ARIA should be discontinued if new or worsening symptoms of CHF appear.

5.4 Demyelinating Disorders

Use of TNF-blockers, of which SIMPONI ARIA is a member, has been associated with rare cases of new onset or exacerbation of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS) and peripheral demyelinating disorders, including Guillain-Barré syndrome. Cases of central demyelination, MS, optic neuritis, and peripheral demyelinating polyneuropathy have rarely been reported in patients treated with the subcutaneous formulation of golimumab. Prescribers should exercise caution in considering the use of TNF-blockers, including SIMPONI ARIA, in patients with central or peripheral nervous

system demyelinating disorders. Discontinuation of SIMPONI ARIA should be considered if these disorders develop.

5.5 Use with Abatacept

In controlled trials, the concurrent administration of another TNF-blocker and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; and the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of TNF-blockers including SIMPONI ARIA and abatacept is not recommended [see *Drug Interactions (7.2)*].

5.6 Use with Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater portion of serious infections and neutropenia and no additional benefits compared with the TNF-blocker alone. Therefore, the combination of anakinra with TNF-blockers, including SIMPONI ARIA, is not recommended [see *Drug Interactions (7.2)*].

5.7 Switching Between Biological Disease Modifying Antirheumatic Drugs (DMARDs)

Care should be taken when switching from one biologic product to another biologic product since overlapping biological activity may further increase the risk of infection.

5.8 Hematologic Cytopenias

There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anemia, and thrombocytopenia in patients receiving TNF-blockers. In clinical studies, cases of pancytopenia, leukopenia, neutropenia, and thrombocytopenia have also occurred in SIMPONI ARIA-treated patients. Caution should be exercised when using TNF-blockers, including SIMPONI ARIA, in patients who have or have had significant cytopenias.

5.9 Vaccinations

Patients treated with SIMPONI ARIA may receive vaccinations, except for live vaccines. No data are available on the response to live vaccination or the risk of infection, or transmission of infection after the administration of live vaccines to patients receiving SIMPONI ARIA.

5.10 Hypersensitivity Reactions

In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following administration of the subcutaneous formulation of golimumab. Some of these reactions occurred after the first administration of golimumab. If an anaphylactic or other serious allergic reaction occurs, administration of SIMPONI ARIA should be discontinued immediately and appropriate therapy instituted.

6 ADVERSE REACTIONS

The most serious adverse reactions were:

- Serious Infections [*see Warnings and Precautions (5.1)*]
- Malignancies [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety data described below are based on one, randomized, double-blind, controlled Phase 3 trial in patients with RA receiving SIMPONI ARIA by intravenous infusion (Trial 1). The protocol included provisions for patients taking placebo to receive treatment with SIMPONI ARIA at Week 16 or Week 24 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Comparisons between placebo and SIMPONI ARIA were based on the first 24 weeks of exposure.

Trial 1 included 197 control-treated patients and 463 SIMPONI ARIA-treated patients (which includes control-treated patients who switched to SIMPONI ARIA at Week 16). The proportion of patients who discontinued treatment due to adverse reactions in the controlled phase of Trial 1 through Week 24 was 3.5% for SIMPONI ARIA-treated patients and 0.5% for placebo-treated patients. Upper respiratory tract infection was the most common adverse reaction reported in the trial through Week 24 occurring in 6.5% of SIMPONI ARIA-treated patients as compared with 7.6% of control-treated patients, respectively.

Infections

Serious infections observed in SIMPONI ARIA-treated patients included sepsis, pneumonia, cellulitis, abscess, opportunistic infections, tuberculosis (TB), and invasive fungal infections. Cases of TB included pulmonary and extrapulmonary TB. The majority of the TB cases occurred in countries with a high incidence rate of TB [*see Warnings and Precautions (5.1)*].

In the controlled phase of Trial 1 through Week 24, infections were observed in 27% of SIMPONI ARIA-treated patients compared with 24% of control-treated patients, and serious infections were observed in 0.9% of SIMPONI ARIA-treated patients and 0.0% of control-treated patients. Through Week 24, the incidence of serious infections per 100 patient-years of follow-up was 2.2 (95% CI 0.61, 5.71) for the SIMPONI ARIA group, and 0 (0.00, 3.79) for the placebo group. In the controlled and uncontrolled portions of Trial 1, 958 total patient-years of follow-up with a median follow-up of approximately 92 weeks, the incidence per 100 patient-years of all serious infections was 4.07 (CI: 2.90, 5.57) in patients receiving SIMPONI ARIA [*see Warnings and Precautions (5.1)*]. In the controlled and uncontrolled portions of Trial 1, in SIMPONI ARIA treated patients, the incidence of active TB per 100 patient-years was 0.31 (95% CI: 0.06; 0.92) and the incidence of other opportunistic infections per 100 patient-years was 0.42 (95% CI: 0.11, 1.07).

Malignancies

One case of malignancy other than lymphoma and NMSC with SIMPONI ARIA was reported through Week 24 during the controlled phase of Trial 1. In the controlled and uncontrolled portions through approximately 92 weeks, the incidence of malignancies per 100 patient years, other than lymphoma and NMSC, in SIMPONI ARIA-treated patients was 0.31 (CI: 0.06, 0.92) and the incidence of NMSC was 0.1 (95% CI: 0.00, 0.58).

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers.

In the controlled phase of Trial 1, through Week 24, ALT elevations ≥ 5 x ULN occurred in 0.6% of SIMPONI ARIA-treated patients and 0% of control-treated patients and ALT elevations ≥ 3 x ULN occurred in 2.4% of SIMPONI ARIA-treated patients and 2.5% of control-treated patients.

Since many of the patients in the Phase 3 trial were also taking medications that cause liver enzyme elevations (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], methotrexate [MTX], or isoniazid prophylaxis), the relationship between SIMPONI ARIA and liver enzyme elevation is not clear.

Autoimmune Disorders and Autoantibodies

The use of TNF-blockers, of which SIMPONI ARIA is a member, has been associated with the formation of autoantibodies and, rarely, with the development of a lupus-like syndrome.

At Week 20 in Trial 1, 17% of SIMPONI ARIA-treated patients and 13% of control patients were newly ANA-positive (at titers of 1:160 or greater). Of these patients, one SIMPONI ARIA-treated patient and no control-treated patients had newly positive anti-dsDNA antibodies.

Administration Reactions

In the controlled phase of Trial 1 through Week 24, 1.1% of SIMPONI ARIA infusions were associated with an infusion reaction compared with 0.2% of infusions in the control group. The most common infusion reaction in SIMPONI ARIA treated patients was rash. No serious infusion reactions were reported.

Immunogenicity

Antibodies to SIMPONI ARIA were detected in 13 (3%) golimumab-treated patients following IV administration of SIMPONI ARIA in combination with MTX through Week 24 of Trial 1.

All patients who were positive for antibodies to golimumab had neutralizing antibodies based on an in vitro cell-based assay. The small number of patients positive for antibodies to SIMPONI ARIA limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

The data above reflect the percentage of patients whose test results were considered positive for antibodies to SIMPONI ARIA in an ELISA assay. The ELISA assay is subject to interference by co-present golimumab and thus the results are an underestimate of the rate of product immunogenicity and are in addition highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SIMPONI ARIA with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% in the SIMPONI ARIA + MTX group with a higher incidence than in the placebo + MTX group during the controlled period of Trial 1 through Week 24.

Table 1: Adverse Drug Reactions Reported by ≥ 1% of SIMPONI ARIA-Treated Patients and with a Higher Incidence than Placebo-Treated Patients in Trial 1 through Week 24

	SIMPONI ARIA + MTX	Placebo + MTX
Patients treated	463	197
Adverse Reaction		
Infections and Infestations		
Upper respiratory tract infection (such as upper respiratory tract infection, nasopharyngitis, pharyngitis, laryngitis, and rhinitis)	13%	12%
Viral infections (such as influenza and herpes)	4%	3%
Bacterial infections	1%	0%
Bronchitis	3%	1%
Vascular disorders		
Hypertension	3%	2%
Skin and subcutaneous disorders		
Rash	3%	1%
General disorders and administration site conditions		
Pyrexia	2%	1%
Blood and lymphatic disorders		
Leukopenia	1%	0%

Other and less common clinical trial adverse drug reactions

Adverse drug reactions that do not appear in Table 1 or that occurred <1% in SIMPONI ARIA - treated patients during Trial 1 through Week 24 that do not appear in the Warnings and Precautions section included the following events listed by system organ class:

Infections and Infestations: Superficial fungal infection, sinusitis, abscess, lower respiratory tract infection (pneumonia), pyelonephritis

Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, neutrophil count decreased

Nervous system disorders: Dizziness, paresthesia

Gastrointestinal disorders: Constipation

6.2 Post-marketing Experience

There is no post-marketing experience available for SIMPONI ARIA. The following adverse reactions have been identified during post-approval use of the subcutaneous formulation of golimumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to golimumab exposure.

Neoplasm Benign and Malignant: Melanoma [see Warnings and Precautions (5.2)]

Immune System Disorders: Serious systemic hypersensitivity reactions (including anaphylactic reaction) [see Warnings and Precautions (5.11)], sarcoidosis

Skin and subcutaneous tissue disorders: Skin exfoliation

7 DRUG INTERACTIONS

7.1 Methotrexate

SIMPONI ARIA should be used with methotrexate (MTX) *[see Clinical Studies (14.1)]*. Following IV administration, concomitant administration of methotrexate decreases the clearance of SIMPONI ARIA by approximately 9% based on population PK analysis. In addition, concomitant administration of methotrexate decreases the SIMPONI ARIA clearance by reducing the development of anti-golimumab antibodies.

7.2 Biologic Products for RA

An increased risk of serious infections has been seen in clinical RA studies of other TNF-blockers used in combination with anakinra or abatacept, with no added benefit; therefore, use of SIMPONI ARIA with other biologic products, including abatacept or anakinra is not recommended *[see Warnings and Precautions (5.5 and 5.6)]*. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF-blocker. The concomitant use of SIMPONI ARIA with biologics approved to treat RA is not recommended because of the possibility of an increased risk of infection.

7.3 Live Vaccines

Live vaccines should not be given concurrently with SIMPONI ARIA *[see Warnings and Precautions (5.10)]*.

Infants born to women treated with SIMPONI ARIA during their pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to SIMPONI ARIA *in utero* is not recommended for 6 months following the mother's last SIMPONI ARIA infusion during pregnancy *[see Use in Specific Populations (8.1)]*.

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF α) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of SIMPONI ARIA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B – There are no adequate and well-controlled studies of SIMPONI ARIA in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, it is not known whether SIMPONI ARIA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI ARIA should be used during pregnancy only if clearly needed.

An embryofetal developmental toxicology study was performed in which pregnant cynomolgus monkeys were treated subcutaneously with golimumab during the first trimester with doses up to 50 mg/kg twice weekly (200 times greater than the maximum recommended human dose-MHRD) and has revealed no evidence of harm to maternal animals or fetuses. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. In this study, *in utero* exposure to golimumab produced no developmental defects to the fetus.

A pre- and post-natal developmental study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the second and third trimesters, and during lactation at doses up to 50 mg/kg twice weekly (33 times and 12 times greater than the maximal steady state human blood levels for maternal animals and neonates, respectively) and has revealed no evidence of harm to maternal animals or neonates. Golimumab was present in the neonatal serum from the time of birth and for up to six months postpartum. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants.

IgG antibodies are known to cross the placenta during pregnancy and have been detected in the serum of infants born to patients treated with these antibodies. Since SIMPONI ARIA is an IgG antibody, infants born to women treated with SIMPONI ARIA during their pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to SIMPONI ARIA *in utero* is not recommended for 6 months following the mother's last SIMPONI ARIA infusion during pregnancy [*see Warnings and Precautions (5.10)*].

8.3 Nursing Mothers

It is not known whether SIMPONI ARIA is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from SIMPONI ARIA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

In the pre- and post-natal development study in cynomolgus monkeys in which golimumab was administered subcutaneously during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 400-fold lower than the maternal serum concentrations.

8.4 Pediatric Use

Safety and effectiveness of SIMPONI ARIA in pediatric patients less than 18 years of age have not been established. Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with other TNF-blocking agents [*see Warnings and Precautions (5.2)*].

8.5 Geriatric Use

In Trial 1 in RA, the number of patients ages 65 or older was too small to make comparisons with younger SIMPONI ARIA -treated patients. Because there is a higher incidence of infections in the geriatric population in general, caution should be used in treating geriatric patients with SIMPONI ARIA.

10 OVERDOSAGE

In a clinical study, 5 patients received single infusions of up to 1000 mg of SIMPONI ARIA without serious adverse reactions or other significant reactions.

11 DESCRIPTION

SIMPONI ARIA (golimumab) is a human IgG1 κ monoclonal antibody specific for human tumor necrosis factor alpha (TNF α) that exhibits multiple glycoforms with molecular masses of approximately 150 to 151 kilodaltons. SIMPONI ARIA was created using genetically engineered mice immunized with human TNF, resulting in an antibody with human-derived antibody variable and constant regions. SIMPONI ARIA is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

The SIMPONI ARIA drug product is a sterile concentrated solution of the golimumab antibody supplied in a 4 mL glass vial for intravenous infusion.

SIMPONI ARIA does not contain preservatives, natural rubber or latex. The solution is colorless to light yellow with a pH of approximately 5.5. Each 4 mL vial of SIMPONI ARIA contains 50 mg golimumab, 9.5 mM histidine, 4.5% (w/v) sorbitol, and 0.015% (w/v) polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNF α . This interaction prevents the binding of TNF α to its receptors, thereby inhibiting the biological activity of TNF α (a cytokine protein). There was no evidence of the golimumab antibody binding to other TNF superfamily ligands; in particular, the golimumab antibody did not bind or neutralize human lymphotoxin. Golimumab did not lyse human monocytes expressing transmembrane TNF in the presence of complement or effector cells.

Elevated TNF α levels in the blood, synovium, and joints have been implicated in the pathophysiology of rheumatoid arthritis. TNF α is an important mediator of the articular inflammation that is characteristic of RA. Golimumab modulated the *in vitro* biological effects mediated by TNF in several bioassays, including the expression of adhesion proteins responsible for leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of proinflammatory cytokines (IL-6, IL-8, G-CSF and GM-CSF). The clinical relevance of these findings is unknown.

12.2 Pharmacodynamics

Following treatment with SIMPONI ARIA in patients with RA, decreases from baseline were observed in tissue inhibitor of metalloproteinases 1 (TIMP-1), matrix metalloproteinase-1 (MMP-1), matrix metalloproteinase-3 (MMP-3), resistin, interleukin-6 (IL-6), macrophage inflammatory protein-1 (MIP-1b), vascular endothelial growth factor (VEGF), serum amyloid A (SAA), S100A12, and high sensitivity C-Reactive protein (hsCRP). Conversely, increases from baseline were observed in abstract tartrate-resistant acid phosphatase (TRAP-5b). The clinical relevance of this information is not known.

12.3 Pharmacokinetics

Absorption

Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, a mean C_{max} of 44.4 $\pm$ 11.3 μ g/ml was observed in patients with RA. Data directly comparing 2 mg/kg intravenous administration and 50 mg subcutaneous administration are not available.

Distribution

Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, the mean volume of distribution was estimated to be 115 $\pm$ 19 ml/kg in healthy subjects, and 151 $\pm$ 61 ml/kg in patients with RA. The volume of distribution of golimumab may indicate that golimumab is distributed primarily in the circulatory system with limited extravascular distribution.

Elimination

The elimination pathways for golimumab have not been characterized.

Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, the systemic clearance of golimumab was estimated to be 6.9 ± 2.0 ml/day/kg in healthy subjects and 7.6 ± 2.0 ml/day/kg in patients with RA. The mean terminal half-life was estimated to be 12 ± 3 days in healthy subjects and the mean terminal half-life in RA patients was 14 ± 4 days.

When 2 mg/kg SIMPONI ARIA was administered intravenously to patients with RA at weeks 0, 4 and every 8 weeks thereafter, serum concentrations reached steady state by Week 12. Following IV administration, concomitant administration of methotrexate decreases the clearance of SIMPONI ARIA by approximately 9% based on population PK analysis. In addition, concomitant administration of methotrexate decreases the SIMPONI ARIA clearance by reducing the development of anti-golimumab antibodies. With concomitant use of MTX, treatment with 2 mg/kg golimumab every 8 weeks resulted in a mean steady-state trough serum concentration of approximately 0.4 ± 0.4 µg/ml in patients with active RA despite MTX therapy.

Population PK analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of SIMPONI following SC administration.

Patients who developed anti-golimumab antibodies generally had low trough steady-state serum concentrations of golimumab.

No formal study of the effect of renal or hepatic impairment on the PK of golimumab was conducted.

Linearity

Golimumab exhibited approximately dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous dose.

Effect of weight on pharmacokinetics

Following intravenous administration, patients with higher body weight tended to have higher serum golimumab concentrations than patients with lower body weights when golimumab was administered on a mg/kg (body weight) basis. However, based on population PK analysis, there were no clinically relevant differences in golimumab exposure following intravenous administration of 2 mg/kg SIMPONI ARIA in patients across a range of different body weights.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of golimumab have not been conducted to evaluate its carcinogenic potential. Mutagenicity studies have not been conducted with golimumab. A fertility study conducted in mice using an analogous anti-mouse TNF α antibody administered by the intravenous route at doses up to 40 mg/kg once per week showed no impairment of fertility.

14 CLINICAL STUDIES

The efficacy and safety of SIMPONI ARIA were evaluated in one multicenter, randomized, double-blind, controlled trial (Trial 1) in 592 patients $\geq$ 18 years of age with moderately to severely active RA despite concurrent MTX therapy and had not previously been treated with a biologic TNF-blocker. Patients were diagnosed according to the American College of Rheumatology (ACR) criteria, at least 3 months prior to administration of study agent and were required to have at least 6 swollen and 6 tender joints. Patients were randomized to receive either SIMPONI ARIA 2 mg/kg (n=395) or placebo (n=197) over a 30 minute intravenous infusion at Weeks 0, 4 and every 8 weeks thereafter in addition to their weekly maintenance MTX dose (15-25 mg/kg). All patients receiving placebo + MTX received SIMPONI ARIA + MTX after Week 24, but the trial remained blinded until all patients had completed 52 weeks of treatment. Efficacy data were collected and analyzed through Week 52. Patients were allowed to continue stable doses of concomitant low dose corticosteroids (equivalent to $\leq$ 10 mg of prednisone a day) and/or NSAIDs and patients may have received oral MTX during the trials. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

The primary endpoint in Trial 1 was the percentage of patients achieving an ACR 20 response at Week 14. In Trial 1, the majority of subjects were women (82%) and were Caucasian (81%) with a median age of 52 years and a median weight of 70 kg. Median disease duration was 4.7 years, and 50% of the patients used at least one DMARD other than MTX in the past. At baseline, 81% of patients received concomitant NSAIDs and 81% of patients received low dose corticosteroids (equivalent to $\leq$ 10 mg of prednisone a day). The median baseline DAS28-CRP was 5.9 and the median van der Heijde-Sharp score at baseline was 28.5.

Clinical Response

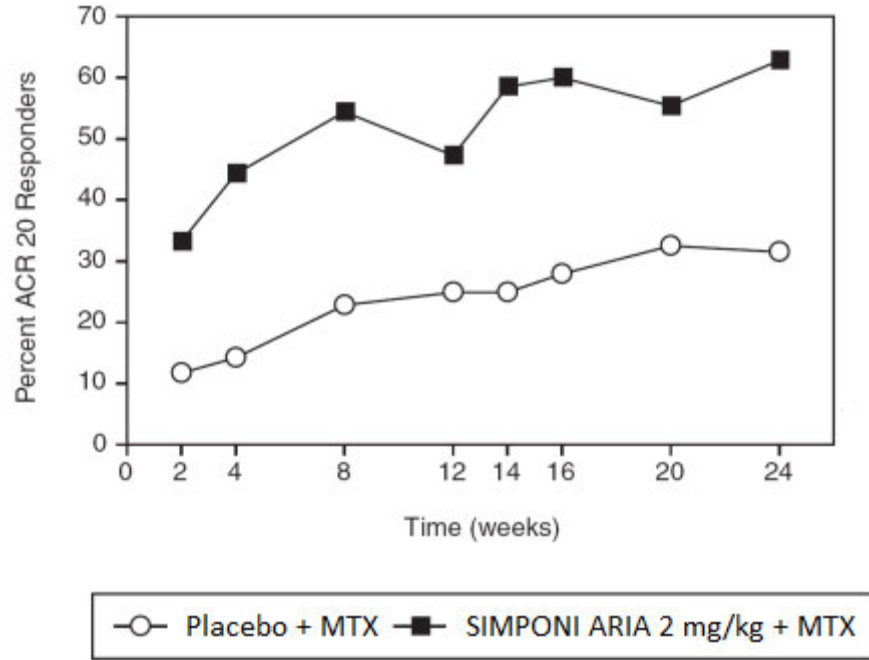
A greater percentage of patients treated with the combination of SIMPONI ARIA + MTX achieved ACR 20 at Week 14 and ACR50 at Week 24 versus patients treated with the placebo + MTX as shown in Table 2. The percent of patients achieving ACR 20 responses by visit for Trial 1 is shown in Figure 1.

Table 2: Trial 1 – Proportion of Patients with an ACR Response

Trial 1			
Active RA, despite MTX			
	Placebo + MTX	SIMPONI ARIA + MTX	95% CI^a
N ^b	197	395	
ACR 20			
Week 14	25%	59%	25.9, 41.4
Week 24	32%	63%	23.3, 39.4
ACR 50			
Week 14	9%	30%	15.3, 27.2
Week 24	13%	35%	15.1, 28.4
ACR 70			
Week 14	3%	12%	5.3, 13.4
Week 24	4%	18%	8.8, 18.1

^aFor difference in proportions
^bN reflects randomized patients.

Figure 1: Trial 1 – Percent of Patients Achieving ACR 20 Response Over Time: Randomized Patients



The analysis is based on the intent-to-treat population. Last observation carried forward was performed for missing data. Patients who discontinued treatment due to lack of efficacy were counted as non-responders, as were patients who started prohibited medication or failed to achieve at least a 10% improvement in joint counts at Week 16.

The improvement in all components of the ACR response criteria for the SIMPONI ARIA + MTX group was greater compared to the placebo + MTX group in Trial 1 as shown in Table 3.

Table 3: Trial 1 – Components of ACR Response at Week 14

	Trial 1 Active RA, despite MTX	
	Placebo + MTX	SIMPONI ARIA + MTX
N ^a	197	395
Number of swollen joints (0-66)		
Baseline	15	15
Week 14	11	6
Number of tender joints (0-68)		
Baseline	26	26
Week 14	20	13
Patient's assessment of pain (0-10)		
Baseline	6.5	6.5
Week 14	5.6	3.9
Patient's global assessment of disease activity (0-10)		
Baseline	6.5	6.5

Week 14	5.5	4.0
Physician's global assessment of disease activity (0-10)		
Baseline	6.3	6.2
Week 14	4.9	3.1
HAQ score (0-3)		
Baseline	1.6	1.6
Week 14	1.4	1.1
CRP (mg/dL) (0-1)		
Baseline	2.2	2.8
Week 14	1.8	0.9
Note: All values are means. ^a N reflects randomized patients; actual number of patients evaluable for each endpoint may vary.		

At Week 14, a greater proportion of patients treated with SIMPONI ARIA + MTX achieved a low level of disease activity as measured by a DAS28-CRP less than 2.6 compared with the placebo + MTX group (15% compared to 5%; 95% confidence interval for difference [6.3%,15.5%]).

Radiographic Response

In Trial 1, structural joint damage was assessed radiographically and expressed as a change in van der Heijde-Modified Sharp Score (vdH-S) and its components, the erosion score and Joint Space Narrowing (JSN) score, at Week 24 compared to baseline. The SIMPONI ARIA + MTX treatment group inhibited the progression of structural damage compared with placebo + MTX, as assessed by total vdH-S score as shown in Table 4.

Table 4: Trial 1 – Radiographic Change From Baseline at Week 24

	Placebo + MTX (N=197)^a	SIMPONI ARIA + MTX (N=395)^{a,b}
	Mean	Mean
Change Total vdH-S Score	1.1	0.03*
Change Erosion Score	0.5	-0.1
Change JSN Score	0.6	0.1
^a N reflects randomized patients ^b p-value is displayed only for the major secondary endpoint * p≤0.001		

At Week 24, a greater proportion of patients in the SIMPONI ARIA + MTX group (71%) had no progression of structural damage (change in the total vdH-S score ≤ 0), compared to 57% of patients in the placebo + MTX group. At Week 52, the mean change from baseline in total vdH-S score was 1.2 in patients originally randomized to placebo + MTX who crossed over to SIMPONI ARIA + MTX at Week 16 or 24, and 0.1 in patients originally randomized to SIMPONI ARIA + MTX who remained on active treatment.

Physical Function Response in Patients with RA

Physical function was assessed by the disability index of the Health Assessment Questionnaire (HAQ-DI) At Week 14, the SIMPONI ARIA + MTX group showed greater mean improvement

in the HAQ-DI compared with placebo + MTX (0.5 compared to 0.2; 95% confidence interval for difference [0.2, 0.4]).

16 HOW SUPPLIED/STORAGE AND HANDLING

SIMPONI ARIA is available in packs of 1 vial NDC 57894-350-01

Vial

Each vial contains 50 mg of SIMPONI ARIA per 4 mL of solution.

Storage and Stability

SIMPONI ARIA must be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from light. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. Do not use SIMPONI ARIA beyond the expiration date (EXP) on the vial label.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Advise patients of the potential benefits and risks of SIMPONI ARIA. Instruct patients to read the Medication Guide before starting SIMPONI ARIA therapy and to read it each time the prescription is renewed.

Infections

Inform patients that SIMPONI ARIA may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and hepatitis B reactivation.

Malignancies

Patients should be counseled about the risk of lymphoma and other malignancies while receiving SIMPONI ARIA.

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, demyelinating disorders, autoimmune diseases, liver disease, cytopenias, or psoriasis.

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Horsham, PA 19044

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Cilag AG

Schaffhausen, Switzerland

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MEDICATION GUIDE

SIMPONI® ARIA™ (SIM-puh-nee AHR-ee-uh) **(golimumab)** **For Infusion**

Read the Medication Guide for SIMPONI ARIA before each infusion. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. It is important to remain under your doctor's care while receiving SIMPONI ARIA.

What is the most important information I should know about SIMPONI ARIA?

SIMPONI ARIA is a medicine that affects your immune system. SIMPONI ARIA can lower the ability of your immune system to fight infections. Some people have serious infections while taking SIMPONI ARIA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that spread throughout their body. Some people have died from these serious infections.

- Your doctor should test you for TB and hepatitis B before starting SIMPONI ARIA.
- Your doctor should monitor you closely for signs and symptoms of TB during treatment with SIMPONI ARIA.

You should not receive SIMPONI ARIA if you have any kind of infection unless your doctor says it is okay.

Before receiving SIMPONI ARIA, tell your doctor if you:

- think you have an infection or have symptoms of an infection such as:
 - fever, sweat, or chills
 - muscle aches
 - cough
 - shortness of breath
 - blood in phlegm
 - weight loss
 - warm, red, or painful skin or sores on your body
 - diarrhea or stomach pain
 - burning when you urinate or urinate more often than normal
 - feel very tired
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live, have lived, or traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may

happen or become more severe if you receive SIMPONI ARIA. Ask your doctor if you do not know if you have lived in an area where these infections are common.

- have or have had hepatitis B.
- use the medicine ORENCIA (abatacept), KINERET (anakinra), ACTEMRA (tocilizumab) or RITUXAN (rituximab).

After receiving SIMPONI ARIA, call your doctor right away if you have any symptoms of an infection. SIMPONI ARIA can make you more likely to get infections or make worse any infection that you have.

Cancer

- For children and adults receiving TNF-blocker medicines, including SIMPONI ARIA, the chances of getting cancer may increase.
- There have been cases of unusual cancers in children and teenage patients taking TNF-blocking agents.
- People with inflammatory diseases including rheumatoid arthritis especially those with very active disease, may be more likely to get lymphoma.
- Some people treated with SIMPONI ARIA developed skin cancer. If any changes in the appearance of your skin or growths on your skin occur during or after your treatment with SIMPONI ARIA, tell your doctor.
- You should see your doctor periodically for skin examinations, especially if you have a history of skin cancer.

What is SIMPONI ARIA?

SIMPONI ARIA is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker. SIMPONI ARIA is used with the medicine methotrexate to treat adults with moderately to severely active rheumatoid arthritis (RA).

SIMPONI ARIA is not for children under 18 years of age.

What should I tell my doctor before starting treatment with SIMPONI ARIA?

SIMPONI ARIA may not be right for you. Before receiving SIMPONI ARIA, tell your doctor about all your medical conditions, including if you:

- have an infection (see "What is the most important information I should know about SIMPONI ARIA?")
- have or have had lymphoma or any other type of cancer.
- have or had heart failure
- have or have had a condition that affects your nervous system, such as multiple sclerosis or Guillain-Barré syndrome
- have a skin problem called psoriasis
- have recently received or are scheduled to receive a vaccine. People receiving SIMPONI ARIA should not receive live vaccines. People receiving SIMPONI ARIA can receive non-live vaccines.

- have a baby and you received SIMPONI ARIA during your pregnancy. Tell your baby's doctor before your baby receives any vaccine. Your baby may have an increased chance of getting an infection for up to 6 months after birth.
- are pregnant or planning to become pregnant. It is not known if SIMPONI ARIA will harm your unborn baby.
- are breastfeeding. It is not known if SIMPONI ARIA passes into your breast milk. You and your doctor should decide if you will receive SIMPONI ARIA or breastfeed. You should not do both without talking to your doctor first.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your doctor if you:

- use ORENCIA (abatacept) or KINERET (anakinra). You should not receive SIMPONI ARIA while you are also taking ORENCIA (abatacept) or KINERET (anakinra).
- use other TNF-blocker medicines, including REMICADE (infliximab), HUMIRA (adalimumab), ENBREL (etanercept), or CIMZIA (certolizumab pegol).
- receive RITUXAN (rituximab) or ACTEMRA (tocilizumab).

Ask your doctor if you are not sure if your medicine is one listed above.

Keep a list of all your medications with you to show your doctor and pharmacist each time you get a new medicine.

How should I receive SIMPONI ARIA?

- SIMPONI ARIA is prepared and given by a healthcare provider through a needle placed in your vein (infusion). The infusion is usually given in your arm and should take 30 minutes.
- Your doctor will decide how much SIMPONI ARIA you will receive based on your weight. Your usual schedule for receiving SIMPONI ARIA after your first treatment should be:
 - 4 weeks after your first treatment
 - every 8 weeks after that
- If you forget or miss an appointment to receive SIMPONI ARIA, make another appointment as soon as possible.
- You may continue to use other medicines for your treatment while taking SIMPONI ARIA, such as non-steroidal anti-inflammatory drugs (NSAIDs), prescription steroids, and pain relief medicines.

What are the possible side effects of SIMPONI ARIA?

SIMPONI ARIA can cause serious side effects, including:

- See **"What is the most important information I should know about SIMPONI ARIA?"**

- **Hepatitis B infection in people who carry the virus in their blood.** If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you receive SIMPONI ARIA. Your doctor should do blood tests before you start treatment with SIMPONI ARIA and while you are receiving SIMPONI ARIA. Tell your doctor if you have any of the following symptoms of a possible hepatitis B infection:
 - feel very tired
 - clay-colored bowel movements
 - dark urine
 - fevers
 - skin or eyes look yellow
 - little or no appetite
 - vomiting
 - muscle aches
 - chills
 - stomach discomfort
 - skin rash

- **Heart failure, including new heart failure or worsening of heart failure that you already have.** New or worse heart failure can happen in people who use TNF-blocker medicines including SIMPONI ARIA.
 - If you have heart failure, your condition should be watched closely while you receive SIMPONI ARIA.
 - Call your doctor right away if you get new or worsening symptoms of heart failure while receiving SIMPONI ARIA (such as shortness of breath, swelling of your lower legs or feet, or sudden weight gain).

- **Nervous System Problems**
 Rarely, people using TNF-blocker medicines, including SIMPONI ARIA, have nervous system problems such as multiple sclerosis or Guillain-Barré syndrome. Tell your doctor right away if you get any of these symptoms:
 - vision changes
 - weakness in your arms or legs
 - numbness or tingling in any part of your body

- **Liver Problems**
 Liver problems can happen in people who use TNF-blocker medicines, including SIMPONI ARIA. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms:
 - feel very tired
 - skin or eyes look yellow
 - poor appetite or vomiting
 - pain on the right side of your stomach (abdomen)

- **Blood Problems**
 Low blood counts have been seen with TNF-blockers, including SIMPONI ARIA. Your body may not make enough blood cells that help fight infections or help stop bleeding. Symptoms include fever, bruising or bleeding easily, or looking pale. Your doctor will check your blood counts before and during treatment with SIMPONI ARIA.

- **Allergic Reactions**

Allergic reactions can happen in people who use TNF-blocker medicines including SIMPONI ARIA. Some reactions may be serious and can be life threatening. Some of these reactions can happen after receiving your first dose of SIMPONI ARIA. Call your doctor right away if you have any of these symptoms of an allergic reaction:

- hives
- swollen face
- breathing trouble
- chest pain

The most common side effects of SIMPONI ARIA include:

- upper respiratory infection (runny nose, sore throat, and hoarseness or laryngitis)
- viral infections such as flu and cold sores in the mouth
- bronchitis
- high blood pressure
- rash

Other side effects with SIMPONI ARIA include:

- **Immune System Problems.** Rarely, people using TNF-blocker medicines have developed symptoms that are like the symptoms of Lupus. Tell your doctor if you have any of these symptoms:
 - a rash on your cheeks or other parts of the body
 - sensitivity to the sun
 - new joint or muscle pains
 - becoming very tired
 - chest pain or shortness of breath
 - swelling of the feet, ankles, or legs

These are not all of the side effects with SIMPONI ARIA. Tell your doctor about any side effect that bothers you or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

General Information about SIMPONI ARIA

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not use SIMPONI ARIA for a condition for which it was not prescribed.

This Medication Guide summarizes the most important information about SIMPONI ARIA. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about SIMPONI ARIA that is written for health professionals.

For more information go to www.SimponiAria.com or call 1-800-JANSSEN (1-800-526-7736).

What are the ingredients in SIMPONI ARIA?

Active ingredient: golimumab

Inactive ingredients: L-histidine, L-histidine monohydrochloride monohydrate, sorbitol, polysorbate 80, and water for injection. SIMPONI ARIA does not contain preservatives, natural rubber or latex.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
US License No. 1864 at
Cilag AG
Schaffhausen, Switzerland

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Approved: July 2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type BLA
Application Number 125433
Priority or Standard Standard

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and Rheumatology Products
(DPARP)/ODEII

Reviewer Name Rosemarie Neuner, MD, MPH
Review Completion Date June 14, 2013

Established Name Intravenous (IV) Golimumab
Trade Name Simponi Aria[®]
Therapeutic Class TNF inhibitor
Applicant Janssen Biotech, Inc.

Formulation 50 mg/4 mL Vial
Dosing Regimen 2 mg/kg at Weeks 0 and 4,
then every 8 weeks
Indication Treatment of Moderate to
Severe Rheumatoid Arthritis
Intended Population Adults with Inadequate
Response to Methotrexate

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends approval of this application for intravenous (IV) golimumab as a treatment for adult patients with moderately to severely active rheumatoid arthritis. The data contained in this application is sufficient to support a finding of efficacy and safety for golimumab when administered at a dose and dosing regimen of 2 mg/kg via intravenous infusion at Weeks 0 and 4, and every 8 weeks thereafter with concomitant methotrexate

1.2 Risk Benefit Assessment

The efficacy of IV golimumab in the treatment of active RA was demonstrated by the successful results from a single, international, multicenter, double-blind, randomized, placebo-controlled trial, CNTO148ART3001. In this pivotal trial, IV golimumab when administered at a dose and dosing regimen of 2 mg/kg at Week 0 and 4, and then every 8 weeks thereafter was shown to effectively reduce signs and symptoms of active arthritis in patients with moderate to severe RA with an inadequate response to methotrexate therapy as measured by a plethora of assessments that included the ACR 20 response rate at Week 14 as the primary endpoint. Positive outcomes were also seen for improvement in physical function and inhibiting progression of joint damage as assessed by the HAQ-DI at Week 14 and van der Heijde Modified Sharp (vdHS) Score at Week 24 which were assessed as major secondary endpoints. The results from sensitivity analyses involving the application of different imputation methodologies for missing data were supportive of both the primary and major secondary efficacy results attesting to their robustness.

The risk assessment for IV golimumab was based on data generated from 24-weeks of controlled safety data from Study CNTO148ART3001 supplemented by long term continuous exposure data of greater than 52 weeks in duration from this ongoing study as well as selected safety data of interest (e.g., deaths, anaphylaxis, serious infections, and malignancies) from the other Phase 3 study, C0524T12, contained in this submission which evaluated doses and dosing regimens of IV golimumab different than the proposed to-be-marketed dose and dosing regimen. The overall rate of serious adverse events was low in Study CNTO148ART3001 and no unexpected safety signals were observed for this new formulation of golimumab. The majority of serious events including deaths contained in the safety database submitted in support of IV golimumab's safety profile were the type of events (e.g., major cardiovascular events, gastrointestinal pain and hemorrhage, infection and malignancies) expected to occur in an older population with long-standing RA at risk for other co-morbid conditions particularly as a result of the concomitant use of such medications as NSAIDs,

corticosteroids and MTX that have overlapping spectrums of additive toxicities (e.g., increased cardiovascular risk and immunosuppression). The exposure-adjusted rate of death seen with long term administration of 2 mg/kg every 8 weeks of IV golimumab was consistent with that reported in other trials of therapeutic biologics as well as below the reported rates of death observed in RA patient cohorts in general.

Review of the adverse events of interest (e.g., serious infections, hepatotoxicity, congestive heart failure, demyelinating disorders, hypersensitivity reactions, infusion reactions, autoimmunity, and hematological cytopenias) did not identify any potential or unexpected safety issues associated with this TNF inhibitor's dose, dosing regimen or route of administration as compared to the approved SC formulation of golimumab or the other four members of this therapeutic biologic class. However, CNTO148ART3001 was not powered to specifically determine safety risk and the comparison to the SC formulation is based on cross-study comparisons, not head-to-head data. The types of and exposure-adjusted rates for serious infections and infections of interest (e.g., sepsis, pneumonia, tuberculosis, opportunistic infections and cellulitis) were similar to those observed with other TNF inhibitors, including the SC formulation of this product. As the proposed dosing regimen for IV golimumab is weight based, review of serious infections by weight based quartile did not identify any potential safety concerns for increasing immunosuppression with increasing dose.

Since the protocols for both Phase 3 studies permitted the use of prophylactic medications (e.g., antihistamines and corticosteroids) for infusion reactions at the discretion of study investigators and no consistent methodology was used in the IV golimumab clinical development program for capturing and classifying the spectrum of hypersensitivity reactions that includes infusion reactions and anaphylaxis, there had been concerns that IV golimumab's immunogenic profile may have not been fully characterized based on the data contained in the safety database submitted in support of this application. The rate of antibody formation for the to-be-marketed IV golimumab was 4% which is higher than reported for the 50 mg every 4 weeks SC formulation (2% in patients taking concomitant MTX), and there were no serious or severe infusion reactions reported with its administration. A review of the individual line listings did not suggest any unidentified cases of anaphylaxis among the reported infusion reactions.

The types of and exposure-adjusted rates for malignancy in both Phase 3 IV golimumab studies were also similar to what had been observed in the RA clinical development program for the SC formulation. This is reassuring in view of the number of patients who actually received the proposed to-be-marketed dose of IV golimumab.

Based on the scope of the data contained in the safety database reviewed in support of this application's safety profile, no strengthening of the TNF inhibitor class WARNINGS and PRECAUTIONS is warranted. Given the totality of evidence reviewed, the overall risk/benefit assessment is in favor of approving this application.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A risk evaluation and mitigation strategies (REMS) is not necessary for IV golimumab since its safety profile including the risk for serious infection appears to be similar to the other members of the tumor necrosis factor (TNF) inhibiting class of therapeutic biologic agents.

1.4 Recommendations for Postmarket Requirements and Commitments

As per provisions of the Pediatric Research Equity Act (PREA), the Applicant has submitted a request for a partial waiver not to conduct a study in neonates and infants up to 1 year, 11 months since Juvenile inflammatory arthritis (JIA) does not present at birth and the disease is not typically clinically evident before 1 year of age and patients are rare, and a deferral to conduct a study in children ages ≥ 2 through ≤ 17 years old with JIA since studies of IV golimumab in adult RA are completed and the application is ready for approval. Pursuant to this request, this submission contained a proposed pediatric development plan to evaluate the safety, efficacy, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of IV golimumab in 158 children between the ages 2 to 17 years and 11 months with polyarticular JIA despite standard therapy with methotrexate via a single, randomized withdrawal, controlled Phase 3 study of 52 weeks duration. The primary endpoint for the proposed study is the proportion of subjects with a disease flare between Week 20 and Week 52 (the double-blind, randomized-withdrawal portion of the study). Secondary endpoints include the ACR Pediatric 30 response rate at Weeks 20 and 52, the proportion of ACR Pediatric 30 responders who have inactive disease at Week 52, and the proportion of ACR Pediatric 30 responders at Week 20 who are in protocol defined clinical remission while on medication for JIA at Week 52. Clinical PK endpoints include serum golimumab concentrations over time. Safety variables include frequency of AEs, including AEs of interest such as tuberculosis and demyelinating disorders, infusion reactions, vascular events, pregnancies and malignancies, as well as changes in clinical lab tests and immunogenicity. Subjects will undergo efficacy and safety assessments at baseline and Week 2, then every 4 weeks until the study is completed (Week 52). The Applicant plans to submit the pediatric protocol in the fourth quarter of 2013 with initiation of the study anticipated in the first quarter of 2014 and submission of the 52-week study report in the third quarter of 2017. Based on discussions held at the May 1, 2013 meeting of the Pediatric Review Committee (PeRC), it was agreed that the Applicant's proposed partial waiver for studies in neonates and infants up to 1 year, 11 months in age and deferral for pediatric studies in children ≥ 2 through ≤ 17 years of age was acceptable.

2 Introduction and Regulatory Background

2.1 Product Information

The established name of the subject product of this application is intravenous (IV) golimumab and the proposed trade name is Simponi Aria[®]. The established name will be used in this review to refer to the product. Intravenous golimumab is supplied as a colorless to light yellow, sterile, preservative-free, solution in a single-use 4 mL glass vial with a (b) (4) stopper. Each vial contains 12.5 mg/mL golimumab (50 mg/4mL), 9.5 mM L-histidine, 4.5% sorbitol, and 0.015% polysorbate 80, at a pH 5.5.

Golimumab is a human is a human IgG1κ therapeutic monoclonal antibody that binds with high affinity and specificity to both soluble and transmembrane forms of human tumor necrosis factor alpha (TNFα) thus inhibiting this proinflammatory cytokine's bioactivity. It was initially designed using genetically engineered mice immunized with human TNF to produce an antibody with human-derived antibody variable and constant regions. Golimumab is commercially produced via a cultured, recombinant cell line and has a molecular weight of approximately 150 to 151 kilodaltons.

The proposed indication for IV golimumab is for the treatment of moderately to severely active rheumatoid arthritis (RA) in adults in combination with methotrexate (MTX) at a proposed dosing regimen of 2 mg/kg administered as an IV infusion over 30 minutes at weeks 0 and 4, and then every 8 weeks thereafter as prepared by a healthcare professional.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 lists the currently approved small molecule products, which includes disease modifying anti-rheumatic drugs (DMARDs) and immunosuppressives, as well as therapeutic biologic treatments for RA that are available in the United States (U.S.):

Table 1 – Approved Disease Modifying Anti-Rheumatic Drugs (DMARDs), Immunosuppressants and Therapeutic Biologics for the Treatment of RA in the U.S.

Drug/Product	NDA/BLA	Sponsor	Year of Approval
Sulfasalazine	7-073	Pfizer	1950
Methotrexate sodium	8-085 (PO) 11719 (IV)	Multiple Sponsors	1953
Hydroxychloroquine	9-768	Sanofi-Aventis	1955
Prednisone	Many ANDAs	Multiple Sponsors	1955
Azathioprine	16-324	Prometheus Labs	1968
Penicillamine	19-853	Aton	1970
Auranofin	18-689	Prometheus Labs	1985
Cyclosporin	50-715 50-625	Novartis	1995 1990
Leflunomide	20-905	Sanofi-Aventis	1998
Infliximab	103772	Centocor	1999
Etanercept	103795	Immunex	1998
Anakinra	103950	Amgen	2001
Adalimumab	125057	Abbot	2002
Abatacept	125118	Bristol Myers Squibb	2005
Rituximab	103705	Genentech and Biogen Idec	2006
Certolizumab pegol	125160	UCB Inc	2008
Golimumab	125289	Centocor	2008
Tocilizumab	125276	Genentech	2010
Tofacitinib citrate	203214	Pfizer	2012

In addition to the above listing, there are a number of nonsteroidal anti-inflammatory drugs (NSAIDs) that are approved for the reduction of the signs and symptoms of RA marketed in this country.

2.3 Availability of Proposed Active Ingredient in the United States

Golimumab is an approved therapeutic biologic product that is available and marketed in the U.S. (since 2008) and in 57 countries worldwide (as of October 2012) as a subcutaneous (SC) injectable formulation at a dose of 50 mg every 4 weeks for the treatment of patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.

2.4 Important Safety Issues With Consideration to Related Drugs

A number of safety concerns have been identified associated with the use of TNF inhibitors. These are listed under the Warnings and Precautions section of the various labels for TNF class products and include: increased susceptibility to serious infections such as opportunistic infections, tuberculosis, histoplasmosis and reactivation of hepatitis B; increased risk for malignancies particularly lymphomas and hepatosplenic T-cell lymphoma; hepatotoxicity, hypersensitivity disorders, demyelinating disorders,

cytopenias, worsening congestive heart failure, autoimmune disorders, and infusion-related/injection-site reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following are highlights of the regulatory activity that occurred during the development program for IV golimumab under IND 9925.

In lieu of a face-to-face PreIND/Pre-Phase 3 meeting, written responses to the Applicant's meeting questions were conveyed via fax on May 10, 2006. The following items summarize the understandings reached between the Applicant and the Division at that time:

- Agreement reached on proposed development plan for IV golimumab formulation and design of Phase 3 Study C0524T12
- Overall efficacy, safety and immunogenicity of IV regimen should be comparable to the SC dosing regimen in order to extrapolate data from the SC dosing regimen to support approval for the same claims
- Due to Agency concerns about potential PK, efficacy and safety differences between the 2 formulations sponsor decided to pursue more frequent IV dosing interval resulting in similar trough but greater C_{max} and AUC values than SC regimen

An End-of-Phase 2 meeting teleconference was held on May 18, 2009. Agreements and discussions of key clinical and regulatory issues at that time include:

- Agreement reached on the adequacy of the design of the Phase 3 study CNT0148ART3001 including controlling for Type 1 error in analyzing major secondary endpoints
- Need for positive endpoint results to support each individual RA marketing claim
- Concerns regarding adequacy of long term exposure data in the proposed safety database to assess the IV formulation's safety profile for potential safety signals (i.e., malignancy risk and deaths)

A Pre-BLA filing meeting was held on October 3, 2011. The following items summarize the understandings reached between the Applicant and the Division and the key clinical and regulatory issues that were discussed at that time.

- Since Study C0524T12 did not provide independent substantiation of efficacy since it used different dosing regimens than the proposed regimen and the primary efficacy endpoint was not successful, the Applicant was told by the Division they would need positive results from 2 adequate and well-controlled studies assessing the proposed IV dosing regimen to support efficacy of the new formulation or they would have to provide a rationale for a single pivotal study.
- The adequacy of a single pivotal study to support licensure of IV golimumab would be a review issue. Robust radiographic results at Week 24 from Study

CNT01483001ART may help to provide supportive evidence for the efficacy of the IV regimen in the Applicant's sBLA submission

- Concerns were raised by the Division regarding the Applicant's proposal to use extrapolated SC data to substantiate efficacy for the IV formulation based on differences in the observed and simulated PK profiles for the 2 formulations. To account for these differences the Applicant would have to provide a rationale why the lower trough levels seen with IV versus SC golimumab are not clinically meaningful.
- Applicant agreed to provide long term safety data from CNT0148ART3001 to support risk/benefit for prolonged administration of IV formulation due to higher exposure as compared to SC regimen as a result of the higher maintenance dose regimen employed by the IV formulation and dose-related safety concerns raised by the Agency such as a higher number of malignancies and deaths observed in Study C0524T12
- Agreement for separate USPIs for SC and IV formulations in order to avoid medication errors and since the Agency considers them to be two separate and distinct products because they have different pharmacokinetic characteristics, dosing regimens, and product presentations despite having the same drug substance
- The Applicant's proposed proprietary name [REDACTED] (b) (4) was unacceptable
- Additional agreements reached regarding the potential inclusion of marketing claims in the proposed label (e.g., ACR response, ACR response over time, improvement in ACR components, HAQ-DI and DAS28 (CRP) score <2.6), cross referencing information previously submitted in support of licensure of the SC formulation of golimumab, and submission of data in the 120-day safety update.

2.6 Other Relevant Background Information

According to the Applicant, the early development of IV golimumab was conducted by Centocor Research & Development and its European subsidiaries. Due to a corporate name change in June 2011, this company subsequently became Janssen Biotech, Inc. The clinical development of both the SC and IV formulations of golimumab in the U.S. was conducted under the same IND 9925.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Janssen Biotech's submission was appropriately organized to allow information to be reviewed in an acceptable manner. No major amendments were submitted by the Applicant.

3.2 Compliance with Good Clinical Practices

According to statements included in the reports for the Phase 3 trials, C0524T12 and CNTO148ART3001, the Applicant certified that these studies were conducted in compliance with the following: Good Clinical Practice standards as outlined in the Declaration of Helsinki or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, with the institutional review board regulations as per 21 CFR (56), and the informed consent regulation as per 21 CFR (50).

The Division of Scientific Investigation (DSI) inspected a total of 2 clinical sites that participated in the pivotal Phase 3 trial, CNTO148ART3001: 1 foreign site in Poland and 1 domestic site in the U.S. Both sites were chosen based on high study enrollment (20 subjects and 15 subjects, respectively). No regulatory violations or evidence of under-reporting of adverse events were noted during the inspections of these clinical sites. The final conclusion by the DSI medical officer was that the data generated by these inspected sites appears to be reliable to support this application.

3.3 Financial Disclosures

The financial disclosure form 3454 signed by the Applicant certified that only one investigator who participated (b) (4), had a financial arrangement as a paid consultant as defined in 21 CFR 54.2(a). According to the submitted Form 3455, (b) (4), (b) (6) had a consulting agreement with Centocor B.V. and Schering Plough., for which he received two payments totaling \$32,247 in compensation from the Applicant as a consultant for the joint assessor training program at two investigator meetings held for (b) (4) RA and psoriatic arthritis clinical development programs. Based on the (b) (4) patients enrolled into (b) (4) from (b) (4), (b) (6) site, it is unlikely that this investigator's financial interest affected the final results of this trial which failed to capture its primary endpoint.

Additionally, none of the principal investigators or sub investigators reportedly had a proprietary interest in this product or a significant equity in Janssen Biotech Inc., which is commercially developing IV golimumab for licensing in this country as described in 21 CFR 54.2(b).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC data submitted in support of this application crossed referenced the complete drug substance information submitted and reviewed under BLA 125289 in support of the approval of the SC formulation of golimumab. Dr. Eric Reid from the Division of Monoclonal is recommending approval of this application since the final vialled (FV) drug product (DP) for the IV formulation contains the same antibody and excipients as well as stability profile as the approved SC formulation.

4.2 Clinical Microbiology

Dr. Reyes Candau-Chacon from the Office of Compliance/DMPQ/DGMPA/BMAB reviewed the microbial control, CMC sterility assurance and microbiology product quality data for this application and recommends approval with the following PMRs:

- Increase in-process sample size (b) (4) and adjust acceptance criteria (b) (4)

(b) (4)

In addition, after production of 10 batches using the new bioburden sample size action and alert limits will be implemented. These changes will be submitted to the Agency in the Annual Report for BLA 125433, once approved.

- (b) (4)
- Perform the Rabbit Pyrogen Test in additional batches of golimumab FVP (IV) DP and submit results to the Agency in a CBE-0 by September 2013.
- Perform LAL spiking studies in undiluted golimumab FVP (IV) DP samples and test the samples after different hold times and submit the results to the Agency in the next Annual Report for BLA 125433 once approved.

4.3 Preclinical Pharmacology/Toxicology

The clinical pharmacology/toxicology data included in this application was reviewed by Dr. Mamata De who recommends approval of this application based on the following:

- Non-clinical information referenced by the Applicant from the SC formulation of golimumab (BLA 125289)
- IV golimumab should be classified as Pregnancy Category B based on re-calculation of exposure margins for the reproductive toxicity assessments conducted in monkeys in support of the SC formulation and the mean steady state human exposure (AUC_{0-8} weeks) for IV golimumab

4.4 Clinical Pharmacology

Dr. Liang Zhao reviewed the clinical pharmacology data contained in this application. Dr. Liang recommends approval of this application based on the following:

- Weight was the only significant intrinsic factor identified on review of the data generated from the Applicant's population PK model
- No dose adjustments are warranted based on albumin level, CRP level, or concomitant use of MTX

4.4.1 Mechanism of Action

Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane forms of human TNF- α . This interaction prevents the binding of TNF- α to its receptors, thus inhibiting the biological activity of this pro-inflammatory cytokine. Elevated levels of TNF- α have been implicated in the pathophysiology of several chronic inflammatory diseases such as RA, PsA and AS. Studies have shown that TNF- α is an important mediator of the articular inflammation that is characteristic of these diseases.

4.4.2 Pharmacodynamics

Multiple pharmacodynamic (PD) markers of inflammation (e.g., TNF-R1, TRAP-5b, TIMP-1, MPO, MMP-1, MMP-3, Resistin, IL-6, MIP-1b, BDNF, RANTES, VCAM-1, tPAI-1, RANKL, VEGF, SAA, S100A12, hsCRP) were evaluated at baseline and at Weeks 4 and 14 in the Phase 3 study, CNTO148ART3001. Since the relationship between changes in all of these PD markers and the efficacy of products for the treatment of the signs and symptoms of RA have not been clearly established and other well-established, clinically meaningful efficacy parameters (e.g., ACR response and DAS28 [CRP] response) were evaluated in the pivotal Phase 3 trial, these results were not reviewed.

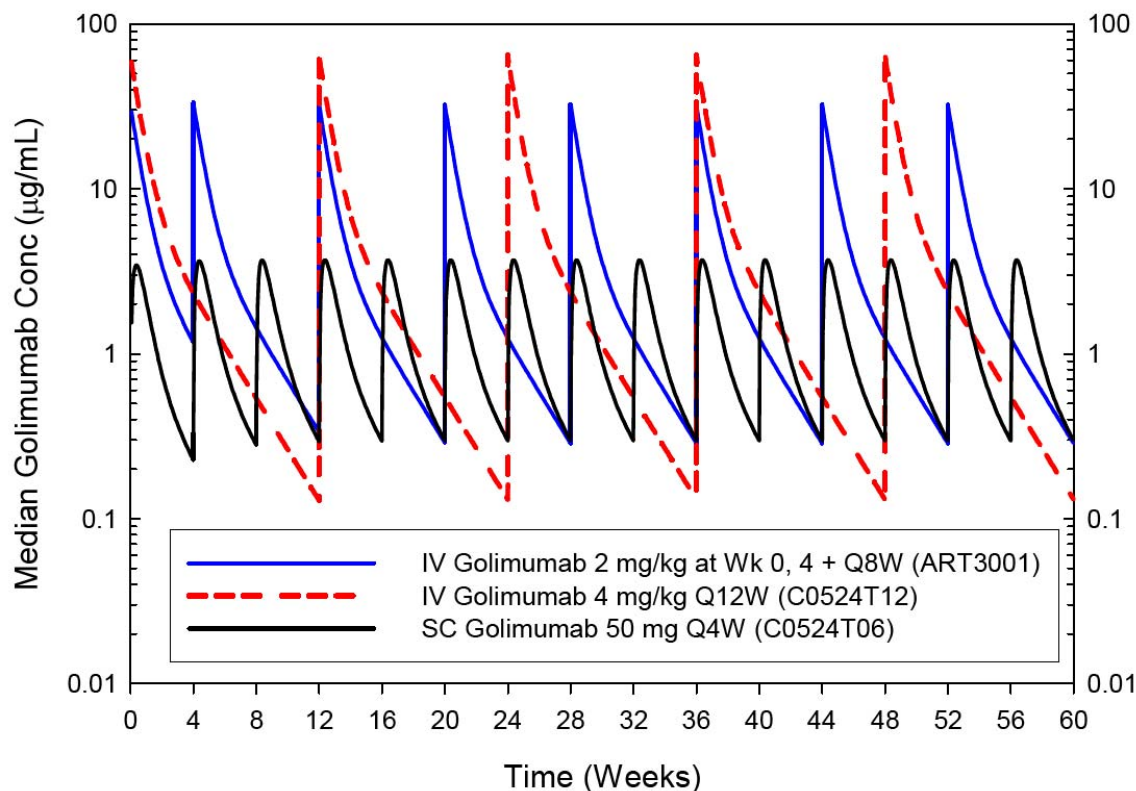
4.4.3 Pharmacokinetics

The pharmacokinetic (PK) profile of IV golimumab was assessed in one Phase 1 study (C0524T14) and the two Phase 3 studies (C0524T12 and CNTO148ART3001) conducted in RA subjects and was shown to have the following characteristics:

- Dose-proportional in RA patients (0.1-10 mg/kg IV)
- T_{1/2}: 2 weeks in healthy volunteers, patients with RA, PsA, or AS (12-14 days following IV infusion)
- Time to reach steady state: 12 Weeks (same for SC formulation)
- Renal/hepatic impairment
 - No formal study of the effect of renal or hepatic impairment on the PK of golimumab was conducted.
- Patients positive for anti-golimumab antibodies generally had lower steady-state serum trough concentrations

While no direct comparisons between the 50 mg SC and 2 mg/kg IV doses were provided, cross-study comparisons and PK modeling indicate that the C_{max} and AUC of the 2 mg/kg every 8 weeks IV formulation is approximately 14-fold and 2-3-fold higher, respectively, than the SC formulation as shown in Figure 1.

Figure 1 – Median Serum Golimumab Concentration-Time Profiles Following IV or SC Administration of Golimumab



Adapted from Summary of Clinical Pharmacology Figure 7; p 49.

In terms of golimumab's immunogenicity:

- The combined antibody to golimumab incidence across all subjects treated in the two Phase 3 IV studies was 4.6% (26/560) and 7.0% (43/613) through Weeks 48 and 52, respectively
 - Subjects positive for anti-golimumab antibodies were 100% positive for neutralizing antibodies to the product
- MTX as co-medication reduced the immunogenic response of golimumab
 - Through Week 52, for subjects who did not receive MTX (i.e., golimumab monotherapy) the antibody to golimumab incidence was 12% (30/251) while the incidence was 4.2% (39/922) for subjects who were treated with golimumab + MTX

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program for IV golimumab includes two Phase 3 studies which are summarized in Table 2:

Table 2- Key Design Features of the IV Golimumab RA Clinical Trials

Study/Objectives	Study Design; Durat.; No. Study Sites	Dosage Regimen; Route of Adm.	No. of Subjects	Dx/ Entry Criteria	Endpoints (EP)
C0524T12 Objectives: 1. Assess the clinical efficacy and safety of golimumab IV infusions every 12 weeks with and without MTX compared with MTX alone, in subjects with active RA despite concurrent MTX treatment; 2. Evaluate the effects on physical function and QOL, the population PK and PD of IV golimumab in subjects with active RA; 3. Evaluate the safety of SC golimumab after transition from IV golimumab	48-wk, Phase 3, MC, R, DB, PC, parallel group study with early escape at Wk 16 and dose regimen adjustment at Wk 24 based on < 20% improvement over baseline in both swollen and tender joint counts 5 sites South America (232 subjects); 24 sites Europe (153 subjects); 19 sites North America (148 subjects); 15 sites Asia-Pacific (110 subjects)	Group 1: IV golimumab 2 mg/kg at Wk 0 then q 12 wks thereafter through Wk 48 with continuation of baseline stable dose of MTX Group 2: IV golimumab 2 mg/kg at Wk 0 then q 12 wks thereafter with concomitant placebo capsules (sham MTX) Group 3: IV golimumab 4 mg/kg at Wk 0 then q 12 wks thereafter through Wk 48 with continuation of baseline stable dose of MTX Group 4: IV golimumab 4 mg/kg at Wk 0 then q 12 wks thereafter through Wk 48 with concomitant placebo capsules (sham MTX) Group 5: IV placebo at Wk 0 then q 12 wks thereafter through Wk 48 with continuation of baseline stable dose of MTX	N=643 Group 1: n=129 Group 2: n=128 Group 3: n=128 Group 4: n=129 Group 5: n=129	Adults age $\geq$ 18 years with RA for $\geq$ 3 months prior to screening who tolerated at least 15-25 mg/wk of MTX for $\geq$ 3 months with clinically active disease defined as $\geq$ 4 swollen and 4 tender joints	¹ EP: Proportion of patients with ACR 50 response at Wk 14 Major ² EPs: 1. Proportion of patients with ACR 50 response at Wk 24; 2. Proportion of patients with ACR 20 response at Wk 14; 3. Proportion of patients with DAS28 response rate at Wk 14; 4. Physical component summary score of the SF-36 at Wk 14 Other ² EPs: ACR 70/90; ACR response rates over time, ACR-N; DAS28 moderate/good response; DAS28 remission, HAQ-DI, and SF-36
CNT0148ART3001 Objectives: 1. Evaluate the clinical efficacy of IV golimumab 2 mg/kg +MTX versus MTX alone in subjects with active RA despite MTX; 2. assess the safety of IV golimumab in RA patients; 3. assess physical function and disability in patients treated with IV golimumab; 4. determine population PK and PD of IV golimumab; 5. assess effects of IV golimumab on structural damage	52-wk, Phase 3, MC, R (2:1), DB, PC, parallel group study with early escape at Wk 16 based on < 20% improvement over baseline in both swollen and tender joint counts Total 103 sites: Argentina (9 sites: n=82); Australia (5 sites: n=9); Columbia (4 sites: n=37); Hungary (5 sites: n=31); Korea (4 sites: n=16); Lithuania (7 sites: n=64); Malaysia (8 sites: n=26); Mexico (5 sites: n=92); New Zealand (2 sites: n=6); Poland (14 sites: n=101); Russia (10 sites: n=69); Ukraine (12 sites: n=90); and U.S. (7 sites: n=23)	Group 1: IV golimumab 2 mg/kg at Wks 0, 4 and then q 8 wks thereafter + MTX Group 2: Placebo IV at Wks 0, 2, 12, 16 and 20 +MTX following which they were to have been crossed over to IV golimumab 2 mg/kg at Wk 24 with study infusions of golimumab at Wks 24 and 28 and then q 8 wks thereafter + MTX	Group 1: n= 197 Group 2: n=395	Adults age $\geq$ 18 years with RA for $\geq$ 3 months prior to screening who tolerated at least 15-25 mg/wk of MTX for $\geq$ 3 months with clinically active disease defined as $\geq$ 4 swollen and 4 tender joints	¹ EP: Proportion of patients with ACR 20 response at Wk 14 Major ² EPs: 1. Proportion of subjects with moderate/good DAS28 response ; 2. Δ from baseline in HAQ-DI at Wk 14; 3. Proportion of subjects with ACR50 response at Wk 24; 4. Δ from baseline in van der Heijde Modified Sharp score at Wk 24 Other ² EPs: ACR 70/90; ACR response rates over time; DAS28 response over time; DAS28 remission, SF-36, and FACIT-Fatigue

Adapted from Module 5.2 Tabular Listing of Clinical Studies; p. 1-3.

5.2 Review Strategy

The Applicant conducted two randomized controlled trials, Studies C0524T12 and CNTO148ART3001, in support of efficacy for this application. C0524T12 will not be reviewed in support of IV golimumab's efficacy as a treatment for RA in adults since it evaluated doses and dosing regimens different than the dose and dosing regimen proposed for marketing in addition to failing to demonstrate efficacy as assessed by its primary endpoint.

The safety database included all subjects who participated in the two Phase 3 trials, as well as safety data collected from Phase 1 and Phase 2 studies that evaluated both the IV and SC formulations of golimumab and selected safety data of adverse events of interest from Phase 3 studies conducted in RA patients with the SC formulation. This review focuses primarily on data for the proposed dose of 2 mg/kg every 8 weeks from CNTO148ART3001. These data will be discussed in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

The efficacy of the proposed for marketing dose of IV golimumab was evaluated by the Applicant in a single Phase 3 clinical study, CNTO148ART 3001 whose protocol design is discussed below. An abbreviated study report of C0524T12 may be found in Section 10.

5.3.1 Protocol CNTO148ART3001

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Golimumab, an Anti-TNF- α Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy.

Dates Conducted: This trial was started on September 14, 2009 and completed on November 25, 2011. Database lock was March 1, 2012.

Objectives:

Primary Objective:

- To evaluate the clinical efficacy of intravenous (IV) administration of golimumab 2 mg/kg plus methotrexate (MTX) compared with MTX alone in subjects with active rheumatoid arthritis (RA) despite MTX therapy

Secondary Objective:

- To assess safety parameters
- To assess physical function and disability
- To determine population pharmacokinetics (PK) and pharmacodynamics (PD) of IV golimumab
- To assess effects of IV golimumab on structural damage

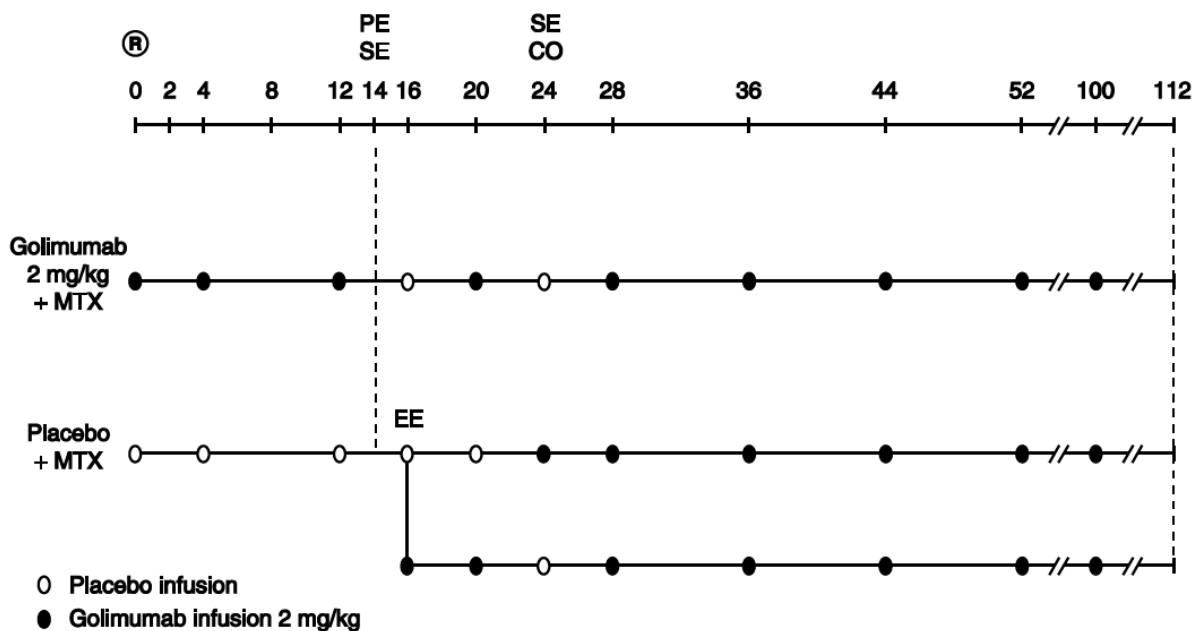
Overall Design:

This multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel group, Phase 3 study conducted at 92 international sites evaluated the effectiveness and safety of IV golimumab as a treatment for RA in 592 patients with moderate to severely active RA despite concurrent MTX therapy. Eligible subjects were randomized via a 2:1 ratio stratified by screening C-reactive protein (CRP) level (<1.5 mg/dL or ≥ 1.5 mg/dL) and investigation site to the following 2 treatment groups:

- Golimumab 2 mg/kg IV infusion + MTX
- Placebo IV infusion + MTX

Study infusions were to be administered at Weeks 0, 4, and every 8 weeks thereafter through completion of the trial at Week 100. At the Week 16 visit, placebo patients who had demonstrated $< 10\%$ improvement in both tender and swollen joint counts were eligible for early escape consisting of treatment with active study agent + MTX for the remainder of the study. Placebo patients who did not qualify for early escape were to continue receiving placebo infusions + MTX until Week 24 when they were to have been crossed-over to receive treatment with active study agent for the remaining duration of the trial. The protocol mandated a 12-week safety follow-up of all subjects upon completion of study treatment. Figure 1 is a schematic of the overall trial design, scheduled study visits and assessments:

Figure 2 – Schematic Design of Study CNTO148ART3001



I18090a_v4

Sponsor's Fig. 1; p. 19 Study protocol

Eligibility:

Table 3 summarizes the major inclusion and exclusion criteria for Study CNTO148ART3001:

Table 3 – Tabular Summary of Major Inclusion and Exclusion Criteria for Study CNTO148ART3001

Major Inclusion Criteria:

1. Males or females $\geq$ 18 years old
2. Diagnosis of active RA for at $\geq$ 3 months prior to screening defined by 1987 ARA criteria
3. Treated and tolerated MTX a dose of at least 15 mg/week for at least 3 months prior to screening, and have been on a stable dose of MTX $\geq$ 15 mg/week and $\leq$ 25 mg/week for at least 4 weeks prior to screening
4. CRP $\geq$ 1.0 mg/dL at screening
5. Anti-cyclic citrullinated peptide (anti-CCP) antibody-positive or rheumatoid factor (RF) positive at screening
6. Subjects using NSAIDs or other analgesics for RA must be on a stable dose for at least 2 weeks prior to first administration of study agent
7. Dose of corticosteroids not to exceed prednisone equivalent of $\leq$ 10 mg/day that must be

stable for at least 2 weeks prior to first administration of study agent. If currently not taking corticosteroids, subjects must have not received oral corticosteroids for at least 2 weeks prior to first administration of study agent.

8. Men capable of fathering children and females of childbearing potential must be using adequate birth control measures as listed in the protocol and a negative pregnancy test.
9. Comply with the following tuberculosis (TB) screening criteria: no history of (H/O) latent or active TB prior to screening; no signs/symptoms suggestive of active TB upon medical history and/or physical exam; no recent close contact with a person with active TB or if such contact has occurred evaluation and appropriate treatment for latent TB (if warranted) prior to or simultaneously with first administration of study agent; must have a negative QuantiFERON-TB Gold or negative TB skin test within 6 weeks prior to first administration of study agent; and a negative chest x-ray within 3 months prior to first administration of study agent with no evidence of current active TB or old, inactive TB as read by a qualified radiologist
10. Have the following screening lab test results: hemoglobin ≥ 8.5 g/dL; WBC $\geq 3.5 \times 10^3$ cells/ μ L; neutrophils $\geq 1/5 \times 10^3$ cells/ μ L; platelets $\geq 100 \times 10^3$ cells/ μ L; ALT and AST $\leq 1.5 \times$ upper limits of normal (ULN); and serum creatinine ≤ 1.5 mg/dL

Major Exclusion Criteria:

1. H/O inflammatory diseases such as psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, or Lyme disease that might confound study evaluations
2. Treated with DMARDs other than MTX or immunosuppressives such as D-penicillamine, hydroxychloroquine, chloroquine, oral or parenteral gold, sulfasalazine, leflunomide, azathioprine, cyclosporine, mycophenolate mofetil during the 4 weeks prior to first administration of study agent
3. Received intra-articular, intra-muscular, or IV corticosteroids including adrenocorticotrophic hormone during the 4 weeks prior to first administration of study agent
4. H/O hypersensitivity to human Ig proteins or other components of golimumab
5. Received any commercial or investigation anti-TNF therapy such as infliximab, golimumab, adalimumab, certolizumab pegol, or etanercept
6. Received rituximab, efalizumab, abatacept, natalizumab or other agents that target alpha-4-integrin
7. Received anakinra during the 4 weeks prior to first administration of study agent
8. Received alefacept within the 3 months prior to the first administration of the study agent
9. Used cytotoxic agents such as chlorambucil., cyclophosphamide, nitrogen mustard, or other alkylating agents
10. Treated with any investigational drug within 5 half-lives of that drug prior to the first administration of study agent
11. Pregnant, nursing or planning pregnancy or fathering a child within 6 months after receiving last administration of study agent
12. H/O latent or active granulomatous infection including histoplasmosis, or coccidioidomycosis prior to screening
13. Had bacilli Calmette-Guerin (BCG) vaccination within 12 months of screening
14. Chest X-ray within 3 months prior to first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection including TB
15. H/O nontuberculosis mycobacterial infection or opportunistic infection (e.g., cytomegalovirus, pneumocystosis, aspergillosis) within 6 months prior to screening
16. Received or expected to receive any live virus or bacterial vaccination within 3 months

prior to first administration of study agent, during the study or within 6 months after the last administration of study agent

17. H/O infected joint prosthesis, or have received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced
18. H/O serious infection, hospitalization for an infection, or treatment with IV antibiotics for an infection within 2 months prior to first administration of study agent.
19. H/O or ongoing chronic/recurrent infectious disease (e.g., chronic renal infection, chronic chest infection, sinusitis, recurrent UTI, or open, draining or infected skin wound or ulcer)
20. H/O HIV, hepatitis B or C infection
21. H/O demyelinating diseases such as multiple sclerosis or optic neuritis
22. Have current signs/symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, GI, endocrine, pulmonary, cardiac, neurologic, psychiatric or cerebral disease
23. H/O recurrent or medically controlled asymptomatic CHF
24. H/O or signs of lymphoproliferative disease
25. H/O malignancy within last 5 years (with the exception of nonmelanoma skin cancer treated without recurrence)
26. H/O transplanted organ with the exception of corneal transplant (>3 months)
27. H/o substance abuse within the last 3 years

Treatment:

Placebo used in this study was 0.9% normal saline supplied as a sterile liquid for IV infusion in single-use infusion bags. Golimumab was supplied as a sterile liquid for IV infusion in single use 4 mL vials containing 50 mg (12.5 mg/mL) of the product. A pharmacist unblinded to study treatment was to have prepared the golimumab IV infusions administered during this study according to the subject's weight and treatment assignment. All study infusions were to have been administered over 30 minutes at Weeks 0, 4 and then every 8 weeks thereafter. In order to maintain study blind, subjects randomized to treatment with golimumab 2 mg/kg also received a placebo infusion at Weeks 16 and 24, while early escape patients were to have started receiving golimumab 2 mg/kg IV infusions at weeks 16 and 20 and then every 8 weeks thereafter. Placebo patients not eligible for early escape were to have crossed over at Week 24 to initiate treatment with golimumab 2 mg/kg IV infusions administered at Week 24 and 28 after which they were to have continued to receive golimumab 2mg/kg infusions every 8 weeks. All subjects were to have been observed for symptoms of infusion reactions while receiving their study infusions and for 60 minutes after completion of each study infusion.

Rescue Medications:

The protocol prohibited the use of rescue medications over the course of the study.

Concomitant Medications:

The protocol required all subjects to maintain a stable dose of concomitant MTX (between 15 and 25 mg/week) for the duration of the study. Temporary discontinuations or reductions in the dose of MTX were permitted in the event of abnormal lab test

results, side effects, concurrent medical illness or surgery. Patients were also allowed to continue taking doses that had been stable for at least 2 weeks prior to study entry of background NSAIDs, analgesics, and oral corticosteroids, (i.e., doses of ≤ 10 mg/day of prednisone or equivalent). Oral corticosteroid doses could be reduced in the event of unacceptable side effects. The administration of intra-muscular or IV corticosteroids over the course of the trial was prohibited. The protocol permitted the concomitant use of inhaled corticosteroids for the control of chronic respiratory diseases as well as short courses of prophylactic oral or IV corticosteroids prior to surgery (stress dose corticosteroids) or as treatment of concomitant illnesses. Subjects were encouraged to take oral folic acid (≥ 5 mg/week) while participating in the study.

Use of the following concomitant treatments by patients was prohibited while participating in the trial:

- Biological agents
- Cytotoxic agents
- Disease modifying anti-rheumatic drugs (DMARDs) other than MTX
- Systemic immunosuppressive agents
- Investigational drugs

Removal of Patients from Treatment or Assessment:

Subjects were to have been withdrawn from the study if they requested to be discontinued from the trial for any reason, continuation in the study was determined to be detrimental to the patient's well being, required the initiation of a non-permitted concomitant biological agent or drug, incurred unblinding of study drug, or the occurrence of any of the following:

- Serious infection
- Opportunistic infection
- Malignancy (excluding nonmelanoma skin cancer)
- Pregnancy or pregnancy planned within 6 months after last study infusion administration
- Congestive heart failure (CHF)
- Demyelinating disease
- Active TB; symptoms or a chest x-ray suggestive of active TB; recent close contact with a person with active TB and could not undergo additional evaluation
- Prematurely discontinued or noncompliant with treatment for latent TB
- Bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension that occurred during or following study agent administration
- Symptoms suggestive of serum sickness (e.g., myalgia; arthralgia; fever; rash; pruritus; facial, hand, or lip edema; dysphagia; urticaria; sore throat; and/or headache) occurring 1 to 14 days after an infusion of study agent

Study Procedures:

The following Tables are a tabular flow chart of the scheduled study visits that were to have been completed within ± 7 days as well as protocol specified procedures and evaluations:

Table 4- Schedule of Procedures and Evaluations for Study CNTO148ART3001

Attachment 1.1 Study Schedule of Events Through Week 112																					
Assessments ^a	Screen	Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 36	Wk 44	Wk 52	Wk 60	Wk 68	Wk 76	Wk 84	Wk 92	Wk 100	Wk 112
Consent	X																				
Demography/ med. history	X																				
Physical examination	X													X							X
Duration of morning stiffness	X	X																			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																				
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray ^b	X																				
TB screening ^b	X																				
TB evaluation ^c	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of entry criteria	X	X																			
Serum pregnancy test	X																				
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4 (cont.) – Schedule of Procedures and Evaluations for Study CNTO148ART3001

Attachment 1.1 Study Schedule of Events Through Week 112																					
Assessments ^a	Screen	Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 36	Wk 44	Wk 52	Wk 60	Wk 68	Wk 76	Wk 84	Wk 92	Wk 100	Wk 112
Randomization		X																			
Infusion ^d		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Rheumatoid factor	X																				
Anti-CCP antibodies	X																				
Efficacy evaluations ^e		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	
SF-36		X				X		X		X				X							X
FACIT-F		X				X		X		X				X							X
EQ-5D		X				X		X		X				X							X
HEcon		X		X		X		X		X				X							X
Radiographs of hands and feet		X						X ¹		X				X						X	
CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	
ANA/anti-dsDNA antibodies		X							X												
Serum biomarkers		X	X	X			X														
Hepcidin		X					X														
DNA markers ^f		X																			
RNA markers		X					X														
AE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4 (cont.) – Schedule of Procedures and Evaluations for Study CNTO148ART3001

Attachment 1.1 Study Schedule of Events Through Week 112																					
Assessments ^a	Screen	Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 36	Wk 44	Wk 52	Wk 60	Wk 68	Wk 76	Wk 84	Wk 92	Wk 100	Wk 112
Routine laboratory analyses (except LFTs)	X	X		X		X			X		X		X		X		X		X		X
Liver function tests	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Golimumab concentration ^b		2X	X	2X	X	2X	X	X	2X			2X		2X			2X				2X
Random golimumab concentration ^b								←X→													
Antibodies to golimumab		X							X					X			X				X

^a All assessments are to be completed prior to study agent administration, unless otherwise specified. Subjects will be evaluated every 8 weeks after Week 28 for the purpose of this study. However, treating physicians should monitor subjects for MTX and other therapies in accordance with appropriate clinical practice guidelines. For subjects who discontinue study agent injections, see Section 5.3.2 for required follow-up assessments.

^b In countries in which QuantiFERON-TB Gold test is not approved/registered, a tuberculin skin test will also be performed.

^c If TB is suspected at any time during the study, a tuberculin skin test will also be performed in countries in which QuantiFERON-TB Gold test is not approved/registered.

^d Infusion schedule as outlined in protocol. All subjects must be observed carefully for symptoms of an infusion reaction during the infusion and for 60 minutes after the IV infusion of study agent is complete. If a subject has an infusion reaction, the subject must complete the EQ-5D questionnaire prior to leaving the treatment facility.

^e Efficacy evaluations include: joint assessment, patient pain assessment, Patient's and Physician's Global Assessments of Disease Activity, and HAQ.

^f This test is strictly voluntary and results will remain confidential. It is not a requirement for sites and subjects to participate in this study. Samples will be collected for DNA analysis at Week 0.

^g At each of the Week 0, 4, 12, 20, 36, 52, 76, and 100 visits, 2 samples for serum golimumab concentrations (indicated by "2X" in the Schedule above) will be collected (1 sample will be collected immediately prior to infusion and the other collected one hour after the end of the infusion). For each of the remaining visits, only 1 sample for serum golimumab concentrations will be collected, which should be taken prior to infusion if an infusion of the study agent is administered. One additional sample for serum golimumab concentration will be collected from all subjects at any time between Weeks 14 and 20 other than at the time of the Week 14, Week 16, and Week 20 visits; this sample must be collected at least 24 hours prior to or after a study agent administration.

^h Radiographs will be performed for all subjects with < 10% improvement in tender and swollen joints from baseline at Week 16.

Outcome Measures:

The following efficacy assessments were to have been performed:

Primary efficacy endpoint:

The primary efficacy variable was to have been the proportion of patients with an ACR20 response at Week 14. The ACR 20 response rate is a validated, regulatory standard endpoint used in clinical trials evaluating treatments for RA. Responders are defined as patients whose improvement from baseline to Week 14 fulfilled all of the following criteria:

- ≥20% reduction in the tender joint count (0-28)
- ≥20% reduction in the swollen joint count (0-28)
- ≥20% reduction in three of the five following additional measures:
 - Patient's assessment of pain (100 mm visual assessment scale [VAS])
 - Patient's global assessment of disease activity (100 mm VAS)
 - Physician's global assessment of disease activity (100 mm VAS)
 - HAQ-DI
 - CRP or ESR as acute phase reactant

At each visit, study investigators were to have performed a standardized joint examination assessing the following 28 joints bilaterally for swelling and tenderness

(based on applied pressure and range of motion): shoulder, elbow, wrist (radiocarpal, carpal, and carpometacarpal were collectively designated wrist), metacarpophalangeal I-V, thumb interphalangeal, proximal interphalangeal II-V, and knee. The swollen joint count represented the number of joints in which there was synovial fluid and/or soft tissue swelling, but not if bony overgrowth was found. The tender joint count represented the number of joints in which pain was reported after a maneuver.

Determination of the ACR50, 70 and 90 response rates (secondary endpoints) is based on $\geq 50\%$, 70% and 90% improvement from baseline to a prespecified time point, respectively, of the same criteria listed above used to determine the ACR20 response rate.

Secondary efficacy endpoint:

The study had a number of secondary endpoints defined as follows:

Major secondary efficacy variables (4):

- Proportion of subjects with a moderate or good DAS28 Response (using CRP) at Week 14: The DAS28 score is another validated, regulatory standard endpoint commonly used by foreign regulatory authorities to assess efficacy of treatments in RA trials. It is a composite index score comprised of the number of tender and swollen joints based on a 28 joint count, an acute phase reactant (e.g., ESR or CRP), and the patient's global disease assessment. Its score is calculated via a standardized formula and ranges from 0-10 with higher scores consistent with higher disease activity. Patients were classified as patients with good, moderate, or no response based on their change in DAS28 score as shown in the following Table 5:

Table 5 – Characterization of RA Disease Status by DAS28 Score

Baseline DAS28	Improvement >1.2	Improvement >0.6 to ≤ 1.2	Improvement ≤ 0.6
≤ 3.2	Good response	Moderate response	No response
>3.2 to ≤ 5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

- Change from baseline in HAQ-DI at Week 14: This is a validated, self-reported functional status instrument that was used to measure disability over the initial 14 weeks of treatment as assessed by 8 domains of functionality. The highest scores from the 8 domains (range: 0-24) are summed and divided by 8 to yield a Functional Disability Index (range: 0-3 with higher scores indicative of increased functional disability). The mean clinically important difference for the HAQ-DI score is -0.22.
- Proportion of subjects with ACR50 response at Week 24
- Change from baseline in van der Heijde Modified Sharp (vdHS) Score at Week 24: The vdHS Score is a validated, regulatory x-ray scoring system generated

from the blinded evaluation by two radiologists of bilateral radiographic images of the hands and feet involving 32 bilateral hand/wrist joints and 12 bilateral foot joints. Each joint is evaluated via a 5-point scoring system for severity of erosion based on the surface area involved (0= no erosion to 5= more than half of articulating bone is eroded) and a 4-point scoring system for joint space narrowing (JSN) (0= normal to 4 =bony ankylosis or complete subluxation). The total vdH-S score (0-448) is the sum of joint erosion score (0 to 280) and JSN score (0 to 168).

Other secondary efficacy variables to have been assessed included:

- ACR50 response rate at Week 14
- ACR70 response rate at Weeks 14 and 24
- Proportion of subjects achieving ACR20 response at Week 2
- Proportion of subjects achieving ACR responses of 20, 50, and 70 over time
- Percent improvement from baseline in ACR components over time
- Percent improvement from baseline in ACR components at Weeks 14 and 24
- Proportion of subjects with a moderate or good DAS28 (using CRP) response at Week 24
- Proportion of subjects with a moderate or good DAS28 (CRP) response over time
- Proportion of subjects with a DAS28 (CRP) remission (<2.6) at Week 14 and 24
- Proportion of subjects with a DAS28 (CRP) remission (<2.6) over time
- Change from baseline in DAS28 (CRP) scores over time
- Change from baseline in HAQ-DI score at Week 24
- Improvement from baseline in HAQ-DI score over time
- Proportion of subjects with clinically meaningful improvement (≥ 0.25) from baseline in the HAQ-DI score at Week 14 and Week 24
- Changes from baseline in Short Form (SF-36) Health Status Survey at Weeks 16 and 24: The SF-36 is a validated, 36-item, self-reported questionnaire comprised of 8 subdomains that was used to calculate the 2 summary scores: physical component summary (PCS) and mental component summary (MCS). Average scores in healthy normal population age 55-64 for males and females combined are 47 for PCS and 52 for MCS. Higher scores represent better mental and physical quality of life.
- Changes from baseline in the physical and mental component summary scores of SF-36
- Summary of change from baseline in the fatigue subset of the FACIT Questionnaire at Weeks 16 and 24: The 13-item fatigue sub-questionnaire from this validated self-administered assessment tool was used to evaluate the effect of fatigue on patient's daily activity and function based on the following 5-point grading system: 0= not at all, 1=a little bit, 2= somewhat, 3 =quite a bit and 4=very much. The overall score was the sum average of the subscales.

- Proportion of subjects who achieve ≥ 4 point change from baseline in FACIT-Fatigue at Weeks 14 and 24
- Change from baseline in vdHS score at Weeks 52 and 100

Statistical Design, Definitions of Analyzed Populations and Analysis Plan:

With a projected enrollment of 564 subjects randomized via 2:1 (golimumab 2 mg/kg = 376 subjects; placebo n=188), this study was to have approximately 99% power to show a significant difference in the proportion of patients achieving an ACR 20 response at Week 14 assuming a 52% response rate for golimumab 2 mg/kg group and a placebo response rate of 27% using a two-sided chi-square test at a significance level of 0.05. This sample size was selected to ensure adequate power for the major secondary endpoint assessing radiographic progression (change from baseline in vdH-S score at Week 24) as well as an adequate number of subjects exposed to IV golimumab 2 mg/kg to conduct safety assessments.

Study Populations:

Two populations were to have been used for analysis. They were defined as follows:

1. Intent-to-treat (ITT) Population: was defined as all patients who were randomized regardless of whether or not they received the assigned treatment. The ITT population was to have been used to assess all efficacy endpoints.
2. Treated Population: was defined as all patients who had received at least one IV infusion of study agent. The treated population was to have been used to for all safety and clinical pharmacology analyses.

Efficacy Evaluation:

The statistical analysis plan (SAP) stipulated that the primary endpoint (ACR20 response rate at Week 14) was to have been analyzed via Cochran-Mantel-Haenszel (CMH) test stratified by CRP level at screening with last observation carried forward (LOCF) and nonresponder imputations to account for missing data required to calculate subjects' ACR20 response or early escape patients, and drop-outs due to treatment failure, respectively. A subject was to be considered a treatment failure or non-responder if they discontinued study infusions due to unsatisfactory therapeutic effect, required an increase above baseline in their concomitant MTX dose, initiated treatment with any of the prohibited biological products or medications (DMARDs), initiated treatment or required an increase in background oral corticosteroids, or received IV or IM corticosteroids as treatment for RA over the course of the trial. Secondary endpoints were to have been analyzed as follows:

1. Binary categorical data were to have been analyzed via the CMH test when stratification (e.g., CRP level at screening) was employed or the chi-square test.
2. Continuous data was to have been analyzed via the analysis of variance (ANOVA) test on van der Waerden normal scores.

All efficacy endpoints were to have been conducted on the ITT population using 2-sided testing with an alpha level of 0.05. To control for multiplicity, a sequential procedure was

to have been used for testing the primary endpoint followed by the major secondary endpoints in a prespecified descending order. No multiplicity adjustments were prespecified in the SAP in analyzing the non-major secondary endpoints. Linear extrapolation was to have been used to impute missing data in analyzing the major secondary endpoint, the change over baseline in vdHS score for radiographic progression, while last observation carried forward (LOCF) was to have been the imputation technique used in the analyses of the remaining secondary endpoints (both major and non-major).

Clinical pharmacology assessments were to have included a population PK analysis.

Safety Evaluation:

The analysis of safety assessment was to have been conducted on the treated population. Safety assessment was to have included treatment emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), clinical lab data, physical exam findings and vital signs. All TEAEs were to have been coded using the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary (Version 13.1). The incidences of TEAEs were to have been summarized by system organ class (SOC) and preferred term by overall and treatment group. TEAE of interest such as infections, serious infections, infusion reactions, vascular events, and malignancies were to have been presented separately.

Clinical lab data results for hematology, serum chemistry and urinalysis testing as well as changes in serologies (occurrence of ANA and anti-dsDNA antibodies), immunogenicity (occurrence of antibodies to golimumab), vital signs and physical exam were to have been reviewed and summarized for within treatment changes and for changes from baseline for each treatment group.

Study Conduct:

In addition to a country specific protocol amendment required by the health regulatory agency of South Korea which will not be discussed, there were two protocol amendments to Study CNTO148ART3001:

1. Amendment 1 (implemented on September 10, 2009)
 - Inclusion criterion 10d were revised to clarify that indeterminate results of a tuberculin skin test were to be handled as outlined in the Section 5.1 of the protocol. Additionally, a negative tuberculin skin test is required if the QuantiFERON-TB Gold test is not approved/registered in that country (adherence to local guidelines).
 - Clarification regarding pre-randomization procedures involved for TB testing and evaluation
 - Clarification regarding discontinuation of study agent and the appropriate work-up of a subject with evidence of active tuberculosis

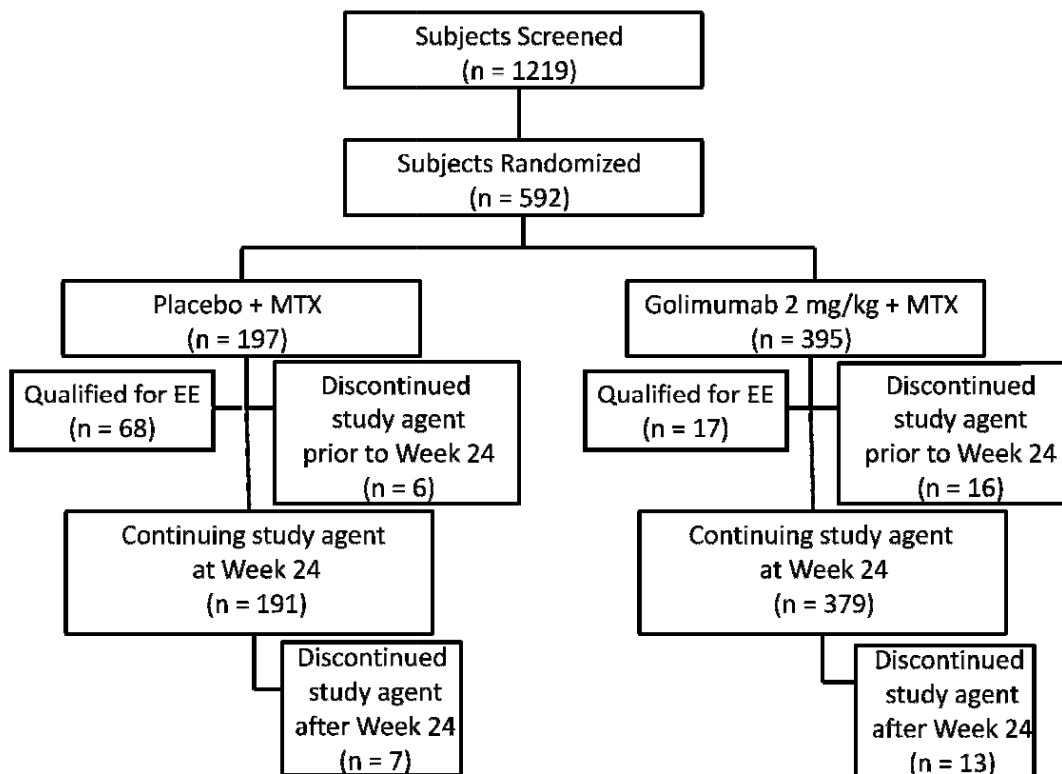
- Number of editorial corrections that updated the SF-36 Healthy Survey to be used in the study from version 1.0 to 2.0; and change in the analysis time point of the SF-36 from Week 14 to Week 16
2. Amendment 2 (implemented on January 13, 2012)
- Sponsor personnel who would have access to unblinded data following the Week 24 locking of the study database would be documented in the analysis release plan prior to unblinding
 - Completion of the EQ-5D questionnaire would no longer be required by patients post-infusion reaction
 - Clarification of the infusion schedule that mandated observation of all subjects during the administration of study infusions and for 60 minutes post-infusion for symptoms of an infusion reaction.

Study Results:

Patient Disposition:

This study was conducted at 103 centers worldwide located in Argentina (n=82; 14%), Australia (n=9; 2%), Columbia (n=37; 6%), Hungary (n=31; 5%), Korea (n=16; 3%), Lithuania (n=64; 11%), Malaysia (n=26; 4%), Mexico (n=38; 6%), New Zealand (n=6; 1%), Poland (n=101; 17%), Russia (n=69; 12%), Ukraine (n=90; 15%), and the United States (n=23; 4%). Of the 1,219 potential patients screened for this study, 592 were randomized to study treatment. An additional 28 patients were randomized than stipulated by the protocol due to the high screening failure rate (approximately 51%). A flow chart of subjects' disposition over the 52-week course of Study CNTO148ART3001 is shown in Figure 3:

Figure 3 – Subject Disposition for the 52 Weeks of Study CNTO148ART3001



Adapted Sponsor's Figure 3; p. 44 of the 52-Week Study Report

The above flow chart Table 6 summarizes patients' disposition for this trial by randomized treatment group, however, at the time of the Week 24 database lock for CNTO148ART, only 6 subjects were reported to have discontinued study agent through Week 24. An additional 2 patients (Subjects 3707-00336 and 6006-00141) discontinued at the Week 24 visit, and their study agent discontinuation forms were not included in the Week 24 database lock, and thus are not reflected in Figure 3.

Table 6 displays an updated disposition of study patients by randomized treatment group over the 52-weeks of CNTOART3001. Of the 592 subjects randomized, 570 (96%) completed the 24-week controlled portion of the study. Twenty-four (24; 4%) patients discontinued study treatment prior to or at the Week 24 visit while another 18 patients discontinued study treatment following the Week 24 visit through Week 52 (total discontinued: 42 subjects; 7%). Overall, the rates for study drop-outs were similar for both treatment groups. The most common reasons for premature discontinuation over the 52-week course of Study CNTOART3001 were adverse events (18 subjects; 3%) and withdrawal of consent (11 subjects; and 2%). Of the 197 patients randomized initially to treatment with placebo, 68 (35%) qualified for early escape and initiated

golimumab therapy at Week 16 as compared to 17 patients (4%) initially randomized to treatment with golimumab.

Table 6 – Subject Disposition By Randomized Treatment Group over the 52 Weeks of Study CNTO148ART3001

	Placebo + MTX	Golimumab 2 mg/kg + MTX	Total
Number of Subjects Randomized	197	395	592
Number of Subjects Completed Week 24	191	379	570
Number of Subjects Withdrawn Prior to Week 24	76	16	92
Week 16 Early Escape	68	0	68
Discontinued Treatment	8	16	24
Subjects Treated:	197	395	592
Placebo + MTX	197 (100%)	0	197 (33%)
Placebo + MTX → Golimumab 2mg/kg + MTX			
Week 16 Early Escape	68 (35%)	N/A	N/A
Week 24 Crossover	121(61%)	N/A	N/A
Golimumab 2 mg/kg + MTX	0	395 (100%)	395 (67%)
Total Number of Subjects Withdrawn Prematurely	13 (7%)	29 (7%)	42 (7%)
Death	1 (1%)	1 (0%)	2 (0%)
Lost to Follow-Up	0 (0%)	1 (0%)	1 (0%)
Withdrawal of Consent	5 (3%)	6 (2%)	11 (2%)
Adverse Event	4 (1%)	14 (4%)	18 (3%)
Lack of efficacy	2 (1%)	2 (1%)	4 (1%)
Protocol Violation	1 (1%)	2 (1%)	3 (1%)
Other	0 (0%)	3 (1%)	3 (1%)

Adapted from the 52-week study report Table 1; p. 45 and the May 28, 2013 information request Table 2; p. 5.

Protocol Deviations:

A total of 249 patients incurred one or more protocol deviation over the course of this 52 week trial as shown in Table 7. The rate of protocol deviations was comparable between the two randomized treatment groups. Protocol deviations for this trial most commonly fell under the category “Other” which included the following: incorrect entry of tender or swollen joint counts, out of window visits, assessments performed by an improperly trained joint assessor, missed study visits, dose of corticosteroids or NSAIDs outside of study specifications, incorrect CRP value, or improperly signed informed consent for (ICF) (i.e., delayed signing of an updated ICF).

Table 7 – Cumulative Summary of Subjects with a Major Protocol Deviation by Randomized Treatment Group for Study CNTO148ART3001

	Placebo + MTX ¹ (n=197)	Golimumab 2 mg/kg + MTX (n=395)	Total (N=592)
Number of Subjects with ≥ 1 Protocol Deviation	84 (43%)	165 (42%)	249 (42%)
Deviation:			
Entered Study Without Meeting Entry Criteria	15 (8%)	37 (9%)	52 (9%)
Received Wrong Treatment or Incorrect Dose	4 (2%)	6 (2%)	10 (2%)
Received Prohibited Concomitant Medication	0	0	0
Other	74 (38%)	136 (34%)	210 (36%)

¹Includes subjects who early escaped at Week 16 and started receiving golimumab at Week16. All subjects started receiving golimumab at Week 24.

Adapted Sponsor's Attachment 1.10; p. 143 52-week study report

Demographics:

Table 8 displays the baseline demographics of study participants. The baseline demographic characteristics were similar for both treatment groups. Subjects who participated in this trial had a mean age of 52 years and were overwhelmingly female (82%) and Caucasian (80%). Since the majority (87%) of subjects who enrolled in the trial came from European (60%) and Latin American (27%) countries, there was a poor representation of other racial groups (0% Black, American Indian/Native Alaskan 2% and 7% Asian).

Table 8 – Baseline Demographic Characteristics of Subjects Enrolled in Study CNTO148ART3001

Demographic Characteristic	Placebo + MTX (n=197)	Golimumab 2 mg/kg + MTX (n=395)	Total (N=592)
Age (years):			
Mean (SD)	51 (11)	52 (13)	52 (12)
Gender:			
Female	157 (80%)	326 (83%)	483 (82%)
Male	40 (20%)	69 (18%)	109 (18%)
Race:			
White	160 (81%)	315 (80%)	475 (80%)
Black	0 (0%)	1 (0%)	1 (0%)
Asian	12 (6%)	31 (8%)	43 (7%)
American Indian/Alaska Native	4 (2%)	7 (2%)	11 (2%)
Other	21 (11%)	40 (10%)	61 (10%)
Ethnicity (Hispanic/Latino)			
Yes	59 (30%)	120 (30%)	179 (30%)
No	138 (70%)	272 (69%)	411 (69%)
Unknown	0 (0%)	2 (1%)	2 (0%)
Weight (kg)			
Mean (SD)	72 (17)	72 (16)	72 (16)
Height (cm)			
Mean (SD)	163 (9)	163 (9)	163 (9)
BMI (kg/m²)			
Mean (SD)	27 (6)	27 (6)	27 (6)

SD= standard deviation; kg = kilograms; cm= centimeters; BMI=body mass index
 Adapted from Sponsor's Table 8; p. 59-61.

Disease Characteristics:

A tabular summary of subjects' baseline RA disease characteristics and activity status is shown in Table 9. The mean duration of RA disease was 6.9 years for the study population, with the majority of the subjects classified as Functional Class II (72%). The two treatment groups were balanced in terms of baseline disease activity as assessed by a number of parameters. Overall, the study population enrolled in this trial was representative of patients with moderate to very active RA who could potentially benefit from treatment with IV golimumab.

Table 9 – Summary of Baseline RA Disease Characteristics and Activity for Subjects Participating in Study CNTO148ART3001

Baseline Disease Characteristics	Placebo + MTX (n=197)	Golimumab 2 mg/kg + MTX (n=395)	Total (N=592)
Duration of Rheumatoid Arthritis (years): Mean (SD)	7.0 (7.2)	6.9 (7.0)	6.9 (7.0)
Functional Class :			
Class I	22 (11%)	33 (8%)	55 (9%)
Class II	140 (71%)	284 (72%)	424 (72%)
Class III	35 (18%)	78 (20%)	113 (19%)
Class IV	0 (0%)	0 (0%)	0 (0%)
Extra-Articular Manifestations:			
Rheumatoid Nodules	29 (15%)	56 (14%)	85 (14%)
Vasculitis	1 (1%)	5 (1%)	6 (1%)
Sicca Syndrome	7 (4%)	17 (4%)	24 (4%)
Lymphadenopathy	0 (0%)	6 (2%)	6 (1%)
Interstitial Lung Fibrosis	1 (1%)	7 (2%)	8 (1%)
Peripheral Neuropathy	0 (0%)	5 (1%)	5 (1%)
Duration of Morning Stiffness (minutes) Mean (SD)	149 (189)	149 (176)	149 (181)
Prior Joint Procedures or Injections	59 (30%)	123 (31%)	182 (31%)
Number of Swollen Joints (Range:0-66): Mean (SD)	15 (6)	15 (8)	15 (8)
Number of Tender Joints (Range: 0-68): Mean (SD)	26 (14)	26 (14)	26 (14)
CRP (mg/dL): Mean (SD)	2.33 (1.88)	2.85 (2.86)	2.64 (2.59)
Physician's Global Assessment of Dis. (VAS:0-10 cm): Mean (SD)	6.3 (1.6)	6.2 (1.7)	6.2 (1.6)
Patient's Global Assessment of Dis. (VAS:0-10 cm): Mean (SD)	6.5 (1.9)	6.5 (1.8)	6.5 (1.9)
Patient's Assessment of Pain (VAS: 0-10 cm): Mean (SD)	6.5 (2.0)	6.5 (1.9)	6.5 (1.9)
HAQ Disability Index (DI) (Range: 0-3) Mean (SD)	1.5 (0.6)	1.6 (0.7)	1.6 (0.7)
Short Form-36 (SF-36):			
Physical Component Summary	30.1 (7.3)	30.8 (6.8)	30.8 (7.0)
Mental Component Summary	38.5 (11.6)	37.1 (11.1)	37.6 (11.3)

SD= standard deviation; CRP= C-reactive protein; Dis.= Disease; VAS= Visual analogue scale; cm= centimeter
Adapted from Sponsor's Tables 1.11, 9 and 10; p. 156-157 and 61-63 of the 24-week study report

Table 10 displays the RA medications used by study participants prior to enrolling in this trial. Overall, the proportions of subjects who used DMARDs, immunosuppressives other than MTX, systemic corticosteroids and NSAIDs was comparable for both treatment groups.

Table 10 – Summary of RA Medications Used Prior to Enrollment in Study CNTO148ART3001

	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	Total (N=592)
Subjects Who Took Any DMARDs	92 (47%)	206 (52%)	298 (50%)
1-2 DMARDs	87 (95%)	190 (92%)	277 (93%)
> 2 DMARDs	5 (5%)	16 (8%)	21 (7%)
Gold Preparation	11 (12%)	12 (6%)	23 (8%)
Chloroquine	18 (20%)	48 (23%)	66 (22%)
Hydroxychloroquine	28 (30%)	58 (28%)	86 (29%)
Sulfasalazine	57 (62%)	113 (55%)	170 (57%)
Penicillamine	1 (1%)	6 (3%)	7 (2%)
Leflunomide	22 (24%)	67 (33%)	89 (30%)
Other DMARDs	2 (2%)	4 (2%)	6 (2%)
Subjects Who Took Any Immunosuppressive	14 (7%)	22 (6%)	36 (6%)
Cyclosporine	4 (29%)	6 (27%)	10 (28%)
Tacrolimus	0 (0%)	1 (5%)	1 (3%)
Mycophenolate Mofetil	0 (0%)	0 (0%)	0 (0%)
Azathioprine	8 (57%)	13 (59%)	21 (58%)
Other Immunosuppressives	3 (21%)	4 (18%)	7 (19%)
Subjects Who Took Systemic Corticosteroids	164 (83%)	316 (80%)	480 (81%)
Subjects Who Took NSAIDs	156 (79%)	323 (82%)	479 (81%)

Adapted Sponsor's Attachment 1.16; p. 164 of the 24-week study report

The protocol mandated that patients were to continue taking stable doses of concomitant RA medications over the course of the study to treat their underlying disease. This information is summarized in Table 11. Overall, the use of concomitant RA medications was similar for the two treatment groups with the majority of patients (68%) taking 15 mg/week of concomitant MTX.

Table 11 – Summary of Baseline RA Medications for Subjects Enrolled in Study CNTO148ART3001

Concomitant Medications	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	Total (N=592)
Methotrexate (MTX)			
<15 mg/week	0 (0%)	1 (0%)	1 (0%)
=15 mg/week	136 (69%)	267 (68%)	403 (68%)
≥ 17.5 mg/week ≤ 20 mg/week	49 (25%)	102 (26%)	151 (26%)
> 22.5 mg/week ≤ 25 mg/week	12 (6%)	25 (6%)	37 (4%)
Oral Corticosteroids:			
Number of Subjects	134 (68%)	251 (64%)	385 (65%)
Mean Dose (SD) (mg/d)	7.0 (2.5)	7.0 (2.5)	7.0 (2.5)
Dose Range (mg/d)	(2.5, 10.0)	(2.5, 10.0)	(2.5, 10.0)
NSAIDs			
Number of Subjects	156 (79%)	323 (82%)	479 (81%)

Adapted Sponsor's Tables 1.31 and 11; p. 230 and 65 of the 24-week study report

Efficacy:

Primary Efficacy Results:

The primary efficacy parameter for Study CNTO148ART3001 was the ACR 20 response rate at Week 14. The results generated for the primary analysis using nonresponder imputation for missing data (e.g., worse case) are shown in Table 12. A statistically higher response rate for the ACR 20 was observed in patients treated with IV golimumab as compared to placebo at Week 14.

Table 12 – Primary Endpoint: ACR 20 Response at Week 14 for Study CNTO148ART3001

Primary Endpoint	Placebo + MTX (n=197)	Golimumab 2 mg/kg + MTX (n=395)	P-value
ACR 20 at Week 14	49 (25%)	231 (59%)	<0.001

Adapted Sponsor's Table 18; p. 77 of the 24-week study report

Secondary Efficacy Endpoints:

This study was designed to have four major secondary endpoints: DAS28 (CRP) response at Week 14, improvement in HAQ-DI at Week 14, ACR 50 response rate at Week 24, and change from baseline in total vdHS score at Week 24. The results of the analyses for these major secondary endpoints are shown in Table 13. Response rates

for the sign and symptom secondary endpoints, DAS28 (CRP) at Week 14 and ACR50 at Week 24, were significant higher in the IV golimumab treatment group as compared to placebo. For the patient reported outcome endpoint, HAQ-DI at Week 14, the decrease in the median score over baseline was significant higher in the IV golimumab group as compared to placebo. Subjects in the IV golimumab group also had significantly less progression on their x-rays compared to placebo treated subjects as measured by the van der Heijde Modified Sharp (vdHS) Score at Week 24.

Table 13 - Analyses of the Major Secondary Endpoints for Study CNTO148ART3001

Major Secondary Endpoints	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	P-value
DAS28 (CRP) Response at Week 14	40%	81%	<0.001
HAQ-DI (Median) at Week 14	0.125	0.500	<0.001
ACR50 at Week 24	13%	35%	<0.001
Change from Baseline in Total vdHS Score at Week 24: Mean (SD)	1.09 (3.194)	0.03 (1.899)	<0.001

Other Secondary Efficacy Endpoints:

There were multiple secondary endpoints analyzed for this study which are summarized in the following

Table 14. No multiplicity correction was planned in the protocol or implemented here for the secondary endpoints. Due to multiplicity concerns, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate.

**Table 14 – Tabular Summary of Secondary Endpoint Analyses for Study
CNT0148ART3001**

Secondary Endpoints	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	P-value
ACR 50 at Week 14	9%	30%	<0.001
ACR 70 at Week 14	3%	12%	<0.001
Week 24	4%	18%	<0.001
Proportion of Subjects Achieving at Week 2: ACR 20	12%	33%	<0.001
ACR 50	3%	6%	p=0.048
ACR70	0%	1%	p=0.114
Proportion of Subjects Achieving ACR 20, 50, 70 and 90 Over Time:	Increasing proportion of golimumab + MTX treated subjects trended to achieve ACR responses over time as compared to placebo + MTX that peaked at Week 24		
Percent Δ from Baseline in ACR Components at Week 14:			
Number of Swollen Joints	25%	68%	<0.001
Number of Tender Joints	13%	62%	<0.001
Patient's Pain Assessment via 10 cm VAS	7.4%	38%	<0.001
Patient's Assessment of Dis. Act. via 10 cm VAS	7.3%	37%	<0.001
Physician's Dis. Act. Assessment via 10 cm VAS	15.5%	52.1%	<0.001
HAQ-DI	6.7%	28.6%	<0.001
CRP Level	29.3%	77.8%	<0.001
Percent Δ from Baseline in ACR Components at Week 24:			
Number of Swollen Joints	27%	75%	<0.001
Number of Tender Joints	14%	64%	<0.001
Patient's Pain Assessment via 10 cm VAS	10.8%	42.9%	<0.001
Patient's Assessment of Dis. Act. via 10 cm VAS	13.9%	40.5%	<0.001
Physician's Dis. Act. Assessment via 10 cm VAS	23.7%	54.5%	<0.001
HAQ-DI	8.7%	30.0%	<0.001
CRP Level	21.4%	76.8%	<0.001
DAS(CRP) "Good to Moderate" Response at: Week 24	45%	81%	<0.001

DAS28 (CRP) Remission (<2.6) Over Time at: Week 14 Week 24	4.6% 5.1%	15.4% 17.7%	<0.001 <0.001
Δ from Baseline in DAS28 (CRP) Scores Over Time	Starting at Week 2, decreases in median response rates occurred that were higher in the golimumab + MTX group as compared to PLO + MTX which were maintained over time		

Table 15 – Tabular Summary of Secondary Endpoint Analyses for Study CNTO148ART3001 (cont.)

Secondary Endpoints	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	P-value
Δ from Baseline in HAQ-DI Score at Week 24: Mean (SD)	0.21 (0.55)	0.53 (0.64)	<0.001
Δ from Baseline in HAQ-DI Score over Time	Starting at Week 2, improvements in median scores that were higher in the golimumab + MTX group as compared to PLO + MTX which were maintained over time.		
Proportion of Subjects with Clinically Meaningful Improvement (≥0.25) from Baseline in HAQ-DI at: Week 14 Week 24	43% 45%	68% 67%	<0.001 <0.001
Δ from Baseline in SF-36: Physical Composite score: Week 16 Mean (SD) Week 24 Mean (SD) Mental Composite Score Week 16 Mean (SD) Week 24 Mean (SD)	3.8 (7.5) 3.8 (7.3) 1.3 (9.7) 1.2 (10.0)	7.42 (8.1) 8.28 (8.3) 7.2 (10.3) 6.9 (10.3)	<0.001 <0.001 <0.001 <0.001
Δ from Baseline in FACIT-Fatigue at: Week 16 Mean (SD) Week 24 Mean (SD)	2.2 (9.7) 2.5 (10.2)	7.5 (10.5) 8.0 (10.8)	<0.001 <0.001

Efficacy Conclusions:

Treatment of RA patients with IV golimumab resulted in a significantly higher ACR20 response rate (59%) as compared to placebo (25%) after 14 weeks of therapy. Patients treated with IV golimumab also experienced significant improvements in major secondary endpoints that further assessed signs and symptoms of RA (ACR50 and DAS28 [CRP], patient reported outcomes (HAQ-DI) and radiographic inhibition of joint damage as measured by the van der Heijde Modified Sharp Score at Week 24. Positive

outcomes that also favored IV golimumab were seen for the other secondary endpoints assessed in this study, but declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate due to multiplicity concerns.

6 Review of Efficacy

Efficacy Summary

The efficacy of golimumab in the treatment of active RA was demonstrated by the successful results from a single, international, multicenter, double-blind, randomized, placebo-controlled trial, Study CNTO148ART3001. In this pivotal trial, IV golimumab when administered at a dose and dosing regimen of 2 mg/kg at Week 0 and 4, and then every 8 weeks thereafter was shown to effectively reduce signs and symptoms of active arthritis in patients with moderate to severe RA with an inadequate response to methotrexate therapy as measured by a plethora of assessments that included the ACR 20 response rate at Week 14 as the primary endpoint. Positive outcomes were also seen for improvement in physical function and inhibiting progression of joint damage as assessed by the HAQ-DI at Week 14 and van der Heijde Modified Sharp (vdHS) Score at Week 24 which were assessed as major secondary endpoints. The results from sensitivity analyses involving the application of different imputation methodologies for missing data were supportive of both the primary and major secondary efficacy results.

The majority of the other secondary endpoints assessed in this study trended in favor of treatment with IV golimumab and were supportive of the results from the primary and major secondary endpoint analyses. However, declaring statistical significance of the secondary endpoints evaluated in these trials using unadjusted p-values would be inappropriate since no multiplicity correction was planned in the protocols or implemented during the analyses of the secondary endpoints other than for the four major secondary endpoints.

6.1 Indication

The proposed indication for IV golimumab is the treatment of moderately to severely active RA in patients with an inadequate response to MTX.

6.1.1 Methods

Efficacy data contained in the submission from the 52-week, multicenter, randomized, double-blind, placebo controlled for the first 24 weeks, parallel group trial CNTO148ART3001 conducted in patients with active RA despite concomitant MTX were reviewed to assess this application. Analyses of pertinent subgroups were also

conducted. All primary and major secondary analyses were confirmed by the FDA's statistical reviewer. The design of the protocol was discussed in Section 5.3.1.

6.1.2 Demographics

Demographic information, baseline RA disease characteristics and activity status, RA medications used prior to enrollment and RA medications used at baseline for the efficacy study is presented in detail in Table 8, Table 9, Table 10 and Table 11, respectively, in Section 5.3.1.

6.1.3 Subject Disposition

Patient disposition is described in detail in Section 5.3.1.

6.1.4 Analysis of Primary Endpoint

The primary efficacy parameter for Study CNTO148ART3001 was the percentage of subjects with an ACR 20 response at Week 14. For this analysis, the protocol's statistical analysis plan mandated that missing ACR20 data at Week 14 was to be imputed as treatment failure (nonresponder) and last observation carried forward for all other reasons. As displayed in Table 16 below, a statistically higher response rate for the ACR 20 was observed in patients treated with IV golimumab as compared to placebo at Week 14. To further assess the robustness of the outcome from the primary efficacy analysis, the Applicant conducted the following sensitivity analyses: subjects who discontinued treatment prior to Week 14 due to an adverse event as a nonresponder (the conservative more traditional imputation technique used for ACR response rate analyses), subjects with insufficient data to determine ACR20 response considered nonresponder, excluding patients whose treatment regimen was inadvertently unblinded, and re-randomization using the same data handling rules as the primary analysis (to compensate for adaptive randomization). In general, the results generated from these additional analyses (data not shown) were consistent with those from the study's primary analysis of the ACR20 response at Week 14.

Table 16 - Primary Endpoint: ACR 20 Response at Week 14 for Study CNTO148ART3001

Primary Endpoint	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	P-value
ACR 20 at Week 14	49 (25%)	231 (59%)	<0.001

Adapted Sponsor's Table 18; p. 77 of the 24-week study report

6.1.5 Analysis of Secondary Endpoints

This study was designed to have four major secondary variables: DAS28 (CRP) response at Week 14, improvement in HAQ-DI at Week 14, ACR 50 response rate at Week 24, and change from baseline in total vdHS score at Week 24. In order to control for multiplicity, the statistical analysis plan for this study mandated that the secondary efficacy parameters were to be analyzed via a sequential procedure in a prespecified descending order following testing of the primary endpoint. The results of these analyses which were all positive in favor of IV golimumab are presented in Table 17.

Table 17 - Tabular Summary of Secondary Endpoint Analyses for Study CNTO148ART3001

Major Secondary Endpoints	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	P-value
DAS28 (CRP) (Moderate to Good) Response at Week 14	40%	81%	<0.001
HAQ-DI (Median) at Week 14	0.125	0.500	<0.001
ACR50 at Week 24	13%	35%	<0.001
Change from Baseline in Total vdHS Score at Week 24¹: Mean (SD)	1.09 (3.194)	0.03 (1.899)	<0.001

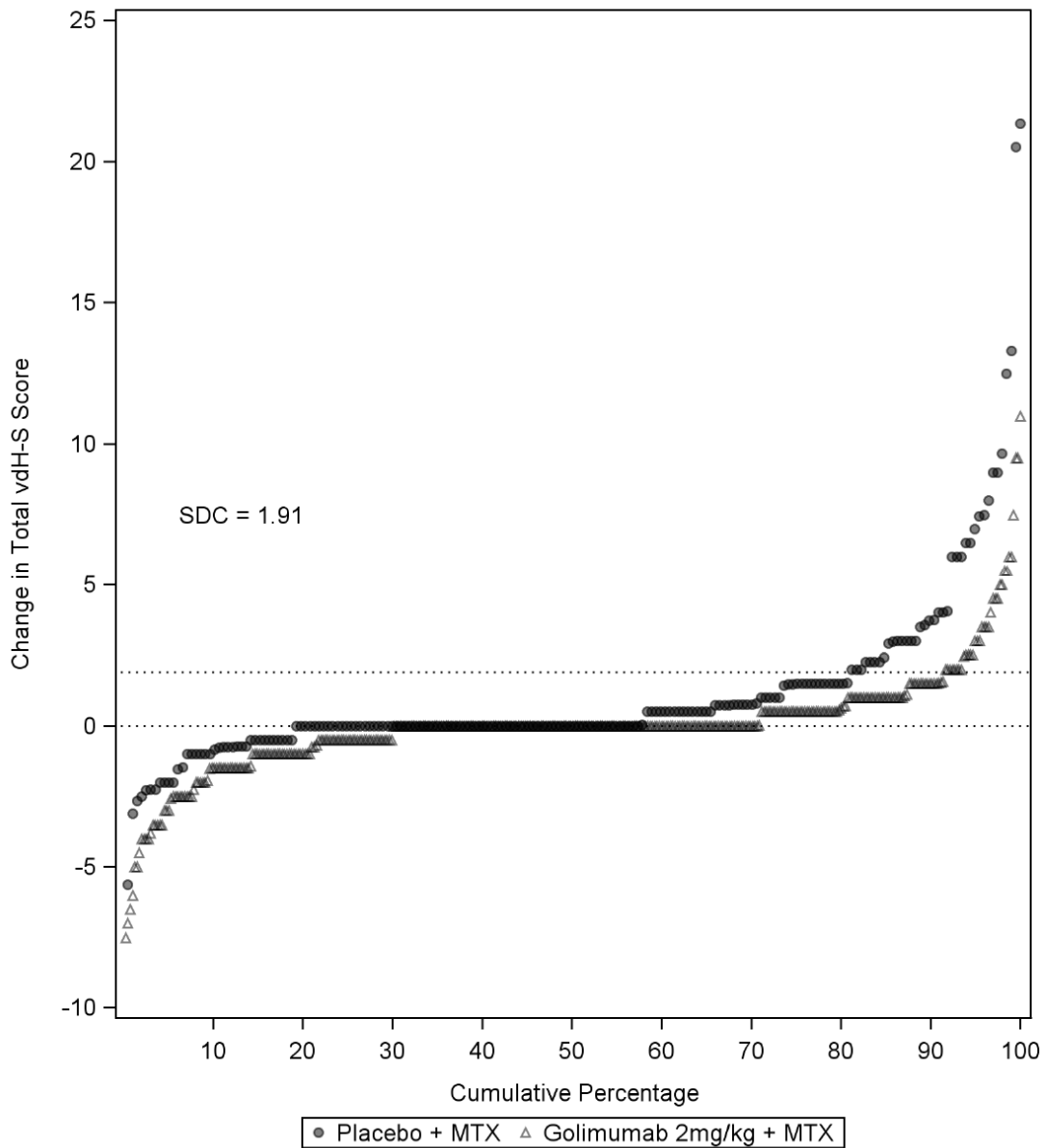
¹Linear extrapolation was used for imputation of missing vdHS scores for 68 (35%) placebo subjects and 21(5%) IV golimumab subjects as a result of early escape at Week 16 or had missing Week 24 and had at least two non-missing vdHS cores prior to Week 24.

Sensitivity testing conducted by the Applicant that evaluated the DAS28 moderate to good response, HAQ-DI and ACR 50 at Week 14 by screening CRP <1.5 mg/dL or ≥ 1.5 mg/dL supported the robustness of these findings. Additional sensitivity testing using nonresponder imputation for missing data as has been used in the evaluation of ACR response rates for other TNF inhibitor applications was also performed by the Applicant and resulted in similar findings.

As shown in Table 17, patients in the IV golimumab group had significantly (p<0.001) less progression on their x-rays compared to placebo treated patients as measured by the total vdH-S score using linear extrapolation to impute missing data. A probability plot for the change from baseline in total vdH-S score at Week 24 is depicted in Figure 4 which shows a clear separation between the two treatment groups with greater inhibition of progression and fewer patients with radiographic progression in the IV golimumab group as compared to the placebo group. Since the results of the radiographic endpoint could potentially be affected by subjects with outlier radiographic scores, an additional analysis was conducted by the agency's statistician that further assessed the robustness of the outcome for the Week 24 change in total vdHS score.

Exclusion from this analysis of the two outliers observed on the far right slope of the placebo + MTX treatment group shown in Figure 4 had minimal impact on the by-treatment group comparison shown in Table 17. (Reader is referred to the agency's statistical review for additional information regarding this analysis.) The Applicant also conducted a number of sensitivity analyses for this endpoint (e.g., excluding subjects with missing baseline total vdHS score, imputing missing Week 24 scores with last observation carried forward, and re-randomization testing using the same data handling rules as the major secondary analysis) the results of which were all consistent with that of the original radiographic endpoint analysis.

Figure 4 –Probability Plot for Change from Baseline in Total van der Heijde Modified Sharp Score at Week 24 for Study CNTO148ART3001 (Randomized Subjects)



Adapted from 52-week study report Figure 6; p. 60.

The Applicant also examined the results of the radiographic endpoint by the type of damage (e.g., erosion and joint space narrowing). As shown in Table 18, IV golimumab treated patients had significantly less progression in their x-rays as compared to the placebo group as assessed by their erosion and joint space narrowing scores.

Table 18 – Total vdHS Score Erosion and Joint Space Narrowing Scores at Week 24 for Study CNTO148ART3001

Endpoints	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	P-value
Change from Baseline in Erosion Score Mean (SD)	0.53 (2.1)	-0.12 (1.1)	<0.001
Change from Baseline in Joint Space Narrowing Score Mean (SD)	0.56 (1.7)	0.14 (1.3)	0.002

Adapted from 52-week study report table 6; p. 62.

6.1.6 Other Endpoints

There were multiple secondary endpoints analyzed for this study which are summarized in preceding

Table 14. No multiplicity correction was planned in the protocol or implemented here for the secondary endpoints. Due to multiplicity concerns, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate.

Endpoints (b) (4) for IV golimumab will be discussed in this section as follows: improvement in signs and symptoms and disability.

6.1.6.1 Signs and Symptom Endpoints

The signs and symptoms of disease manifestations of patient's RA were evaluated by the ACR 20, 50 and 70 responses at Weeks 14 and 24 and are displayed in Table 19. A greater proportion of IV golimumab treated subjects achieved ACR 20, 50 and 70 responses than in the placebo group. The duration of response through the Week 24 time point supports maintenance of therapeutic effectiveness for the product.

Table 19 – Summary of ACR Response Rates for Study CNTO148ART3001

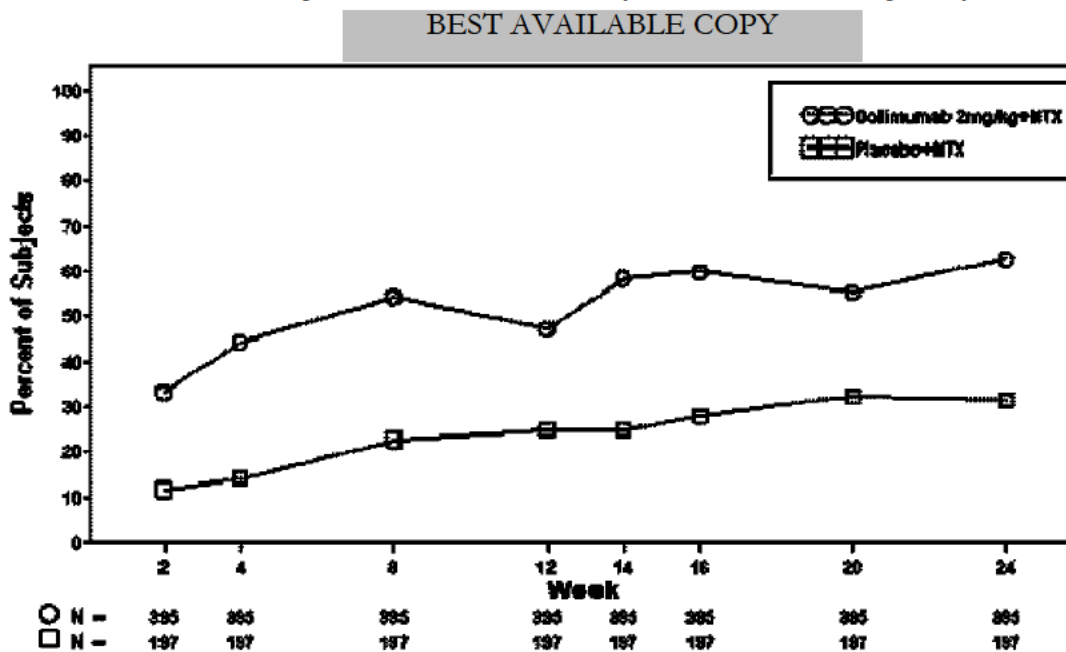
Endpoints	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	P-value
ACR 20			
Week 14 ¹	25%	59%	<0.001
Week 24	32%	63%	<0.001
ACR 50			
Week 14	9%	30%	<0.001
Week 24 ²	13%	35%	<0.001
ACR 70			
Week 14	3%	12%	<0.001
Week 24	4%	18%	<0.001

¹Primary endpoint

²Major secondary endpoint.

The time course of the ACR 20 response rate for both treatment groups in the pivotal study is shown in Figure 5. An increasing proportion of subjects treated with IV golimumab trended to achieve ACR 20 responses over time as compared to placebo that peaked at Week 24.

Figure 5 – Proportion of Patients Achieving ACR 20 Response by Visit through Week 24 in Study CNTO148ART3001 (Randomized Subjects)



Adapted from 24-week study report Fig. 6; p. 83

To determine whether the results in the composite ACR response were broad or were limited to a subset of ACR components, the outcomes of the individual components of the ACR composite score were examined and are listed in Table 20. Golimumab-treated patients in study CNTO148ART3001 had significantly higher rates of improvement compared to the placebo group as measured by each of the 7 individual core ACR response index components ($p < 0.001$) at Weeks 14 and 24.

Table 20 – Summary of ACR Component Response at Week 14 for Study CNTO148ART3001

Endpoints	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	P-value
Swollen Joint Count (0-66)			
Baseline	12	12	<0.001
Week 14	25%	68%	
Week 24	27%	75%	
Tender Joint Count (0-68)			
Baseline	22	24	<0.001
Week 14	13%	62%	
Week 24	14%	64	
Patient's Assessment of Pain (100 mm VAS)			
Baseline	6.9	6.5	<0.001
Week 14	7.4%	38%	
Week 24	11%	43%	
Patient's Global Assessment of Disease Activity (100 mm VAS)			
Baseline	6.9	6.6	<0.001
Week 14	7.3%	37%	
Week 24	14%	41%	
Physician's Global Assessment of Disease Activity (100 mm VAS)			
Baseline	6.3	6.3	<0.001
Week 14	15.5%	52.1%	
Week 24	24%	55%	
Disability Index of the HAQ			
Baseline	1.63	1.63	<0.001
Week 14	6.7%	28.6%	
Week 24	8.7%	30.0%	
CRP (mg/dL)			
Baseline	1.7	2.0	<0.001
Week 14	29.3%	77.8%	
Week 24	21.4%	76.*%	

Adapted from 24-week study report Tables 9 and 22; and Attachment 3.18; p. 61-62, 85 and 303-304.

In addition to looking at the DAS28 (CRP) moderate to good response rate at Weeks 14 and 24, the DAS28 (CRP) remission (< 2.6) was assessed at Weeks 14 and 24. The results of those analyses are displayed in Table 21. Higher proportions of patients

treated with IV golimumab achieved moderate to good responses and qualified for remission criteria at these time points as compared to the placebo group.

Table 21 – Summary of DAS28 (CRP) Responses at Weeks 14 and 24 for Subjects in Study CNTO148ART3001

Endpoints	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	P-value
DAS(CRP) "Good to Moderate" Response at:			
Week 14 ¹	40%	81%	<0.001
Week 24	45%	81%	<0.001
DAS28 (CRP) Remission (<2.6) Over Time at:			
Week 14	4.6%	15.4%	<0.001
Week 24	5.1%	17.7%	<0.001

Adapted from 24-week study report Attachments 3.25 and 3.26; p. 31-316.

¹Major secondary endpoint.

6.1.6.2. Disability

The HAQ-Disability Index (DI) which assesses disease related physical function was also evaluated in the pivotal trial. Improvement in the Week 14 HAQ-DI score for the golimumab group (0.5 units) was significantly greater than for the placebo group score (0.13) ($p < 0.001$) and this difference between treatment arms was maintained until Week 24 of the study (golimumab improvement 0.53 versus 0.21 score for the placebo group; $p < 0.001$). Also a higher proportion of golimumab patients achieved clinically meaningful improvements over baseline scores at Weeks 14 and 24 as compared to the placebo group.

Table 22 – Summary of HAQ-DI Endpoints Evaluated in Study CNTO148ART3001

Endpoints	Placebo + MTX (N=197)	Golimumab 2 mg/kg + MTX (N=395)	P-value
HAQ-DI (Median)			
Week 14 ¹	0.13	0.50	<0.001
Week 24	0.21	0.53	<0.001
Proportion of Subjects with Clinically Meaningful Improvement (≥ 0.25) from Baseline in HAQ-DI at:			
Week 14	43%	68%	<0.001
Week 24	45%	67%	<0.001

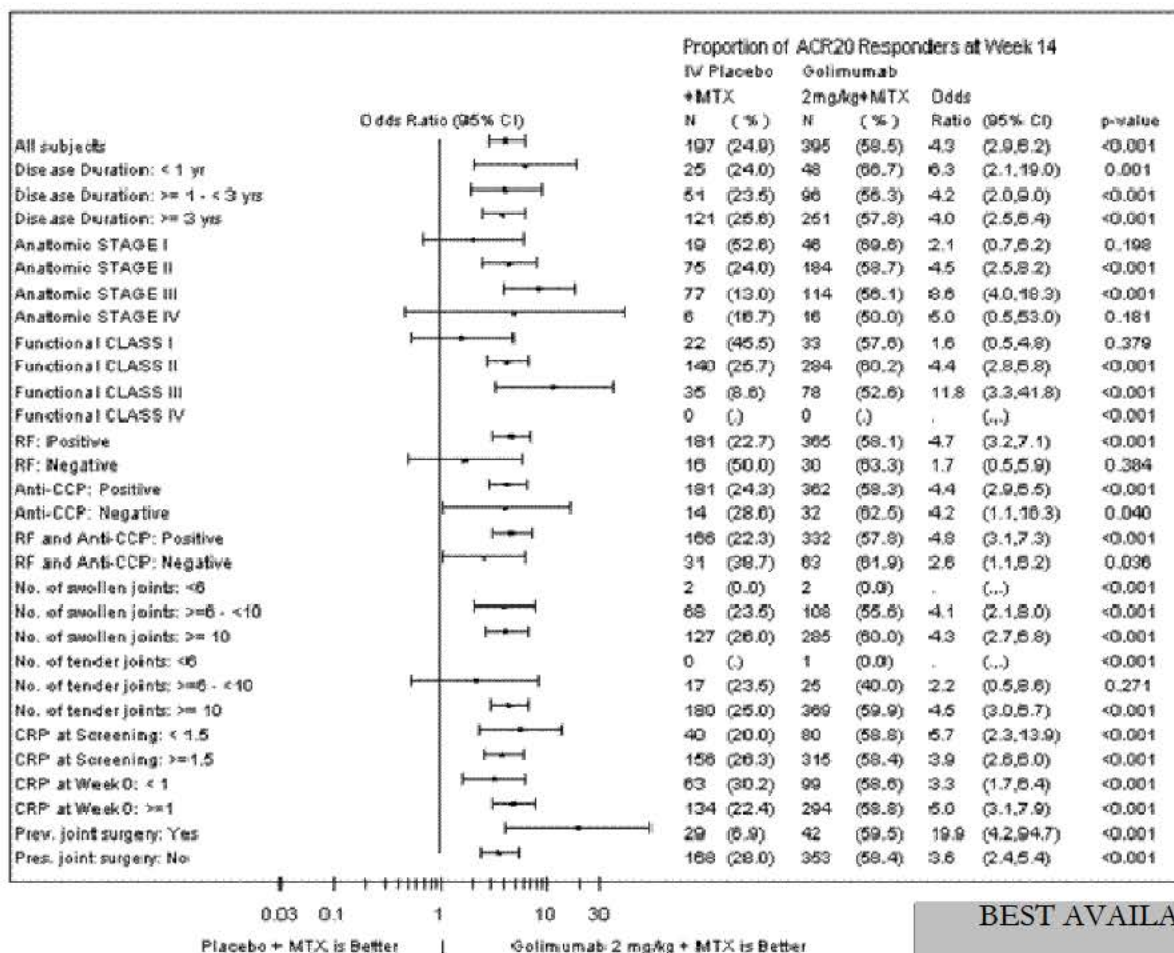
Adapted from 24-week study report Attachments 3.30 and 3.31; p. 330-331.

¹Major secondary endpoint.

6.1.7 Subpopulations

Figure 6 contains a forest plot analysis of ACR20 responders at Week 14 by baseline disease. Review of these data shows a consistent treatment benefit associated with IV golimumab treatment was observed in most of the demographic subgroups.

Figure 6 – Forest Plot of ACR20 Responders at Week 14 by Baseline Disease Characteristics for Study CNTO148ART3001 (Randomized Subjects)



Adapted from 24-week study report Fig. 7; p. 89

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6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant also conducted explorations of dose response derived from ACR 20 and 50 response data from CNTO148ART3001. No apparent dose-response relationship was observed between ACR20 response at Week 14 and trough serum golimumab

levels at Week 12 but a trend in ACR 50 response at Week 14 that plateaued at higher concentration quartiles was reported. Similar results were reportedly observed at Week 24 for the ACR 20 and 50 responses and trough serum golimumab levels.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Due to golimumab's immunogenicity which could potentially impact on the efficacy of the product, the Applicant also looked at ACR 20 and 50 response rates for anti-golimumab antibody positive and negative patients which are displayed in Table 23. A higher percentage of subjects who were anti-golimumab antibody negative achieved ACR 20 and 50 responses than did patients who were anti-golimumab antibody positive. This is not an unexpected finding since the presence of neutralizing antibodies has been associated with higher rates of product clearance and reduced efficacy with other TNF inhibitors.

Table 23 – ACR 20 and 50 Response Rates by Anti-Golimumab Antibody Status in Study CNTO148ART3001

	Treatment Groups Assigned at Randomization		PLO +MTX --> Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO + MTX	Golimumab 2 mg/kg + MTX		
Subjects Treated	129	395	68	463
Subjects with Appropriate Samples	122 (95)	368 (93%)	67(99%)	435 (94%)
Subjects Positive for Antibodies to Golimumab				
n	0	13	0	13
ACR 20	0	6 (46%)	0	6 (46%)
ACR 50	0	3 (23%)	0	3 (23%)
Subjects Positive for Antibodies to Golimumab				
n	122	355	67	422
ACR 20	62 (51%)	231(65%)	0	231 (55%)
ACR 50	26 (21%)	132 (37%)	0	132 (31%)

Adapted from 24-week study report Attachment 3.52; p. 351.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The overall safety profile of IV golimumab was generated from the adequate and well controlled Phase 3 trial CNTO148ART3001 which evaluated a dose and dosing regimen of 2 mg/kg every 8 weeks with concomitant MTX. The overall rate of serious adverse events was low in this study and no unexpected safety signals were observed for this new formulation of golimumab. The majority of serious events including deaths contained in the safety database submitted in support of IV golimumab's safety profile were the type of events (e.g., major cardiovascular events, gastrointestinal pain and hemorrhage, infection and malignancies) expected to occur in an older population with long-standing RA at risk for other co-morbid conditions particularly as a result of the concomitant use of such medications as NSAIDs, corticosteroids and MTX that have overlapping spectrums of additive toxicities (e.g., increased cardiovascular risk and immunosuppression). The exposure-adjusted rate of death seen with long term administration of 2 mg/kg every 8 weeks of IV golimumab was consistent with that reported in other trials of therapeutic biologics as well as below the reported rates of death observed in RA patient cohorts in general.

Review of the adverse events of interest (e.g., serious infections, hepatotoxicity, congestive heart failure, demyelinating disorders, hypersensitivity reactions, infusion reactions, autoimmunity, and hematological cytopenias) did not identify any potential or unexpected safety issues associated with this TNF inhibitor's dose, dosing regimen or route of administration as compared to the approved SC formulation of golimumab or the other four members of this therapeutic biologic class. However, CNTO148ART3001 was not powered to specifically determine safety risk and the comparison to the SC formulation is based on cross-study comparisons, not head-to-head data. The types of and exposure-adjusted rates for serious infections and infections of interest (e.g., sepsis, pneumonia, tuberculosis, opportunistic infections and cellulitis) were similar to those observed with other TNF inhibitors, including the SC formulation of this product. As the proposed dosing regimen for IV golimumab is weight based, review of serious infections by weight based quartile did not identify any potential safety concerns for increasing immunosuppression with increasing dose.

Since the protocols for both Phase 3 studies permitted the use of prophylactic medications (e.g., antihistamines and corticosteroids) for infusion reactions at the discretion of study investigator's and no consistent methodology was used in the IV golimumab clinical development program for capturing and classifying the spectrum of hypersensitivity reactions that includes infusion reactions and anaphylaxis, there had been concerns that IV golimumab's immunogenic profile may have not been fully characterized based on the data contained in the safety database submitted in support of this application. The rate of antibody formation for the to-be-marketed IV golimumab was 4% which is higher than reported for the 50 mg every 4 weeks SC formulation (2%

in patients taking concomitant MTX), and there were no serious or severe infusion reactions reported with its administration. A review of the individual line listings did not suggest any unidentified cases of anaphylaxis among the reported infusion reactions.

The types of and exposure-adjusted rates for malignancy in both Phase 3 IV golimumab studies were also similar to what had been observed in the RA clinical development program for the SC formulation. This is reassuring in view of the number of patients who actually received the proposed to-be-marketed dose of IV golimumab.

Based on the scope of the data contained in the safety database reviewed in support of this application's safety profile, no strengthening of the TNF inhibitor class WARNINGS and PRECAUTIONS is warranted.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In support of this BLA, the Applicant submitted safety data from two Phase 3 RA studies: CNTO148ART3001 and C0524T12. A tabular summary of these trials can be found in Table 2.

In addition to the safety databases generated from these 2 studies, the submission contained supportive safety data for serious infections and malignancies from the clinical development programs for RA (studies C0524T02, C0524T05 and C0524T06), psoriatic arthritis (study C0524T08), and ankylosing spondylitis (studies C0524T09 and C0524T11), as well as studies in patients with asthma (C0524T03), uveitis (C0524T01), and ulcerative colitis (C0524T16, C0524T17, and C0524T18) conducted with the SC formulation of golimumab. Since these safety data refer to a different dose and route of administration and were previously reviewed in support of the safety profile of SC golimumab they will not be discussed in this review. (Refer to medical officer review for BLA 125289 dated March 9, 2009 for additional information regarding these trials.)

Deaths and SAEs occurring March 31, 2012 through August 15, 2012 for the ongoing study CNTO148ART3001 were submitted in the 120-day update on January 17, 2013 and are included in pertinent areas of the following discussion.

Safety data from the two Phase 3 IV golimumab studies were summarized in the individual trial reports, the Integrated Summary of Safety and the electronic datasets for adverse events, lab data and vital signs. All safety analyses were performed on the double-blind safety population from the 52-week study CNTO148ART3001 and the 48-week study C0524T12 conducted by the Applicant as well as the data contained in the 120-day safety update and were examined by this medical officer.

7.1.2 Categorization of Adverse Events

Verbatim terms of adverse events recorded in the case report forms (CRF) by investigators were coded by the Applicant using MedDRA dictionary Preferred Term and System Organ Class (SOC) (version 13.1). A listing of all AEs coded in this manner including the corresponding verbatim terms was included in the CRF for review. The MedDRA coding of the information generated from clinical trials conducted by the applicant was generally acceptable. Additionally, the clinical lab and vital sign ranges for clinically significant abnormal results was reviewed and appeared to be appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The application contained 24-weeks of double-blind, controlled safety data generated from the following trials: CNTO148ART3001 and C0524T12. Assessment of pooled safety data from these studies to increase the probability of identifying potential safety signals associated with the administration of this product would be inappropriate for this application since the trials evaluated different nominal IV doses and dosing regimens that resulted in differing exposure patterns to golimumab. Additionally, some of the dosing regimens evaluated in C0524T12 did not include concomitant use of MTX which the Applicant is requesting as part of the to-be-marketed dosing regimen. In view of these differences, assessment of pooled data from these studies could potentially result in a mischaracterization of IV golimumab's safety profile.

Study CNTO148ART3001 is the focus of the following safety review since it was the only adequate and well controlled Phase 3 study that assessed the to-be-marketed dose of 2 mg/kg every 8 weeks of IV golimumab administered with concomitant MTX. Analyses of the 24-weeks of double-blind, controlled safety data from this study were performed on the safety population which was defined as all patients who were randomized and who received at least one dose of study medication in this trial. Safety data generated from C0524T12 is considered as secondary support for this application since the to-be-marketed dose and dosing regimen of IV golimumab were not evaluated in this trial. Data from this trial is discussed in selected areas of potential safety concern.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Cumulative exposure to IV golimumab for the two Phase 3 trials through the data cut-off date August 15, 2012 for the ongoing trial CNTO148ART3001 is shown in Table 24. A total of 1,210 patients with RA have been exposed to IV golimumab, out of which 584 patients had been treated with the proposed to-be-marketed dose of 2 mg/kg every 8 weeks. Approximately 530 of these subjects had received IV golimumab 2 mg/kg every 8 weeks for > 52 weeks with a median duration of follow-up of 92 weeks. These numbers exceed the minimum safety database recommendations for chronic use products as outlined in the International Conference on Harmonization (ICH) E1A guideline.

Table 24 – Cumulative Exposure to IV Golimumab in Phase 3 Studies C0524T12 and CNTO148ART3001

	Golimumab 2 mg/kg every 12 wks	Golimumab 4 mg/kg every 12 wks	Golimumab 2 mg/kg every 8 wks	Total IV Golimumab
Total Number of Subjects Treated	259	417	584	1210
Number of Administrations				
Mean (SD)	5 (2)	5 (2)	12 (3)	8 (4)
Median (IQ range)	3 (3, 6)	5 (4, 6)	13 (11; 14)	7 (5, 12)
Duration of Follow-Up (week)				
Mean (SD)	57 (24)	60 (19)	85 (23)	74 (24)
Median (IQ range)	60 (28, 72)	60 (48, 72)	92 (76, 100)	73 (60, 92)
Duration of Exposure (weeks)				
≤ 24	41 (16%)	13 (3%)	22 (4%)	76 (6%)
>24 to ≤ 52	44 (17%)	133(32%)	32 (6%)	209 (17%)
>52	174 (67%)	271(65%)	530 (91%)	975 (81%)

Adapted from the 120-day safety update Appendix 1.1 and 1.2; p. 41-42.

7.2.2 Explorations for Dose Response

As part of their product development program for IV golimumab, the Applicant conducted a Phase 3 study dose ranging trial, C0524T12, This study was a randomized, controlled, 5-arm study (C0524T12) of IV administration of placebo, golimumab 2 mg/kg or golimumab 4 mg/kg, with or without MTX, every 12 weeks for 48 weeks in patients with active RA despite concurrent MTX which failed to demonstrate efficacy based on ACR 50 response rates assessed at Week 14 for both treatment

groups. (For additional information regarding this trial, see study report in Appendix 10.) Pharmacokinetic (PK) and pharmacodynamic (PD) analyses of C0524T12 showed response rates decreased when serum trough concentrations of golimumab were undetectable. This data coupled with data from the robust Phase 3, randomized controlled study, C0524T06, which evaluated multiple doses of the SC formulation of golimumab (50 mg and 100 mg every 4 weeks with or without MTX) suggested that maintaining serum drug levels close to or above the trough serum golimumab concentrations associated with the SC golimumab dose of 50 mg every 4 weeks were necessary to achieve robust and sustained ACR responses.

The proposed to-be-marketed IV golimumab dose of 2 mg/kg every 8 weeks evaluated in CNTO148ART3001 was derived from a population PK model using data from C0524T12. Based on simulations conducted by the Applicant, this dose was expected to result in trough serum golimumab concentrations comparable to the approved marketed SC dosing regimen of 50 mg every 4 weeks but with an overall higher drug exposure (area under the serum concentration –time curve).

7.2.3 Special Animal and/or In Vitro Testing

The Applicant did not conduct any special animal and/or in vitro testing with IV golimumab to support its safety profile.

7.2.4 Routine Clinical Testing

The following clinical and lab testing were conducted at baseline and at prespecified frequencies over the course of study CNTO148ART3001 (refer to Table 4) and were submitted in support of IV golimumab's safety profile:

- Physical exam, weight and height
- Vital signs: systolic and diastolic blood pressure, heart rate and respiratory rate
- Complete cell count (CBC) with differential and platelet count, hemoglobin, hematocrit and hepcidin
- Serum chemistries; albumin, alkaline phosphatase, ALT, AST, BUN, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin, and total protein
- Serum pregnancy testing
- Rheumatoid factor, autoantibodies (anti-CCP, ANA, anti-ds-DNA), CRP
- Antibodies to golimumab
- Chest x-ray, radiographs of hands and feet (Weeks 0, 24, 52 and 100)
- Tuberculin skin testing and/or QuantiFERON-TB Gold test
- Biomarkers: Serum IL-6, tumor necrosis factor alpha-receptor II, haptoglobin, von Willebrand factor,

Overall, the types of clinical lab testing and physical assessments as well as the timing of these assessments were appropriate for the population studied in these trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this application since golimumab is a therapeutic biologic protein and is cleared via the reticuloendothelial system.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The safety profile of the TNF inhibitor class has been well documented and includes a number of class-specific adverse events such as increased susceptibility to serious infections (e.g., opportunistic infections, tuberculosis, histoplasmosis and reactivation of hepatitis B), increased risk for malignancies (particularly lymphomas and hepatosplenic T-cell lymphoma); hepatotoxicity, hypersensitivity disorders, demyelinating disorders, cytopenias, worsening congestive heart failure, autoimmune disorders and autoantibody formation, and infusion-related/injection-site reactions. In view of these product-associated toxicities, the clinical trials conducted in support of IV golimumab monitored study subjects for these adverse events via physical examinations, serial tuberculosis screening (skin testing and/or QuantiFERON-TB Gold testing), chest x-rays, complete blood counts, serology testing, and liver function tests. The protocols also contained subject removal criteria in the event that a patient developed one of these adverse events while participating in the Phase 3 trials. Additionally, subjects with active tuberculosis or recent exposure to this disease, or who had underlying hematologic, renal or hepatic impairment were prohibited from enrolling in these studies as were patients with a history of opportunistic or serious viral or bacterial infections, congestive heart failure, organ transplantation, lymphoproliferative disorder or malignancy within the last 5 years.

In support of IV golimumab's safety profile, the Applicant also submitted analyses of adverse events of interest that included serious infections, malignancies, hepatotoxicities, demyelinating disorders, infusion site reactions, autoimmunity and autoantibody formation, and cytopenias. The results of these analyses are discussed in section 7.3.5 of this review.

7.3 Major Safety Results

All safety analyses were performed on the population who had received at least 1 infusion of study medication. Table 25 summarizes adverse events that were reported in the IV golimumab safety database for the 24-weeks of controlled treatment during

CNTO148ART3001 by treatment group. The majority of the patients experienced at least one adverse event (AE) while participating in this trial. The proportion of patients who experienced a serious adverse event (SAE) was higher in the IV golimumab treatment group compared to placebo. A higher proportion of subjects in the IV golimumab group had an AE that resulted in premature discontinuation of treatment compared to the placebo group. Overall, the number of malignancies and deaths were both low with only 1 case of malignancy reported in the IV golimumab group and one death reported in the placebo group during the controlled portion of the study. This death and other deaths that occurred during the uncontrolled portion of Study CNTO148ART3001 and in the supportive study C0524T12 will be discussed further in the following section, 7.3.1.

Table 25 – Summary of Subjects By Randomized Treatment Group Who Experienced Adverse Events and Deaths During the 24-Week Controlled Portion of Study CNTOART3001

	Treatment Groups Assigned at Randomization		PLO +MTX --> Golimumab 2 mg/kg + MTX (Early Escape Group)	Golimumab Combined
	PLO + MTX	Golimumab 2 mg/kg + MTX		
Number of Subjects Treated	197	395	68	463
Number of Subjects with at Least 1 AE	97 (49%)	226 (57%)	19 (28%)	245 (53%)
Number of Subjects with at Least 1 SAE	4 (2%)	19 (5%)	0	19 (4%)
Number of Subjects with at Least 1 Infection	48 (24%)	116 (29%)	6 (9%)	123 (27%)
Number of Subjects with at Least 1 Serious Infection	0	4 (1%)	0	4 (0.9%)
Number of Subjects with at Least 1 Malignancy	0	1 (0.2%)	0	1 (0.2%)
Number of Subjects with at Least 1 AE Leading to Discontinuation	1 (0.5%)	16 (4.1%)	0	16 (3.5%)
Deaths	1	0	0	0

7.3.1 Deaths

As of the 120-day safety update cut-off date August 15, 2012, there were a total of 6 deaths that occurred over the course of ongoing study CNTO148ART3001 as follows: 3 patients died of cardiovascular events (including sudden death and stroke) and 3 patients died as a result of complications related to infectious etiologies. Of these 6 deaths which are listed in Table 26 below, only 1 death (Subject 0705-00240) occurred in the placebo group during the 24-week controlled portion of this trial. The remaining 5 deaths occurred in 2 placebo patients (Subjects 4806-00174 and 0113-00083) following the Week 24 cross-over to treatment with IV golimumab and 3 patients initially randomized to IV golimumab (Subjects 5206-01051, 5205-00647, and 6005-00055) during the uncontrolled portion of the study.

Table 26 – Tabular Summary of Deaths in Study CNTO148ART3001

Subject Number	Age/ Sex	Cause of Death	Days Since 1 st Infusion	Days Since Last Infusion	Pertinent History
Placebo + MTX					
0705-00240	40yo/F	Stroke 2 ^o to Hypertensive Crisis	164	23	H/O Hypertension and obesity (BMI = 40). Concomitant Meds: Lisinopril, folate and methylprednisolone, No autopsy performed
Placebo + MTX → Week 24 Cross-Over to Golimumab 2 mg/kg + MTX					
4806-00174	56yo/ M	Sudden Death	556	23	No pertinent past medical history. Concomitant Meds: folate Died suddenly while swimming (reportedly not due to drowning). Autopsy reportedly planned but report not submitted for review.
0113-00083	64yo/F	Cardiopulmonary Arrest 2 ^o Dehydration due to C.difficile colitis	746	47	H/O liver disease, GI hemorrhage, peripheral vascular disease, toe amputation x 2, atrial fibrillation, mitral regurgitation, coronary atherosclerotic disease, hypertriglyceridemia, leucopenia, UTIs, pneumonia, cellulitis, anemia, hypertension, and osteoporosis. Concomitant Meds: ASA, atenolol, lisinopril, furosemide, omeprazole, folate, iron, cilostazol, prednisone, and alendronate. Hospitalized for dehydration, hypotension, hyponatremia, anorexia, mental confusion, diarrhea, and rectal bleeding for 2 days to rule-out GI hemorrhage. Diagnosed with C. difficile pseudomembranous colitis on colonoscopy and culture (attributed to ciprofloxacin for cellulitis). Death due to cardiopulmonary arrest.
Golimumab 2 mg/kg + MTX					
5206-01051	32yo/F	Myocardial Infarction	255	57	No pertinent past medical history. Concomitant Meds: Paracetamol, ferrous sulfate, folate, and indomethacin. Diagnosed with esophagitis treated with unspecified pain medication and antibiotics after developing mild thoracic pain and difficulty breathing. After failing to improve, was hospitalized with fever, hypotension, and pleural effusion due to myocardial infarction and anemia. Died as a result of myocardial infarction. No autopsy performed or EKGs submitted for review.
5205-00647	48yo/F	Acute Abdominal Syndrome due to Tuberculosis	381	197	H/O Peripheral vascular disease, transient ischemic attack, liver disease, myocardial infarction and chronic stable angina pectoris. Family history positive for early coronary artery disease. Concomitant Meds: Folate, indomethacin, metoclopramide, and omeprazole. Hospitalized with fever, abdominal pain, ascites, nausea, vomiting and cessation of bowel movements due to acute abdominal syndrome. Had a cardiopulmonary arrest during laparotomy and required mechanical ventilation. Condition deteriorated and patient died following second cardiopulmonary arrest. No autopsy performed. Abscess liquid obtain during laparotomy positive for acid fast bacillus (tuberculosis).
6005-00055	57yo/F	Septic Shock Secondary to Pyogenic Lung Abscess (<i>acinetobacter baumannii</i>)	467	39	H/O Latent tuberculosis treated with isoniazid therapy x 6 months. Concomitant Meds: folate, gabapentin, naproxen, calcitriol, and fusidic acid. Hospitalized due to right lower and middle lobe pneumonia following course of Augmentin for URTI and tonsillitis. Chest CT showed right pleural empyema with lung abscess and mediastinal nodes suggestive of tuberculosis versus bronchoalveolar cell carcinoma. Repeat blood and sputum cultures negative for tuberculosis. Patient developed grade 3 ischemia of right lower extremity, hypotension, and acute renal and respiratory failure secondary to sepsis and died. <i>Acinetobacter baumannii</i> causative agent based on endotracheal tube specimen.

There were 6 deaths that occurred during the uncontrolled portion of the supportive study C024T12 in patients receiving IV golimumab as follows: 3 deaths due to cardiovascular events, 1 death due to unknown cause, 1 death due to septic shock, and 1 death due to respiratory insufficiency. Summaries of these 6 deaths are listed in Table 27.

Table 27 - Tabular Summary of Deaths in Study C0524T12

Subject Number	Age/ Sex	Cause of Death	Days Since 1 st Infusion	Days Since Last Infusion	Pertinent History
Golimumab 2 mg/kg every 12 weeks + Placebo					
4020-20253	36yo/F	Inferior Wall Myocardial Infarction	323	72	No pertinent past medical history other than being overweight (BMI: 26). Concomitant Meds: Diclofenac, tramadol, folate, Patient was hospitalized for evaluation of fever, retrosternal chest pain, nausea and anorexia of 4 days duration. GI work-up revealed GERD and moderate-severe H. pylori-associated active chronic gastritis. Patient collapsed after developing chest pain and shortness of breath while hospitalized and died.
1023-20485	65yo/F	Unknown Cause	354	103	H/O hypertension. Concomitant Meds: Enalapril, diclofenac, prednisone, folate, and transdermal chlorhexidine. After withdrawing study consent, the patient presented to hospital with dyspnea at rest, hypotensive, and severely anemic and died. No autopsy performed.
Golimumab 2 mg/kg every 12 weeks + MTX					
1004-20786	50yo/F	Septic Shock	370	33	H/O smoking (past) and right total knee replacement. Concomitant Meds: Naproxen, prednisone, and folate. Hospitalized for septic arthritis of prosthetic right knee. Synovial fluid cultures positive for Staphylococcus aureus. Despite IV antibiotics patient developed multiorgan failure secondary to septic shock and died.
Golimumab 4 mg/kg every 12 weeks + Placebo					
1001-20397	58yo/F	Anterolateral Myocardial Infarction	295	42	H/O hypertension, gastroduodenal ulcer, obstruction of anterior descending coronary artery, smoking (10 cigarettes/d x 10 yrs) and overweight (BWI: 27). Concomitant Meds: Etoricoxib, carvedilol, meprobamate, estradiol, lansoprazole and folate. Patient was hospitalized for evaluation of dyspnea, cough, hemoptysis, and acute abdominal pain. Admission ECG and chest x-ray reportedly normal despite right lower lobe rales. Treated with lansoprazole with improvement and discharged only to be readmitted 24 hrs later with acute shortness of breath and retrosternal chest pain. Repeat chest x-ray showed grade III cardiomegaly and ECG consistent with acute anterolateral myocardial infarction. CK-MB was normal. Patient had a cardiopulmonary arrest and died. No autopsy performed.
1010-20415	52yo/F	Respiratory Failure	458	31	H/O smoking (40 cigarettes/d x 38 yrs). Concomitant Meds: Diclofenac, enalapril, paroxetine, clonazepam, methylprednisolone, ophthalmic dorzolamide and folate. Patient developed sensory deterioration due to cranial hypertension secondary to multiple metastatic lesions seen on CT and MRI of brain. Chest x-ray revealed right middle lobe lung lesion consistent with malignant lung neoplasm. Patient's condition deteriorated and she died due to respiratory failure.
Golimumab 4 mg/kg every 12 weeks + MTX					
3422-20366	59yo/M	Myocardial Infarction	264	11	H/O diabetes mellitus, hypertension, hyperlipidemia, obesity and cigarette smoking (past). Concomitant Meds: Moxonidine, amlodipine, clopamide, vaseretic, potassium, simvastatin, nimesulide, metformin, tramadol, and folate. Patient's spouse informed study investigator that this patient had a myocardial infarction and died. No autopsy performed.

Six (6) out of the 12 deaths in this application's safety database were due to cardiovascular events which is not an unexpected finding in this patient population in view of the documented higher cardiovascular mortality rate in RA patients.¹ Overall, the deaths are consistent with risks related to immunosuppressive therapies and other co-morbidities (e.g., pre-existing conditions compounded by the use of NSAIDs with their associated increased risk for cardiovascular events).

Since no deaths occurred in the IV golimumab treatment group during the 24-weeks of controlled treatment in CNTO148ART3001, the exposure-adjusted incidence rate for death was calculated based on the number of deaths observed in patients receiving IV golimumab through the uncontrolled portion of this study and the 120-day safety-up cutoff date of August 15, 2012. Exposure-adjusted incidence rates for the deaths that occurred during the supportive study C0524T12 were also calculated through the Week 48 database lock based on randomized treatment group. As shown in Table 28 below, the death incidence per 100 subject-years of follow-up for the to-be-marketed dose of 2 mg/kg every 8 weeks of golimumab evaluated in CNTO148ART3001 and the 4 mg/kg every 12 weeks dosing regimen evaluated in C0524T12 were comparable but the death incidence rate per 100 subject-years was almost twice as high for the 2 mg/kg every 12 week dosing regimen that was also evaluated in C0524T12. However, the confidence intervals for the point estimates for death in all three dose groups overlap suggesting that there may be no real difference between the three groups despite differences in the numbers of patients treated and durations of exposure. These exposure-adjusted rates of death associated with the three doses and dosing regimens of IV golimumab presented in Table 28 are well below the reported background rates for reported in the published literature for comparable RA cohorts (approximately 2.4 to 2.5 deaths per 100 subject-years).²

Table 28 – Exposure-Adjusted Rates of Death for IV Golimumab

	C0524T12		CNTO148ART3001
	Golimumab 2 mg/kg every 12 weeks	Golimumab 4 mg/kg every 12 weeks	Golimumab 2 mg/kg every 8 weeks
Number of Subjects	259	417	584
Total Subject-Years of Follow-Up	3 (1.2%)	3 (0.7%)	958
Number of Deaths	282	481	5 (0.9%)
Death Rate/100 Subject-Years	1.06	0.62	0.52
95% Confidence Interval	(0.22, 3.10)	(0.13, 1.82)	(0.17, 1.22)

Adapted 120-day safety update Appendix 1.7; p. 86.

¹ Del Rincon, I et al. High Incidence of Cardiovascular Events in a Rheumatoid Arthritis Cohort Not Explained by Traditional Cardiac Risk Factors. *Arthritis and Rheumatism* 2001; 44 (12): 2737-2745.

² Gonzalez, A et al. The Widening Mortality Gap between Rheumatoid Arthritis Patients and the General Population. *Arthritis and Rheumatism* 2007; 56(11): 3583-3587.

7.3.2 Nonfatal Serious Adverse Events

The following Table 29 summarizes the treatment-emergent serious adverse events reported in the safety population over the 24-weeks of controlled treatment. Overall, the number of serious adverse events reported for Study CNT0148ART3001 was low. A higher proportion of patients experienced treatment-emergent serious adverse events in the IV golimumab group (5%) than in the placebo group (2%). No treatment emergent serious adverse events were reported for placebo patients who underwent early escape at Week 16 and initiated treatment with IV golimumab. Three system organ classes contributed to the higher overall rates of serious adverse events in the IV golimumab group: infections and infestations, musculoskeletal and connective tissue disorders, and renal urinary disorders. Review of the data shown in Table 29 did not reveal any potential patterns or safety signals due to the small numbers of serious adverse events observed during the controlled portion of this study. The higher rate of infections and infestations will be discussed further with other safety areas of interest. As expected, the incidence of serious adverse events associated with IV golimumab treatment increased with increasing exposure as noted on review of the safety data collected through Week 52 of Study CNT0148ART3001 and the 120-day safety update. No patterns or unexpected safety signals were identified with prolong exposure to the product. Review of serious adverse events from supporting study C0524T12 revealed a similar pattern of adverse events.

Table 29 – Serious Adverse Events by Randomized Treatment Group During the 24-Week Controlled Portion of Study CNTO148ART3001

MedDRA System Organ Class/Preferred Term	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Subjects Treated	197	395	68	463
Ave. Duration of Follow-Up (Wks)	21	24	8	21
Ave. exposure (No. of Administrations)	4	4	2	4
Total Number of Subjects with ≥ 1 TE SAE	4 (2%)	19 (5%)	0 (0%)	19 (4%)
Infections and Infestations	0	3 (0.8%)	0	3 (0.6%)
Appendicitis	0	1 (0.3%)	0	1 (0.2%)
Bacteremia	0	1 (0.3%)	0	1 (0.2%)
Upper Respiratory Tract Infection	0	1 (0.3%)	0	1 (0.2%)
Musculoskel. and Connect. Tiss. Disord.	1 (0.5%)	3 (0.8%)	0	3 (0.6%)
Intervertebral Disc Protusion	0	1 (0.3%)	0	1 (0.2%)
Osteonecrosis	0	1 (0.3%)	0	1 (0.2%)
Rheumatoid Arthritis	1 (0.5%)	1 (0.3%)	0	1 (0.2%)
Renal and Urinary Disorders	0	3 (0.8%)	0	3 (0.6%)
Calculus Ureteric	0	1 (0.3%)	0	1 (0.2%)
Nephrolithiasis	0	1 (0.3%)	0	1 (0.2%)
Nephropathy	0	1 (0.3%)	0	1 (0.2%)
Renal Colic	0	1 (0.3%)	0	1 (0.2%)
Gastrointestinal Disorders	2 (1.0%)	2 (0.5%)	0	2 (0.4%)
Abdominal Pain Upper	0	1 (0.3%)	0	1 (0.2%)
Gastric Disorder	0	1 (0.3%)	0	1 (0.2%)
Gastrointestinal Hemorrhage	1 (0.5%)	0	0	0
Inguinal Hernia	1 (0.5%)	0	0	0
Hepatobiliary Disorders	0	2 (0.5%)	0	2 (0.4%)
Cholecystitis	0	1 (0.3%)	0	1 (0.2%)
Hepatitis toxic	0	1 (0.3%)	0	1 (0.2%)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	0	2 (0.5%)	0	2 (0.4%)
Breast Cancer	0	1 (0.3%)	0	1 (0.2%)
Salivary Gland Adenoma	0	1 (0.3%)	0	1 (0.2%)
Nervous System Disorders	1 (0.5%)	2 (0.5%)	0	2 (0.4%)
Cerebral Infarction	0	1 (0.3%)	0	1 (0.2%)
Ischemic Stroke	0	1 (0.3%)	0	1 (0.2%)
Subarachnoid Hemorrhage	0	1 (0.3%)	0	1 (0.2%)
Cerebrovascular Accident	1 (0.5%)	0	0	0
Cardiac Disorders	0	1 (0.3%)	0	1 (0.2%)
Acute Coronary Syndrome	0	1 (0.3%)	0	1 (0.2%)
Metabolism and Nutrition Disorders	0	1 (0.3%)	0	1 (0.2%)
Electrolyte Imbalance	0	1 (0.3%)	0	1 (0.2%)
Reproductive System and Breast Disord.	0	1 (0.3%)	0	1 (0.2%)
Metorrhagia	0	1 (0.3%)	0	1 (0.2%)
Respirat., Thoracic and Mediastinal Disord.	0	1 (0.3%)	0	1 (0.2%)
Interstitial Lung Disease	0	1 (0.3%)	0	1 (0.2%)
Skin and Subcutaneous Tissue	0	1 (0.3%)	0	1 (0.2%)
Rash	0	1 (0.3%)	0	1 (0.2%)

Adapted Sponsor's Attachment 4.9; p.390-391 of 24-week study report

7.3.3 Dropouts and/or Discontinuations

Since adverse events can directly influence the disposition of patients in clinical trials, the safety database for IV golimumab was examined to determine if there were any safety signals generated by subjects who prematurely withdrew from Study CNTO148ART3001 due to golimumab-related adverse events. Table 30 below is a tabular summary of the adverse events experienced by the subjects who discontinued study treatment during the 24-weeks of controlled treatment during this trial. Patients randomized to treatment with IV golimumab (4%) were more likely to withdraw early due to adverse events as compared to placebo patients (0.5%). Review of these data indicated that the differences in rates of premature study discontinuations were primarily due to higher drop-out rates associated with infections in patients randomized to IV golimumab (1.8%) as compared to placebo treated patients (0%). There were no premature withdrawals reported for the early escape group. The rate of premature withdrawal through Week 52 of study treatment was similar (3.6%). Review of these data and the data contained in the 120-day safety update showed that infection was again the most common adverse event resulting in premature withdrawal. This higher rate of premature withdrawal due to infection may have been impacted by the study's individual withdrawal criteria that mandated any subject who developed a serious infection was to have been permanently discontinued from the trial in order to minimize safety risk. No additional safety concerns were raised on review of subjects who discontinued prematurely from supporting study C0524T12.

Table 30 - Premature Discontinuations by Randomized Treatment Group During the 24-Week Controlled Portion of Study CNTO148ART3001

MedDRA System Organ Class/Preferred Term	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Subjects Treated	197	395	68	463
Ave. Duration of Follow-Up (Wks)	21	24	8	21
Ave. exposure (No. of Administrations)	4	4	2	4
Tot. Number of Subjects Who Discontinued Study Agent Due to ≥ 1 TEAEs	1 (0.5%)	16 (4.1%)	0	16 (3.5%)
Infections and Infestations	0	7 (1.8%)	0	7 (1.5%)
Upper Respiratory Tract Infection	0	2 (0.5%)	0	2 (0.4%)
Acute Sinusitis	0	1 (0.3%)	0	1 (0.2%)
Ear Infection	0	1 (0.3%)	0	1 (0.2%)
Esophageal Candidiasis	0	1 (0.3%)	0	1 (0.2%)
Oral Herpes	0	1 (0.3%)	0	1 (0.2%)
Sinusitis	0	1 (0.3%)	0	1 (0.2%)
Hepatobiliary Disorders	0	2 (0.5%)	0	2 (0.4%)
Cholecystitis	0	1 (0.3%)	0	1 (0.2%)
Hepatitis Toxic	0	1 (0.3%)	0	1 (0.2%)
Respirat., Thoracic and Mediastinal Disord.	0	2 (0.5%)	0	2 (0.4%)
Interstitial Lung Disease	0	1 (0.3%)	0	1 (0.2%)
Upper Airway Obstruction	0	1 (0.3%)	0	1 (0.2%)
Skin and Subcutaneous Tissue Disorders	0	2 (0.5%)	0	2 (0.4%)
Rash	0	1 (0.3%)	0	1 (0.2%)
Skin Ulcer	0	1 (0.3%)	0	1 (0.2%)
Blood and Lymphatic System Disorders	0	1 (0.3%)	0	1 (0.2%)
Anemia	0	1 (0.3%)	0	1 (0.2%)
Leukopenia	0	1 (0.3%)	0	1 (0.2%)
Cardiac Disorders	0	1 (0.3%)	0	1 (0.2%)
Acute Coronary Syndrome	0	1 (0.3%)	0	1 (0.2%)
Gastrointestinal Disorder	0	1 (0.3%)	0	1 (0.2%)
Gastric Disorder	0	1 (0.3%)	0	1 (0.2%)
Metabolism and Nutrition Disorders	0	1 (0.3%)	0	1 (0.2%)
Electrolyte Imbalance	0	1 (0.3%)	0	1 (0.2%)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	0	1 (0.3%)	0	1 (0.2%)
Breast Cancer	0	1 (0.3%)	0	1 (0.2%)
Nervous System Disorders	0	1 (0.3%)	0	1 (0.2%)
Ischemic Stroke	0	1 (0.3%)	0	1 (0.2%)
Subarachnoid Hemorrhage	0	1 (0.3%)	0	1 (0.2%)
Renal and Urinary Disorders	0	1 (0.3%)	0	1 (0.2%)
Nephropathy	0	1 (0.3%)	0	1 (0.2%)
Musculoskeletal and Connect. Tiss. Disord.	1 (0.5%)	0	0	0
Spinal Disorder	1 (0.5%)	0	0	0

Adapted from 24-week study report Attachment 4.15; p.399-400.

7.3.4 Significant Adverse Events

Table 31 is a tabular listing of AEs observed during the 24-weeks of controlled treatment in Study CNTO148ART3001 by randomized treatment group that were rated as severe in nature by study investigators. Overall, the rate of severe adverse events was comparable for both placebo and IV golimumab treatment groups. No safety signals were identified on review of the severity data generated from prolonged exposure to IV golimumab in this ongoing trial. Similar findings were noted on examination of safety data generated from the supporting study, C0524T12.

Table 31 – Summary of Severe Treatment Emergent Adverse Events by Randomized Treatment Group During the 24-Week Controlled Portion of Study CNTO148ART3001

MedDRA System Organ Class/Preferred Term	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Subjects Treated	197	395	68	463
Ave. Duration of Follow-Up (Wks)	21	24	8	21
Ave. exposure (No. of Administrations)	4	4	2	4
Tot. Number of Subjects with > 1 Severe TEAE	9 (4.6%)	17 (4.3%)	1 (1.5%)	18 (3.9%)
Musculoskeletal and Connective Tiss. Disord.	5 (2.5%)	6 (1.5%)	0	6 (1.3%)
Rheumatoid Arthritis	2 (1%)	2 (0.4%)	0	2 (0.2%)
Arthralgia	1 (0.5%)	1 (0.3%)	0	1 (0.2%)
Muscle Contracture	0	1 (0.3%)	0	1 (0.2%)
Osteoarthritis	0	1 (0.3%)	0	1 (0.2%)
Osteronecrosis	0	1 (0.3%)	0	1 (0.2%)
Osteoporosis	1 (0.5%)	0	0	0
Pain in Jaw	1 (0.5%)	0	0	0
Gastrointestinal Disorders	2 (0.5%)	4 (1.0%)	1 (1.5%)	5 (1.1%)
Dyspepsia	1 (0.5%)	2 (0.5%)	0	2 (0.4%)
Abdominal Pain Upper	0	1 (0.3%)	0	1 (0.2%)
Diarrhea	0	1 (0.3%)	0	1 (0.2%)
Gastric Disorder	0	1 (0.3%)	0	1 (0.2%)
Gastritis	0	0	1 (1.5%)	1 (0.2%)
Gastrointestinal Hemorrhage	1 (0.5%)	0	0	0
Infections and Infestations	1 (0.5%)	3 (0.8%)	0	3 (0.6%)
Acute Tonsillitis	0	1 (0.3%)	0	1 (0.2%)
Appendicitis	0	1 (0.3%)	0	1 (0.2%)
Upper Respiratory Tract Infection	0	1 (0.3%)	0	1 (0.2%)
Infection	1 (0.5%)	0	0	0
Nervous System Disorders	1 (0.5%)	3 (0.8%)	0	3 (0.6%)
Headache	0	1 (0.3%)	0	1 (0.2%)
Ischemic Stroke	0	1 (0.3%)	0	1 (0.2%)
Radiculitis	0	1 (0.3%)	0	1 (0.2%)
Subarachnoid Hemorrhage	0	1 (0.3%)	0	1 (0.2%)
Cerebrovascular Accident	1 (0.5%)	0	0	0
Respirat., Thoracic, and Mediastinal Disorders	0	2 (0.5%)	0	2 (0.4%)
Interstitial Lung Disease	0	1 (0.3%)	0	1 (0.2%)
Upper Airway Obstruction	0	1 (0.3%)	0	1 (0.2%)
Cardiac Disorders	0	1 (0.3%)	0	1 (0.2%)
Acute Coronary Syndrome	0	1 (0.3%)	0	1 (0.2%)
Hepatobiliary Disorders	0	1 (0.3%)	0	1 (0.2%)
Hepatitis Toxic	0	1 (0.3%)	0	1 (0.2%)
Investigations	0	1 (0.3%)	0	1 (0.2%)
Alanine Aminotransferase Increased	0	1 (0.3%)	0	1 (0.2%)
Metabolism and Nutrition Disorders	0	1 (0.3%)	0	1 (0.2%)
Decreased Appetite	0	1 (0.3%)	0	1 (0.2%)
Neoplasms Benign, Malignant and Unspecified	0	1 (0.3%)	0	1 (0.2%)
Breast Cancer	0	1 (0.3%)	0	1 (0.2%)
Renal and Urinary Disorders	0	1 (0.3%)	0	1 (0.2%)
Nephropathy	0	1 (0.3%)	0	1 (0.2%)

Adapted from 24-week study report Attachment 4.6; p. 385-386

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Serious Infections

Due to their immunosuppressive properties, use of TNF inhibitors is associated with an increased risk of developing infections, particularly those of a serious nature. Table 32 is a summary of subjects who reported one or more infections, serious infections or an infection that required antimicrobial therapy while participating in the 24-week controlled portion of CNTO148ART3001. Overall, the rate of serious infections was very low (1%) in the golimumab 2 mg/kg group in this study. No cases of serious opportunistic infections or tuberculosis occurred in the active treatment group during this portion of the trial. The rates for non-serious infections (27%) and the use of antibiotic treatment for infections (17%) were similar for the combined IV golimumab treatment group as compared to the placebo group (24% and 14%, respectively).

Table 32 – Summary of Infections, Serious Infections, and Infections Requiring Antibiotic Treatment During the 24-Week Controlled Portion of CNTO148ART3001

	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Subjects Treated	197	395	68	463
Ave. Duration of Follow-Up (Wks)	21	24	8	21
Ave. exposure (No. of Administrations)	4	4	2	4
Total Number of Subjects with ≥ 1 Infections	48 (24%)	116 (29%)	6 (9%)	123 (27%)
Total Number of Subjects with ≥ 1 Serious Infections	0	4 (1%)	0	4 (0.9%)
Appendicitis	0	1 (0.3%)	0	1 (0.2%)
Bacteremia	0	1 (0.3%)	0	1 (0.2%)
Upper Respiratory Tract Infection	0	1 (0.3%)	0	1 (0.2%)
Interstitial Lung Disease	0	1 (0.3%)	0	1 (0.2%)
Total Number of Subjects with ≥ 1 Infection Requiring Antibiotic Treatment	27 (14%)	75 (19%)	2 (3%)	77 (17%)

Adapted from the 24-week study report Attachment 4.18, 4.20, and 4.22; p. 407-409 and 412-416.

The exposure-adjusted incidence of serious infections per 100 subject-years of follow-up for the IV golimumab 2 mg/kg every 8 weeks treatment arm was 2.23 (CI: 0.61, 5.71) versus 0 (0.00, 3.79) for the placebo group during the 24-week controlled portion of study CNTO148ART3001. This is consistent with the rates of serious infection observed for other TNF inhibitors (5 to 6 serious infections per 100 subject-years) and is lower

than the rates of serious infections observed in the combined 24-week controlled Phase 3 safety database reviewed in support of the SC formulation of golimumab (3.4 serious infections per 100 subject-years for the 50 mg every 4 weeks SC treatment group and 5.0 serious infections per 100-subject-years for the 100 mg every 4 weeks SC treatment group as per the medical officer review dated June 24, 2009 for BLA 125289).^{3,4}

With increasing exposure, the rate of serious infections in this ongoing study increased to 5.7% as of the 120-day safety update cut-off date of August 15, 2012. The most commonly reported serious infections observed with long term exposure in CNTO148ART3001 were pneumonia (5 cases; 0.9%), and urinary tract infection (3 cases; 0.5%). The remaining cases of serious infections were all single occurrences including 1 case of tuberculosis in a patient (Subject 6002-01077) who crossed-over from placebo + MTX to golimumab 2 mg/kg +MTX at Week 24 and one case each of septic shock, urosepsis, pyelonephritis, and empyema. No serious cases of invasive fungal or opportunistic infections were reported to have occurred with long term exposure to IV golimumab in this ongoing trial. The exposure adjusted incidence for serious infections per 100 subject-years of follow-up through the 120-safety cut-off date of August 15, 2012 for IV golimumab was 4.07 (CI: 2.90, 5.57) which is consistent again with the rates for other TNF inhibitors reported in the published literature and what was observed with long term controlled and uncontrolled pooled exposure to SC golimumab (4.4 serious infections per 100 subject-years (CI: 3.7, 5.3).^{5,6} (Refer to the medical officer review dated June 24, 2009 for BLA 125289 SC golimumab for additional information.)

The exposure adjusted rates for infections of interest that occurred with long term exposure with the to-be-marketed dose of 2 mg/kg every 8 weeks of IV golimumab are listed in Table 33 below and are similar to rates observed with other TNF inhibitors.⁷

³ Listings, J et al. Infections in Patients with Rheumatoid Arthritis Treated with Biologic Agents. *Arthritis and Rheumatism* 2005; 52(11):3403-3412.

⁴ Dixon, WG et al. Serious Infection Following Anti-Tumor Necrosis Factor Alpha Therapy in Patients with Rheumatoid Arthritis. *Arthritis and Rheumatism* 2007; 56(9):2896-2904.

⁵ Listings et al.

⁶ Dixon et al.

⁷ Listing et al.

Table 33 - Exposure Adjusted Incidence Rates for Infections of Interest in Study CNTO148ART3001

Infection of Interest	120-Day Safety Update (Aug. 15, 2012)
Sepsis	0.42 (CI: 0.11, 1.07)
Pneumonia	2.30 (CI: 1.44, 3.48)
Tuberculosis	0.31 (CI: 0.06, 0.92)
Opportunistic Infections	0.42 (CI: 1.36, 3.35)
Cellulitis	2.19 (CI: 1.36, 3.35)

Adapted from 120-day safety update Table 1; p. 17.

For completeness, the occurrence of serious infections over the controlled 24-week portion of C0524T12 was reviewed and is displayed in the following Table 34. Overall, the rate for serious infection associated with exposure to IV golimumab was also very low in this study (2%), but a higher proportion of subjects had serious infections in the 2 mg/kg every 12 week group (3.1%) as compared to the 4 mg/kg every 12 week group (0.8%). No cases of serious opportunistic infections or tuberculosis occurred in the active treatment groups during this portion of the trial. The rates for non-serious infections (39%) and the use of antibiotic treatment for infections (27%) were similar for the combined IV golimumab treatment group as compared to the placebo group (36% and 26%, respectively). The exposure adjusted rate for serious infections during the 24-weeks of controlled treatment in C0524T12 was as follows: Placebo: 5.65 serious infections per 100 subject-years (CI: 1.17, 16.5); Golimumab 2 mg/kg every 12 weeks: 7.67 serious infections per 100 subject-years (CI: 3.51; 14.46); and Golimumab 4 mg/kg every 12 weeks: 2.58 serious infections per 100 subject-years (CI: 0.53; 7.53). The confidence intervals for the point estimates are very wide but overlap for the three treatment arms, suggesting that there may be no real difference between the treatment groups despite varying numbers of subjects and durations of exposure.

With increasing exposure to the product at 39 weeks, these rates increased to 5.8% in the golimumab 2 mg/kg every 12 weeks group and 5.5% in the 4 mg/kg every 12 weeks group in C0524T12. The most commonly reported serious infections observed with long term exposure in this study in the combined golimumab treatment groups were pneumonia (8 cases; 1.2%), cellulitis (5 cases, 0.7%), urinary tract infection (3 cases; 0.4%), and bacterial arthritis (3 cases; 0.4%). The remaining cases were single cases that included sepsis, herpes zoster, and pulmonary tuberculosis. The pattern of serious infections is similar to that observed with long term exposure in CNTO148ART3001. The exposure adjusted rate for serious infections through Week 48 for C0524T12 was calculated as follows: golimumab 2 mg/kg every 12 weeks: 6.37 serious infections per

100 subject-years (CI: 3.78, 10.1); and golimumab 4 mg/kg every 12 weeks: 5.82 serious infections per 100 subjects-years (CI: 3.87, 8.41). Again, this is similar to the rates of serious infection observed for other TNF inhibitors (5 to 6 serious infections per 100 subject-years) as reported in the literature.^{8,9}

Table 34 – Summary of Serious Infections Through Week 24 of C0524T12

	Placebo	IV Golimumab 2 mg every 12 wks	IV Golimumab 4 mg every 12 wks	Combined Golimumab
Subjects Treated	129	259	292	551
Ave. Duration of Follow-Up (Wks)	21	24	22	23
Ave. exposure (No. of Administrations)	3	2	2	2
Total Number of Subjects with $\geq$ 1 Infections	47 (36%)	96 (37%)	113 (39%)	209 (39%)
Total Number of Subjects with $\geq$ 1 Serious Infections:	2 (1.6%)	8 (3.1%)	3 (1.0%)	11 (2.0%)
Pneumonia	1 (0.8%)	2 (0.8%)	0	2 (0.4%)
Appendicitis	0	0	0	0
Arthritis bacterial	0	0	1 (0.3%)	1 (0.2%)
Bacteremia	0	0	0	0
Cellulitis	0	1 (0.4%)	0	1 (0.2%)
Diverticulitis	0	1 (0.4%)	0	1 (0.2%)
Eye Abscess	0	1 (0.4%)	0	1 (0.2%)
Localized Infection	1 (0.8%)	0	1 (0.3%)	1 (0.3%)
Lower Respiratory Tract Infection	0	1 (0.4%)	0	1 (0.2%)
Osteomyelitis	0	1 (0.4%)	0	1 (0.2%)
Pneumonia Bacterial	0	1 (0.4%)	0	1 (0.2%)
Upper Respiratory Tract Infection	0	0	0	0
Urinary Tract Infection	0	0	1 (0.3%)	1 (0.3%)
Post Procedural Infection	1 (0.8%)	0	0	0
Eye Disorders	0	1 (0.4%)	0	1 (0.3%)
Keratitis	0	1 (0.4%)	0	1 (0.3%)
Total Number of Subjects with $\geq$ 1 Infection Requiring Antibiotic Treatment	33 (26%)	65 (25%)	86 (27%)	151 (27%)

Adapted from Integrated Summary of Safety Tables 10, 11 and 12; 56-70.

7.3.5.2 Hepatotoxicity

Class labeling for TNF inhibitors includes a hepatotoxicity WARNING. In view of this, the safety database submitted in support of IV golimumab was reviewed for cases of hepatotoxicity. The Applicant defined clinically important hepatobiliary adverse events as an ALT elevation $\geq$ 3 times the ULN associated with total bilirubin elevation $\geq$ 2 times the ULN (regardless of the presence of symptoms or associated adverse events), or an ALT elevation $\geq$ 3 times the ULN that was associated with a serious adverse event in the Hepatobiliary Disorders system organ class. Review of the safety database

⁸ Listings et al.

⁹ Dixon et al.

generated from the controlled portion of CNTO148ART3001 revealed one case of toxic hepatitis (Subject 4803-00434). This patient was a 51 year-old male with a history of colitis and gastritis who was taking metoprolol, mesalazine, methylprednisolone, diclofenac, omeprazole, pyridoxine and isoniazid prophylactically for a positive QuantiFERON Gold test at baseline. He was hospitalized on study Day 87, two days after receiving his third infusion of IV golimumab, for evaluation of generalized weakness and fever associated with ALT and AST ≥ 5 x ULN (ALT 728 U/L and AST 389 U/L) with a normal serum bilirubin (0.83 mg/dL). Serologies were negative for both hepatitis B and C and toxoplasmosis. Abdominal sonogram was unremarkable. The patient's liver function tests improved with discontinuation of concomitant MTX and isoniazid. As a result of stopping his protocol mandated MTX, this patient was withdrawn from the study on Day 100. The occurrence of a second case of clinically important hepatobiliary events was reported in the 120-day safety update for CNTO148ART3001. This patient (Subject 4804-00281), who had developed cholelithiasis while participating in the ongoing study, presented with an ALT ≥ 3 x ULN (796 U/L) and total bilirubin ≥ 2 x ULN (6.28 mg/dL) as a result of a common bile duct stone. Due to the presence of confounding factors (e.g., use of multiple concomitant hepatotoxic medications and the existence of an underlying biliary disorder), neither of these 2 cases meet the criteria for classification as a true Hy's Law case of drug induced hepatotoxicity (e.g., ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN without the presence of other causative factors). In an attempt to minimize confounding due to additive risk from concomitant drug hepatotoxicity, an additional analysis is presented and discussed in the following section 7.4.2.2.

The safety database for supportive study C0524T12 contained 5 case reports of elevated liver function tests that met the definition for a clinically important hepatobiliary event. In 3 out of these 5 cases, both the ALT and AST were ≥ 5 x ULN, while the remaining 2 cases had isolated elevations of ALT ≥ 5 x ULN. Since none of these 5 cases were associated with an elevated total bilirubin ≥ 2 x ULN they also did not meet the criteria for hepatotoxicity as defined by Hy's law. Of note, all 5 subjects were taking multiple concomitant hepatotoxic medications (e.g., MTX with NSAIDs) and their liver function tests improved while continuing to receive IV golimumab infusions.

7.3.5.3 Congestive Heart Failure

Since treatment with TNF inhibitors has been shown to worsen congestive heart failure (CHF) the protocols for both CNTO148ART3001 and C0524T12 prohibited patients with recurrent or medically controlled asymptomatic CHF from participating in these trials. Review of the safety databases from these Phase 3 studies and the 120-day safety follow-up for ongoing CNTO148ART3001 failed to identify any cases of CHF occurring in subjects who received IV golimumab.

7.3.5.4 Demyelinating Disorders

Cases of demyelinating disorders have been reported associated with the use of TNF-blockers resulting in mandatory information regarding these events in the WARNINGS and PRECAUTIONS section of the class label. There were no cases of demyelinating disorders observed in patients during the 24-week controlled portion of Study CNTO148ART3001. Review of this trial's safety database through Week 52 and information contained in the 120-safety update did not reveal any subjects who developed a demyelinating disorder while participating in this ongoing study. No cases of demyelinating disorders were reported to have occurred in the supporting study, C0524T12

7.3.5.4 Infusion Reactions, Hypersensitivity and Anaphylaxis

Because golimumab is a protein for infusion that contains foreign sequences, a certain level of infusion reactions, hypersensitivity, and anaphylaxis would be expected. Describing these events is difficult to do with accuracy, and no consistent methodology was used in the IV golimumab clinical development program for capturing and classifying these events. For the purposes of their safety analysis for IV golimumab, the Applicant defined infusion reactions as any adverse event occurring during an infusion or within 1 hour after completion of an infusion. However, the protocol for study CNTO148ART3001 permitted the use of prophylactic medications (e.g., antihistamines and corticosteroids) for infusion reactions at the discretion of the investigator which may have blunted or obscured hypersensitivity responses. As shown in Table 35, 3.5% of the combined IV golimumab group experienced an infusion reaction as per the Applicant's definition. None of these infusion reactions were classified as severe or serious in nature or resulted in discontinuation of study treatment. Only 1 subject, who was randomized to treatment with IV golimumab 2 mg/kg + MTX, tested positive for anti-golimumab antibodies and had an infusion reaction during this part of the study.

Table 35 – Summary of Infusion Reactions (IR) by Randomized Treatment Group for the 24-Week Controlled Portion of Study CNTO148ART3001

	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Subjects Treated	197	395	68	463
Ave. Duration of Follow-Up (Wks)	21	24	8	21
Ave. exposure (No. of Administrations)	4	4	2	4
Total Number of Infusions	828	1528	136	1664
Infusions with IR	2 (0.2%)	15 (1.0%)	3 (2.2%)	18 (1.1%)
Subjects with ≥ 1 IR	1 (0.5%)	13 (3.3%)	3 (4.4%)	16 (3.5%)
Subjects with Severe IR	0	0	0	0
Subjects with Serious IR	0	0	0	0
Subjects Discontinued Treatment due to IR	0	0	0	0
Subjects Positive for Antibodies to Golimumab at Any Time:	0/125 [*]	13/373 [*] (3.5%)	0/67 [*]	13/440 [*] (3.0%)
Subjects with ≥ 1 IR Positive for Antibodies to Golimumab at Any Time:	0	1/13 ^{**} (7.7%)	0	1/13 (7.7%)

Adapted from 24-week study report Attachment 4.25 and Attachment 4.7; p. 419 and 421.

^{*}Denominator is number of subjects with appropriate samples for testing for antibodies to golimumab at some time point following their first study agent administration or had 1 or more samples obtained after their last study agent administration.

^{**}Denominator is subjects positive for antibodies to golimumab at any time.

Review of the prolonged exposure safety data through Week 52 of this ongoing study and the 120-day safety update revealed a comparable overall incidence of infusion reactions of 3.9%. None of these infusion reactions that occurred with prolonged exposure to the product were considered serious in nature but 1 subject prematurely discontinued treatment as the result of a nonserious infusion reaction. Review of data from C0524T12 showed a similar rate of infusion reactions for the 4 mg/kg every 12 weeks treatment group (Week 24: 2.1%; Week 48: 3.4%) but a higher rate for these events in the 2 mg/kg every 12 weeks (Week 24: 5.4%; Week 48: 6.6%) compared to CNTO148ART3001. All of the infusion reactions in this trial were also classified as non-serious and did not result in premature discontinuation from the study. A review of the individual line listings did not suggest any unidentified cases of anaphylaxis among the reported infusion reactions.

No occurrences of serum sickness-like or anaphylactic reactions associated with IV golimumab were reported in the safety database submitted in support of this product. Further examination of these data revealed a total of 2 cases classified by the Applicant as anaphylaxis: Subject 3705-00099 from Study CNTO148ART3001 and Subject 7605-20630 from Study C0524T12. The case report form for Subject 3705-00099 contained little information describing the hypersensitivity reaction which occurred during administration of the Week 44 infusion other than it was classified as nonserious in nature by the study investigator and resolved without a change in dose of golimumab. The second case (Subject 3705-00099) was a 48 year-old female who was diagnosed

on Day 275 of Study C0524T12 with pulmonary tuberculosis necessitating discontinuation of study medication. This patient reportedly had anaphylaxis (manifested by rash, hypotension, and respiratory distress requiring intubation) following administration of lidocaine, dipirone and diclofenac during preparation for bronchoscopy on Day 291 which was 38 days since her last dose of golimumab. Based on the time course of events, it is unlikely that this hypersensitivity reaction was due to golimumab.

7.3.5.5 Autoimmunity

Since class labeling for TNF inhibitors also includes information regarding autoantibody formation and the rare occurrence of a lupus-like syndrome associated with the use of these agents, study subjects were tested for the presence of ANA and anti-dsDNA autoantibodies at baseline and by repeat testing at Week 20 prior to the mandatory crossing over of placebo-treated patients to IV golimumab. Table 36 summarizes the change from baseline ANA and anti-dsDNA test results for patients in the controlled portion of study CNTO148ART3001. The seroconversion rates to ANA-positivity were similar for both the placebo and IV golimumab treatment groups in this trial. None of the patients who were newly positive for ANA were found to be positive for anti-dsDNA. Review of the study's safety database through Week 52 and data included in the 120-day safety update did not identify any cases of lupus-like syndrome in patients who participated in this trial.

Table 36 – Summary of Change from Baseline Through Week 20 in ANA and Anti-dsDNA Test Results by Randomized Treatment Groups During the 24-Weeks Controlled Portion of Study CNTO148ART3001

	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Subjects Treated	124	375	68	443
Subjects ANA Negative at Baseline	71	207	33	240
Subjects Newly Positive for ANA	9 (13%)	31 (15%)	9 (27%)	40 (17%)
Subjects Newly Positive for anti-dsDNA	0	0	0	0

Positive ANA $\geq$ 1:160; Positive anti-dsDNA $\geq$ 1:10 Crithidia and $\geq$ 5.4 IU mL Farr RIA
 Adapted from 24-Week Study Report Attachments 4.40 and 4.41; p. 548-549

In C0524T12, the seroconversion rate to ANA-positivity at the Week 24 time point was similar for the placebo group (13%) but lower for the combined all golimumab treated subjects (10%; range: 7-22%). One patient who was newly positive for ANA was found to be positive for anti-dsDNA in this study. No cases of lupus-like syndrome were noted on review of the safety data base from C0524T12.

7.3.5.6 Hematological Cytopenias

The safety database for IV golimumab was also reviewed for cases of cytopenias since the use of TNF-inhibitors has been associated with this hematological finding and has resulted in a labeling class WARNING. Table 37 lists the cytopenic adverse events reported to have occurred during the controlled portion of CNTO148ART3001. Overall, the numbers of these types of events were low but a slightly greater proportion of patients treated with IV golimumab reported anemia and leukopenia AEs as compared to the placebo group. No serious cytopenic adverse events were reported to have occurred during the controlled portion of this study, but one patient was withdrawn prematurely from the study due to hematologic cytopenias as shown in Table 30 above. Subject 6006-00106 was a 50 year-old female taking concomitant diclofenac, famotidine, prednisolone, levothyroxine and ciprofloxacin for an infected skin ulcer who discontinued study treatment on Day 47 while participating in study CNTO148ART3001 due to anemia (hemoglobin 86 g/L; normal range 116-164 g/L) , leucopenia (WBC 3.43 [units not provided] normal range 3.80-10.7; lymphocytes 0.58 [units not provided] normal range 0.91-4.28) and elevated transaminases associated with NSAID-induced nephropathy and gastropathy according to her case report form. Review of the prolonged exposure data through Week 52 and the 120-day safety cutoff date for CNTO148ART300 showed comparable rates of occurrence for hematologic cytopenic adverse events. Similar findings were noted on examination of safety data generated from the supporting study, C0524T12.

Table 37 – Hematological Cytopenic Adverse Events by Randomized Treatment Group During the 24-Week Controlled Portion of Study CNTO148ART3001 by Preferred Term

	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Subjects Treated	197	395	68	463
Ave. Duration of Follow-Up (Wks)	21	24	8	21
Ave. exposure (No. of Administrations)	4	4	2	4
Hemoglobin Decreased	0	1 (0.3%)	0	1 (0.2%)
Anemia	2 (1.0%)	4 (1.0%)	0	4 (0.9%)
Anemia of Chronic Disease	1(0.5%)	0	0	0
Microcytic Anemia	0	1 (0.3%)	0	1 (0.2%)
White Cell Count Decreased	0	1 (0.3%)	0	1 (0.2%)
Leukopenia	0	3 (0.8%)	0	3 (0.6%)
Neutrophil Count Decreased	0	1 (0.3%)	0	1 (0.2%)
Neutrophilia	1 (0.5%)	0	0	0
Thrombocytopenia	0	1 (0.3%)	0	1 (0.2%)

Patients may appear in more than one row.
 Adapted from the 24-week study report Attachment 4.4; p. 372-380.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

As shown in the preceding Table 25, most of the patients (>58%) experienced an adverse event while participating in the controlled portion of CNTO148ART3001. Table 38 lists the frequency of adverse events in this study by randomized treatment group and system organ class. A slightly higher overall rate of treatment emergent adverse events was experienced by patients in the IV golimumab (57%) as compared to the placebo group (49%). This difference appears to be related to the higher incidence of Infections and Infestations adverse events that occurred in the IV golimumab treatment group as compared to the placebo group.

Table 38 – Summary of Common Treatment Emergent Adverse Events by Randomized Treatment Group During the 24-Week Controlled Portion of Study CNTO148ART3001 by System Organ Class

	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape Group)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Subjects Treated	197	395	68	463
Ave. Duration of Follow-Up (Wks)	21	24	8	21
Ave. exposure (No. of Administrations)	4	4	2	4
Tot. Number of Subjects with ≥ 1 TEAE	97 (49%)	226 (57%)	19 (28%)	245 (53%)
Infections and Infestations	47 (24%)	119 (30%)	7 (10%)	126 (27%)
Gastrointestinal Disorders	17 (9%)	37 (9%)	1 (2%)	38 (8%)
Musculoskel. and Connect.Tiss. Disord.	31 (16%)	37 (9%)	1 (2%)	38 (8%)
Nervous System Disorders	11 (6%)	30 (8%)	4 (6%)	34(7%)
Skin and Subcutaneous Tissue Disord.	9 (5%)	33 (8%)	1 (2%)	34 (7%)
Investigations	12 (6%)	28 (7%)	2 (3%)	30 (7%)
Respirat., Thoracic and Mediast. Disord.	6 (3%)	22(6%)	1 (2%)	23 (5%)
Vascular Disorders	6 (3%)	19 (5%)	1 (2%)	20 (4%)
Gen. Disord. and Administrat. Site Condit.	5 (3%)	14 (4%)	1 (2%)	15 (3%)
Metabolic and Nutrition Disorders	0	10 (3%)	1 (2%)	11 (2%)
Blood and Lymphatic System Disorders	4 (2%)	8 (2%)	0	8 (2%)
Injury, Poisoning, and Proced. Complicat.	8 (4%)	8 (2%)	0	8 (2%)
Cardiac Disorders	1 (1%)	6 (2%)	1 (2%)	7 (2%)
Eye Disorders	3 (2%)	6 (2%)	0	6 (1%)
Psychiatric Disorders	2 (1%)	6 (2%)	0	6 (1%)
Ear and Labyrinth Disorders	2 (1%)	3 (1%)	1 (2%)	4 (1%)
Hepatobiliary Disorders	0	4 (1%)	0	4 (1%)
Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)	1 (1%)	4 (1%)	0	4 (1%)
Renal and Urinary Disorders	1 (1%)	4 (1%)	0	4 (1%)
Reproduct. System and Breast Disorders	0	3 (1%)	1 (2%)	4 (1%)
Endocrine Disorders	1 (1%)	2 (1%)	0	2 (0%)
Immune System Disorders	0	2 (1%)	0	2 (0%)
Surgical and Medical Procedures	0	1 (0%)	0	1 (0%)

Adapted from 24-week study report Attachment 4.4; p. 372-380

Table 39 is a truncated list of the most commonly reported adverse events reported by 0.5% or more patients in the IV golimumab treatment group during the controlled portion of this trial. The adverse events by preferred MedDRA term most commonly reported by IV golimumab-treated subjects were: upper respiratory tract infection, headache, hypertension, increased alanine aminotransferase, urinary tract infection, nasopharyngitis, bronchitis, pyrexia and pharyngitis. Overall, the types and incidences of common adverse events are consistent with what would be expected for patients with active RA who had been exposed to immunosuppressive therapies and nonsteroidal anti-inflammatory agents (NSAIDs). No other safety issues were identified on review of

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the adverse event data generated from long-term exposure to IV golimumab generated from the ongoing Study CNTO148ART3001. A similar pattern of adverse events was noted on review of data generated from supporting study C0524T12.

Table 39 - Summary of Common Treatment Emergent Adverse Events Occurring in ≥0.5% of Patients Treated with IV Golimumab by Randomized Treatment Group During the 24-Week Controlled Portion of Study CNTO148ART3001 by Preferred Term

MedDRA Preferred Term	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Upper Respiratory Tract Infection	15 (7.6%)	29 (7.3%)	1 (1.5%)	30 (6.5%)
Headache	5 (2.5%)	19 (4.8%)	3 (4.4%)	22 (4.8%)
Hypertension	4 (2.0%)	14 (3.5%)	1 (1.5%)	15 (3.2%)
Alanine Aminotransferase Increased	7 (3.6%)	11 (2.8%)	2 (2.9%)	13 (2.8%)
Urinary Tract Infection	6 (3.0%)	12 (3.0%)	1 (1.5%)	13 (2.8%)
Nasopharyngitis	5 (2.5%)	10 (2.5%)	2 (2.9%)	12 (2.6%)
Bronchitis	2 (1.0%)	11 (2.8%)	0	11 (2.4%)
Pyrexia	0	9 (2.3%)	1 (1.5%)	10 (2.2%)
Pharyngitis	2 (1.0%)	9 (2.3%)	0	9 (1.9%)
Rheumatoid Arthritis	11 (5.6%)	9 (2.3%)	0	9 (1.9%)
Aspartate Aminotransferase Increased	3 (1.5%)	7 (1.8%)	1 (1.5%)	8 (1.7%)
Diarrhea	2 (1.0%)	8 (2.0%)	0	8 (1.7%)
Rash	1 (0.5%)	8 (2.0%)	0	8 (1.7%)
Respiratory Tract Infection	0	7 (1.8%)	1 (1.5%)	8 (1.7%)
Arthralgia	7 (3.6%)	6 (1.5%)	1 (1.5%)	7 (1.5%)
Influenza	4 (2.0%)	5 (1.3%)	2 (2.9%)	7 (1.5%)
Sinusitis	3 (1.5%)	7 (1.8%)	0	7 (1.5%)
Back Pain	4 (2.0%)	6 (1.5%)	0	6 (1.3%)
Dyspepsia	3 (1.5%)	6 (1.5%)	0	6 (1.3%)
Gastritis	4 (2.0%)	5 (1.3%)	1 (1.5%)	6 (1.3%)
Pruritus	1 (0.5%)	6 (1.5%)	0	6 (1.3%)
Cough	0	5 (1.3%)	0	5 (1.1%)
Cystitis	0	5 (1.3%)	0	5 (1.1%)
Gastroenteritis	1 (0.5%)	5 (1.3%)	0	5 (1.1%)
Respiratory Tract Infection Viral	3 (1.5%)	5 (1.3%)	0	5 (1.1%)
Anemia	2 (1.0%)	4 (1.0%)	0	4 (0.9%)
Conjunctivitis	0	4 (1.0%)	0	4 (0.9%)
Hyperglycemia	0	4 (1.0%)	0	4 (0.9%)
Nausea	3 (1.5%)	4 (1.0%)	0	4 (0.9%)
Viral Infection	1 (0.5%)	4 (1.0%)	0	4 (0.9%)
Abdominal Pain	0	3 (0.8%)	0	3 (0.6%)
Abdominal Pain Upper	0	3 (0.8%)	0	3 (0.6%)
Blood Glucose Increased	0	3 (0.8%)	0	3 (0.6%)
Blood Pressure Increased	0	3 (0.8%)	0	3 (0.6%)
Dyspnea	0	3 (0.8%)	0	3 (0.6%)
Leukopenia	0	3 (0.8%)	0	3 (0.6%)
Oral Herpes	0	3 (0.8%)	0	3 (0.6%)
Rhinitis Allergic	2 (1.0%)	3 (0.8%)	0	3 (0.6%)
Transaminases Increased	1 (0.5%)	3 (0.8%)	0	3 (0.6%)
Vertigo	2 (1.0%)	2 (0.5%)	1 (1.5%)	3 (0.6%)
Viral Upper Respiratory Tract Infection	1 (0.5%)	3 (0.8%)	0	3 (0.6%)
Acne	0	2 (0.5%)	0	2 (0.4%)
Acute Sinusitis	2 (1.0%)	2 (0.5%)	0	2 (0.4%)

Adapted from 24-week study report Attachment 4.3; p. 364-371

7.4.2 Laboratory Findings

Laboratory data from the pivotal controlled Phase 3 trial was presented as follows: change from baseline by parameter and the proportion of markedly abnormal values relative to baseline for selected parameters of clinical interest. The Applicant provided normal range of values for each lab parameter assessed. There were reviewed and the clinically acceptable range for normal appeared appropriate.

7.4.2.1 Hematology Parameters

No safety signals were noted on an analysis of clinically relevant mean changes from baseline in any of the hematological parameters across treatment groups for the controlled safety population in CNTO148ART300 as shown in Table 40. Markedly abnormal hematology parameters (cytopenias) that occurred during this portion of the study are discussed in section 7.3.5.6 above.

Table 40 – Mean Change in Hematology Parameters in Study CNTO148ART3001

Parameter	PLO + MTX		PLO +MTX => Golimumab 2 mg/kg + MTX		Golimumab 2 mg/kg + MTX		Golimumab Combined	
	Baseline	Wk 24	Baseline	Wk 24	Baseline	Wk 24	Baseline	Wk 24
Hemoglobin (g/L)								
<i>N</i>	131	122	67	67	396	373	463	440
<i>Mean (SD)</i>	127 (14)	127 (14)	123 (15)	126 (16)	124 (15)	128 (16)	124 (15)	127 (16)
<i>Median</i>	126	126	125	125	124	128	124	128
<i>Range</i>	(91; 160)	(88; 161)	(80; 161)	(92; 170)	(80; 172)	(77; 187)	(80; 172)	(77; 187)
Hematocrit (fraction)								
<i>N</i>	131	118	67	67	396	369	463	436
<i>Mean (SD)</i>	40 (4.1)	39 (3.9)	38 (4.4)	39 (4.5)	39 (4.4)	39 (4.5)	39 (4.4)	39 (4.46)
<i>Median</i>	40	39	38	38	39	39	39	39
<i>Range</i>	(31; 49)	(30; 49)	(28; 51)	(30; 54)	(25; 54)	(25; 61)	(25; 54)	(25; 61)
WBC (x10⁹/L)								
<i>N</i>	131	122	67	67	396	373	463	440
<i>Mean (SD)</i>	8.4 (2.6)	8.1 (2.6)	9.2 (2.4)	7.7 (2.7)	8.7 (2.66)	7.7 (2.5)	8.8 (2.6)	7.7 (2.5)
<i>Median</i>	8.1	7.8	8.6	7.0	8.4	7.3	8.5	7.2
<i>Range</i>	(3; 18)	(4; 17)	(6; 17)	(3; 16)	(3; 23)	(2; 18)	(3; 23)	(2; 18)
Basophils (%)								
<i>N</i>	131	122	67	67	394	370	461	437
<i>Mean (SD)</i>	0.7 (0.45)	1.0 (0.71)	0.6 (0.35)	0.8 (0.62)	0.7 (0.49)	0.8 (0.58)	0.6 (0.47)	0.8 (0.59)
<i>Median</i>	0.6	0.8	0.5	0.7	0.5	0.7	0.5	0.7
<i>Range</i>	(0; 3)	(0;3)	(0; 2)	(0;3)	(0; 3)	(0; 3)	(0; 3)	(0; 3)
Eosinophils (%)								
<i>N</i>	131	122	67	67	394	370	461	437
<i>Mean (SD)</i>	1.6 (0.97)	2.1(1.4)	2.0 (3.6)	2.3 (1.6)	1.7 (1.2)	2.4 (1.6)	1.7 (1.8)	2.3; (1.6)
<i>Median</i>	1.3	1.7	1.3	1.9	1.5	2.0	1.5	2.0
<i>Range</i>	(0; 5)	(0;8)	(0; 30)	(0; 9)	(0; 12)	(0; 12)	(0; 30)	(0; 12)
Lymphocytes (%)								
<i>N</i>	131	122	67	67	394	370	461	437
<i>Mean (SD)</i>	22 (9.2)	23 (9.0)	19 (6.9)	28 (9.2)	22 (7.9)	27 (9.8)	21 (7.8)	27 (9.7)
<i>Median</i>	22	23	18	28	21	27	21	27
<i>Range</i>	(3; 58)	(4; 46)	(4; 38)	(8; 50)	(4; 48)	(6; 59)	(4;48)	(6; 59)
Monocytes (%)								
<i>N</i>	131	122	67	67	394	370	461	437
<i>Mean (SD)</i>	5.0 (2.1)	5.4 (2.2)	4.7 (1.5)	5.6 (2.1)	5.2 (2.0)	5.6 (1.9)	5.1 (1.9)	5.6 (1.9)
<i>Median</i>	4.7	5.1	4.60	5.7	4.9	5.4	4.9	5.4
<i>Range</i>	(1; 13)	(1; 14)	(2; 10)	(2; 12)	(1; 14)	(1; 13)	(1; 14)	(1; 13)
Neutrophils (%)								
<i>N</i>	131	122	67	67	394	370	461	437
<i>Mean (SD)</i>	70 (10.4)	68 (10.9)	74 (8.9)	63 (10.9)	71 (9.0)	64 (110)	71 (9.1)	64 (11)
<i>Median</i>	71	69	74	63	71	64	71	64
<i>Range</i>	(35; 93)	(39; 92)	(47; 93)	(35; 90)	(35; 94)	(30; 89)	(35; 94)	(30; 90)
Platelets (x10⁹/L)								
<i>N</i>	132	122	65	65	389	364	454	429
<i>Mean (SD)</i>	336 (95)	319 (90)	366 (81)	307 (72)	361 (105)	317 (93)	362 (102)	316 (90)
<i>Median</i>	324	306	374	281	352	304	355	301
<i>Range</i>	(160; 723)	(121; 798)	(220; 612)	(211; 518)	(106; 1160)	(139; 854)	(106; 1160)	(139; 854)

Adapted from Information Request dated May 30, 2013 Table 1; p. 5-6.

7.4.2.2 Chemistry Lab Results

Table 41 displays the markedly abnormal post-baseline chemistry parameters that occurred during the controlled portion of Study CNT0148ART3001. Review of these data did not reveal any clinically significant changes or unexpected safety signals. Similar patterns were observed on review of the long-term exposure data through Week 52 of this ongoing study.

Table 41 – Markedly Abnormal Post-Baseline Chemistry Parameters Through Week 24 of Study CNT0148ART3001

	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Subjects Treated	197	395	68	463
Ave. Duration of Follow-Up (Wks)	21	24	8	21
Ave. exposure (No. of Administrations)	4	4	2	4
Decreased Chloride	1 (0.5%)	0	0	0
Decreased Bicarbonate	7 (4%)	8 (2%)	0	8 (2%)
Elevated Glucose	4 (2%)	3 (1%)	0	3 (1%)
Decreased Glucose	0	2 (0.5%)	0	2 (0.4%)
Decreased Albumin	0	1 (0.3%)	0	1 (0.2%)

Adapted from 24-week study report Attachment 4.31; p. 433-436.

In addition to the review of clinically important hepatobiliary adverse events discussed in preceding section 7.3.5.2, an analysis of clinically relevant mean changes from baseline in any of the hepatic test parameters across treatment groups for the controlled safety population in CNT0148ART300 was also undertaken. Review of these data as shown in Table 42 was unremarkable.

Table 42 – Mean Change in Liver Function Tests in Study CNTO148ART3001

Parameter	PLO + MTX		PLO +MTX => Golimumab 2 mg/kg + MTX		Golimumab 2 mg/kg + MTX		Golimumab Combined	
	Baseline	Wk 24	Baseline	Wk 24	Baseline	Wk 24	Baseline	Wk 24
Alk phos (U/L)								
<i>N</i>	129	124	70	70	397	379	467	449
<i>Mean (SD)</i>	95 (41)	90 (30)	80 (20)	76 (25)	88 (36)	82 (32)	87 (34)	81 (31)
<i>Median</i>	88	86	77	68	82	76	81	75
<i>(Min, Max)</i>	(41; 366)	(37; 197)	(48; 151)	(45; 198)	(35; 434)	(29; 318)	(35; 434)	(29; 318)
ALT/SGPT (U/L)								
<i>N</i>	129	124	68	68	397	376	465	444
<i>Mean (SD)</i>	24 (30)	23 (19)	20 (9.7)	25 (15)	21 (16)	25 (19)	21 (16)	25 (18)
<i>Median</i>	18	17	17	21	17	20	17	20
<i>(Min, Max)</i>	(5; 275)	(5; 146)	(7; 54)	(8; 69)	(4; 239)	(4; 134)	(4; 239)	(4; 134)
AST/SGOT (U/L)								
<i>N</i>	131	123	66	66	396	370	462	436
<i>Mean (SD)</i>	24 (33)	22 (12)	19 (5.2)	23 (7.5)	21 (17)	23 (13)	21 (16)	23 (12)
<i>Median</i>	19	19	19	21	18	20	18	20
<i>(Min, Max)</i>	(8; 384)	(9; 92)	(10; 39)	(12; 43)	(8; 325)	(6; 136)	(8; 325)	(6; 136)
Total bili (mg/dl)								
<i>N</i>	129	124	68	68	397	380	465	448
<i>Mean (SD)</i>	6.6 (2.9)	6.8 (3.0)	6.5 (3.2)	7.2 (3.7)	6.2 (2.7)	7.0 (3.4)	6.2 (2.8)	7.0 (3.4)
<i>Median</i>	6.0	7.0	6.0	6.0	5.0	6.0	6.0	6.0
<i>(Min, Max)</i>	(3; 22)	(3; 20)	(3; 22)	(3; 20)	(3; 23)	(3; 26)	(3; 23)	(3; 26)

Adapted from Information Request dated May 30, 2013 Table 2; p. 7.

To minimize potential confounding of a hepatotoxicity signal by additive hepatotoxic medications, the Applicant also looked at maximum postbaseline changes in ALT and AST in patients taking versus not taking anti-tuberculosis medications through Week 24. The results of these analyses are shown in Table 43 and Table 44 below. The proportion of patients not taking antituberculosis medications who had normal baseline ALT levels that increased with study treatment was higher in the combined IV golimumab + MTX group (28%) as compared to the placebo + MTX group (22%). The proportion of patients not taking antituberculosis medication who had normal baseline AST levels but postbaseline elevations in this parameter was similar for both placebo (16%) and combined golimumab (18%) treatment groups. In subjects taking tuberculosis prophylaxis with normal baseline ALT test results, a higher proportion of the combined IV golimumab + MTX group had post baseline elevations (31%) compared to the placebo + MTX group (21%). Similarly, a higher proportion of patients with normal baseline AST test results from the total IV golimumab + MTX group that were taking concomitant antituberculosis medications had postbaseline elevations in AST (25%) versus the placebo + MTX group (11%). These findings support the use of the TNF inhibitor class WARNING for hepatotoxicity in the product's label.

Table 43 – Summary of Maximum Postbaseline ALT Elevations Through Week 24 of Study CNT0148ART3001

	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Subjects Taking Tuberculosis Prophylaxis	35	51	17	68
Subjects with Baseline ALT ≤ ULN:	34	48	16	64
Subjects with Abnormalities	7 (21%)	19 (40%)	1 (6%)	20 (31%)
≥ 8 x ULN	0	1 (2%)	0	1 (2%)
≥ 5 to < 8 x ULN	0	0	0	0
≥ 3 to < 5 x ULN	0	1 (2%)	0	1 (2%)
≥ 2 to < 3 x ULN	0	6 (13%)	0	6 (9%)
> 1 to < 2 x ULN	7 (21%)	11 (23%)	1 (6%)	12 (19%)
< 1 x ULN	27 (79%)	29 (60%)	15 (94%)	44 (69%)
Subjects with Baseline ALT > ULN:	1	3	1	4
Subjects with Abnormalities	1 (100%)	2 (67%)	1 (100%)	3 (75%)
≥ 8 x ULN	0	0	0	0
≥ 5 to < 8 x ULN	0	0	0	0
≥ 3 to < 5 x ULN	0	1 (33%)	0	1 (25%)
≥ 2 to < 3 x ULN	0	0	0	0
> 1 to < 2 x ULN	1 (100%)	1 (33%)	1 (100%)	2 (50%)
< 1 x ULN	0	1 (33%)	0	1 (25%)
Subjects with ↑ ALT Not Taking Concomitant Tuberculosis Prophylaxis				
Subject Not Taking Tuberculosis Prophylaxis	162	344	51	395
Subjects with Baseline ALT ≤ ULN:	148	309	47	356
Subjects with Abnormalities	32 (22%)	88 (29%)	12 (26%)	100 (28%)
≥ 8 x ULN	0	0	0	0
≥ 5 to < 8 x ULN	0	2 (1%)	0	2 (1%)
≥ 3 to < 5 x ULN	2 (1%)	3 (1%)	0	3 (1%)
≥ 2 to < 3 x ULN	1 (1%)	10 (3%)	3 (6%)	13 (4%)
> 1 to < 2 x ULN	29 (20%)	73 (24%)	9 (19%)	82 (23%)
< 1 x ULN	116 (78%)	221 (72%)	35 (75%)	256 (72%)
Subjects with Baseline ALT > ULN:	13	31	4	35
Subjects with Abnormalities	10 (77%)	24 (77%)	3 (75%)	27 (77%)
≥ 8 x ULN	0	0	0	0
≥ 5 to < 8 x ULN	0	0	0	0
≥ 3 to < 5 x ULN	3 (23%)	3 (10%)	0	3 (9%)
≥ 2 to < 3 x ULN	0	5 (16%)	0	5 (14%)
> 1 to < 2 x ULN	7 (54%)	16 (52%)	3 (75%)	19 (54%)
< 1 x ULN	3 (23%)	7 (23%)	1 (25%)	8 (23%)

Adapted from 24-week study report Attachments 4.34 and 4.35; p. 446-47.

Table 44 - Summary of Maximum Postbaseline AST Elevations Through Week 24 of Study CNTO148ART3001

	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Early Escape)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Subjects with ↑ AST Taking Concomitant Tuberculosis Prophylaxis				
Subjects with Baseline AST ≤ ULN:	35	47	17	64
Subjects with Abnormalities	4 (11%)	15 (32%)	1 (5%)	16 (25%)
≥ 8 x ULN	0	1 (2%)	0	1 (2%)
≥ 5 to < 8 x ULN	0	0	0	0
≥ 3 to < 5 x ULN	0	1 (2%)	0	1 (2%)
≥ 2 to < 3 x ULN	0	3 (6%)	0	3 (5%)
> 1 to < 2 x ULN	4 (11%)	10 (21%)	1 (6%)	11 (17%)
< 1 x ULN	31 (89%)	32 (68%)	16 (94%)	48 (75%)
Subjects with Baseline AST > ULN:	0	4	0	4
Subjects with Abnormalities	0	2 (50%)	0	2 (50%)
≥ 8 x ULN	0	0	0	0
≥ 5 to < 8 x ULN	0	0	0	0
≥ 3 to < 5 x ULN	0	1 (25%)	0	1 (25%)
≥ 2 to < 3 x ULN	0	0	0	0
> 1 to < 2 x ULN	0	1 (25%)	0	1 (25%)
< 1 x ULN	0	2 (50%)	0	2 (50%)
Subjects with ↑ AST Not Taking Concomitant Tuberculosis Prophylaxis				
Subjects with Baseline AST ≤ ULN:	154	323	49	372
Subjects with Abnormalities	25 (16%)	60 (19%)	6 (12%)	66 (18%)
≥ 8 x ULN	0	0	0	0
≥ 5 to < 8 x ULN	0	0	0	0
≥ 3 to < 5 x ULN	0	0	0	0
≥ 2 to < 3 x ULN	4 (3%)	8 (3%)	1 (2%)	9 (2%)
> 1 to < 2 x ULN	21 (14%)	52 (16%)	5 (10%)	57 (15%)
< 1 x ULN	129 (84%)	263 (81%)	43 (88%)	306 (82%)
Subjects with Baseline AST > ULN:	7	17	2	19
Subjects with Abnormalities	4 (57%)	13 (77%)	0	13 (68%)
≥ 8 x ULN	0	0	0	0
≥ 5 to < 8 x ULN	0	0	0	0
≥ 3 to < 5 x ULN	1 (14%)	2 (12%)	0	2 (11%)
≥ 2 to < 3 x ULN	2 (29%)	4 (24%)	0	4 (21%)
> 1 to < 2 x ULN	1 (14%)	7 (41%)	0	7 (37%)
< 1 x ULN	3 (43%)	4 (24%)	2 (100%)	6 (32%)

Adapted from 24-week study report Attachments 4.36 and 4.37; p. 448-49.

7.4.3 Vital Signs

According to the protocol for CNTO148ART3001, patients' vital signs (systolic and diastolic blood pressure, and heart rate) were collected at screening and all subsequent visits as follows: pre-study infusion, 15 minutes post study infusion, 30 minutes after study infusion had ended, and 60 minutes after study infusion had ended. Table 45 summarizes the number of subjects who had abnormal vital signs post baseline. The proportion of patients with abnormal diastolic blood pressure and heart rate were similar across treatment groups. A higher proportion of subjects randomized to placebo had

abnormal systolic blood pressure assessments as compared to those randomized to IV golimumab.

Table 45 - Subjects with Markedly Abnormal Post Baseline Vital Signs by Randomized Treatment Group During the 24-Weeks of Controlled Treatment for Study CNTO148ART3001

	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Escape Group)	Golimumab Combined
	PLO +MTX	Golimumab 2 mg/kg + MTX		
Number of Subjects Treated	197	395	68	463
Systolic Blood Pressure (mm/hg) Subjects with Any Abnormal Value	15 (7.6%)	22 (5.6%)	1 (1.5%)	23 (5.0%)
Diastolic Blood Pressure (mm/hg) Subjects with Any Abnormal Value	4 (2.0%)	6 (1.5%)	0	6 (1.3%)
Heart Rate (beats/min) Subjects with Any Abnormal Value	3 (1.5%)	8 (2.0%)	1 (1.5%)	9 (1.9%)

Adapted Sponsor's Attachment 4.38; p. 450 of 24-week study report

7.4.4 Electrocardiograms (ECGs)

Since no significant abnormalities were identified on review of the serial ECGs performed on subjects who participated in the Phase 3 studies conducted in support of the safety profile of the SC formulation of golimumab, they were not required as part of the safety assessment for IV golimumab.

7.4.5 Special Safety Studies/Clinical Trials

Since the safety profile of the TNF inhibitor class is well characterized, no special safety studies were conducted by the Applicant in support of IV golimumab's safety profile.

7.4.6 Immunogenicity

To assess the formation of antibodies to golimumab, blood samples were tested that were drawn at baseline and Weeks 20, 52, 76, and 100 of Study CNTO148ART3001. As shown in Table 46, approximately 4% of all patients treated with IV golimumab tested positive for anti-golimumab antibodies at the Week 20 time point. No definitive conclusions can be drawn regarding a possible association of anti-product antibody positivity and lack of biological activity due to the small number of patients being anti-product antibody positive since only 1 out of the 13 subjects positive for anti-golimumab antibodies qualified for early escape. With prolonged exposure through Weeks 48/52

among all subjects who had received at least 1 dose of golimumab, the total number of subjects positive for anti-golimumab antibodies continued to be low (26/560; 5%).

Table 46 – Summary of Subjects Positive for Anti-Golimumab Antibodies by Randomized Treatment for Study CNTO148ART3001 at Week 20 Time point

	Placebo + MTX => EE	Golimumab		
		2 mg/kg + MTX =>EE	2 mg/kg + MTX => No EE	2 mg/kg + MTX Combined
Subjects Treated	68	17	378	395
Subjects with Appropriate Antibody Samples	67	16	357	373
Subjects Positive for Anti- Golimumab Antibodies	0	1 (6%)	12 (3%)	13 (4%)
Anti-Golimumab Antibody Level:				
1:10	0	0	4	4
1:20	0	0	6	6
1:40	0	0	1	1
1:80	0	1	1	2

Adapted from the 24-week study report Attachment 2.10 and 2.12; p. 265 and 273.

For completeness, the rates of antibody positivity were reviewed for study C0524T12. Regardless of concomitant MTX use, the rate was similar to that in CNTO148ART3001 with 27 out of 529 (5%) subjects exposed to IV golimumab with appropriate samples testing positive for anti-golimumab antibodies at Week 24. With increasing product exposure, this rate increased to 7% at Week 48 in patients with appropriate samples. These rates of anti-golimumab antibodies are higher than what was observed with both the 50 mg and 100 mg every 4 weeks SC formulation. (Refer to the medical officer review dated June 24, 2009 for BLA 125289 SC golimumab for additional information.)

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Examination of the safety data collected from the dose-ranging study CO524T16 failed to identify any trends suggestive of a possible dose-dependent relationship associated with exposure to IV golimumab.

7.5.2 Time Dependency for Adverse Events

Overall, review of the cumulative long term exposure data generated from the ongoing study CNTO148ART3001 did not reveal any new safety signals associated with prolonged exposure to IV golimumab.

7.5.3 Drug-Demographic Interactions

Subgroup analyses of serious infectious adverse events were conducted by the Applicant on data from CNTO148ART3001 in order to determine if there were any drug-demographic interactions and are displayed in Table 47. Subgroup analysis was limited by small sample size for race, gender (male) and age $\geq$ 65 years. Due to the small sample size of male, patients $\geq$ 65 years of age, and Black, Asian, American Indian/Alaska native, and Native Hawaiian or other Pacific Islander subjects who participated in this trial, no definitive conclusions regarding the risk for developing serious infectious adverse events associated with IV golimumab treatment can be made for any of these demographic groups. Review of serious infections by weight based quartile did not identify any safety concerns.

Table 47 – Demographic Subgroup Analysis of Serious Infectious Adverse Events in Study CNTO148ART3001

	Placebo (n=197)	Golimumab 2 mg/kg every 8 wks (n=397)
Age (years):		
<65 years	49 (25%)	103 (26%)
>65 years	4 (2%)	13 (3%)
Gender:		
Female	41 (21%)	98 (25%)
Male	12 (6%)	18 (5%)
Race:		
White	39 (20%)	81 (21%)
Asian	5 (3%)	15 (4%)
Black	0	0
American Indian/Alaska Native	1 (1%)	3 (1%)
Native Hawaiian or other Pacific Islander	0	0
Other	8 (4%)	17 (4%)
Weight		
< 25 th percentile	15 (8%)	36 (9%)
>25 th percentile to $\leq$ median	13 (7%)	22 (6%)
>median to $\leq$ 75 th percentile	8 (4%)	29 (7%)
>75 th percentile	17 (9%)	29 (7%)

Adapted from June 10, 2013 information request Table 1; p. 4

7.5.4 Drug-Disease Interactions

No drug-disease interaction studies were conducted by the Applicant in patients with hepatic or renal impairment. Review of the safety database did not identify any AEs that appeared related to an interaction with concomitant medications.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were conducted by the Applicant in support of IV golimumab's safety. Golimumab is a therapeutic biologic protein and is not expected to interact with CYP450 enzymes or p-glycoproteins. Review of the database did not identify any adverse events that appeared related to an interaction with concomitant medications.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

RA patients have an underlying increased risk for developing lymphoma that has been documented in the published literature. Since the TNF inhibitors are immunosuppressive and can potentially raise the risk for developing a malignancy, the safety database generated from Study CNTO148ART3001 was examined for cases of malignancy that occurred with exposure to IV golimumab. As shown in Table 48, there was 1 malignancy reported in the IV golimumab group during the controlled portion of study CNTO148ART3001. [Note: One case of adenocarcinoma of the lung diagnosed during screening (Day -21) in a 72 year old female (Subject 6404-00078) randomized to placebo in this study is not included in Table 48 since this neoplasm was present prior to trial entry.) Review of the safety data generated through Week 52 of the study revealed 3 additional cases of malignancies in patients exposed to IV golimumab: 1 case of basal cell cancer, 1 case of cervical carcinoma (Stage 0) and 1 case of worsening chronic lymphocytic leukemia. No additional cases of malignancy were reported in the 120-day safety update from the ongoing study, CNTO148ART3001. There were no cases of lymphoma reported associated with the administration of IV golimumab over the course of this trial.

Table 48 – Malignancies By Randomized Treatment Group During the 24-Weeks of Controlled Treatment in CNTO148ART3001

	Treatment Groups Assigned at Randomization		PLO +MTX => Golimumab 2 mg/kg + MTX (Escape Treatment Group)	Golimumab Combined
	PLO +MTX*	Golimumab 2 mg/kg + MTX		
Subjects Treated	197	395	68	463
Ave. Duration of Follow-Up (Wks)	21	24	8	21
Ave. Exposure (No. of Administrations)	4	4	2	4
Tot. Subjects with $\geq$ 1 Malignancy	0	1 (0.3%)	0	1 (0.2%)
Malignancies: Breast Cancer	0	1	0	1

*Excludes Subject 6404-00078 who had adenocarcinoma of the lung present on screening chest x-ray (Day -21) that was overlooked.

The controlled portion of Study CNTO148ART3001 was not designed to determine the risk for developing a malignancy due to exposure to IV golimumab. Nonetheless, the exposure-adjusted incidence rate were calculated for all malignancies including non-melanoma skin cancers and for non-melanoma skin cancers (NMSC) only based on the number of cases observed in the controlled and uncontrolled portions of this trial and 120-day follow-up cut off date. As shown in Table 49, the exposure-adjusted incidence rates for malignancies in the both the placebo and controlled IV golimumab treatment groups were low and remained low with increasing exposure to the product. Additionally, the confidence intervals for the point estimates of death overlap suggesting that this is not a spurious finding. These rates were comparable to these seen in the RA safety database reviewed in support of the SC formulation. (Refer to the medical officer review dated June 24, 2009 for BLA 125289 SC golimumab for additional information.)

Table 49 – Exposure Adjusted Malignancy Rate During Study CNTO148ART3001

		24-Weeks Controlled Treatment		Combined Controlled and Uncontrolled Portions	
		PLO + MTX	Golimumab 2 mg/kg every 8 wks	Golimumab 2mg/kg every 8 wks (Cutoff date 30 Mar 2012)	Golimumab 2mg/kg every 8 wks (Cutoff date 15 Aug 2012)
All Malignancies excl. NMSC	Number of Subjects	197	395	--	--
	Subject-Yrs of Exposure	179	179	778	958
	No. of Pts. with Malignancy	0	1	3	3
	Malignancies per 100 Subject-Yrs	0.0	0.56	0.39	0.31
	95% Confidence Interval	(0.00, 3.79)	(0.01, 3.11)	(0.08, 1.13)	(0.06, 0.92)
NMSC-only	Number of Subjects	197	396	--	--
	Subject-Yrs of Exposure	79	179	776	958
	No. of Pts. with Malignancy	0	0	1	1
	Malignancies per 100 Subject-Yrs	0.0	0.0	0.13	0.10
	95% Confidence Interval	(0.00, 3.79)	(0.00, 1.67)	(0.00, 0.72)	(0.00, 0.58)

Adapted from the 24-week study report Table 29, p. 96-97; 52-week study report Appendix 57, p. 342-343; and 120-day safety update Appendix 1.47, p. 175-176.

A tabular summary of the 7 malignancies that occurred in patients as of the 48-week database lock for study C0524T12 is shown in Table 50 below. No lymphomas or discernable patterns of malignancy are noted on review of these data.

Table 50 – Summary of Malignancies in Study C0524T12 (48-week data cut-off)

	Placebo	IV Golimumab 2 mg every 12 weeks	IV Golimumab 2 mg every 12 weeks
Total Subjects with ≥ 1 Malignancy	1	2	4
Solid Tumors:			
Bladder Cancer	0	0	1
Colon Cancer	0	0	1
Cervical Carcinoma	0	1	0
Lung Cancer (Presumed) with Brain Mets	0	0	1
Thyroid Cancer	0	0	1
Non-Melanoma Skin Cancer:			
Basal Cell Carcinoma	1	1	0

Adapted from Summary of Clinical Safety Appendix A.56; p. 340-341.

All 6 of the IV golimumab associated malignancies occurred after the 24-weeks of controlled study treatment had been completed while the 1 malignancy in the placebo patient occurred during the controlled portion of C0524T12. Due to the numerical imbalance in malignancies in the two IV golimumab treatment groups, the exposure-adjusted incidence rates for malignancies for the placebo and IV golimumab treatment groups for both the controlled and the combined controlled and uncontrolled portions of C0524T12 were calculated and are shown in Table 51. During the 24-week controlled portion of this trial, the malignancy incidence rate was zero for all malignancies

including NMSC in both golimumab treatment groups; however, with increasing exposure these rates increased to 0.36 malignancies per 100 subject-years for the 2 mg/kg every 12 weeks treatment group and to 0.84 malignancies per 100 subject-years for the 4 mg/kg every 12 weeks treatment group. However, the confidence intervals for the point estimates overlap suggesting that there may be no real difference between the two treatment groups despite varying numbers of subjects and durations of exposure.

Table 51 – Rate of Malignancy in Study C0524T12

		24-Week Controlled Portion			Controlled and Uncontrolled Portions	
		Placebo	Gol 2 mg/kg every 12 wks	Gol 4 mg/kg every 12 wks	Gol 2 mg/kg every 12 wks	Gol 4 mg/kg every 12 wks
All Malignancies excl. NMSC	Total Number Subjects	129	258	255	259	417
	Subject-Yrs of Exposure	53	117	116	281	475
	No. of Pts. with Malignancy	0	0	0	1	4
	Malignancies per 100 Subject-Yrs	0.0	0.0	0.0	0.36	0.84
	95% Confidence Interval	(0.0, 5.6)	(0.0, 2.6)	(0.0, 2.6)	(0.01, 1.98)	(0.23, 2.15)
NMSC-only	Total Number of Subjects	129	258	255	259	417
	Subject-Yrs of Exposure	53	117	116	280	476
	No. of Pts. with Malignancy	1	0	0	1	0
	Malignancies per 100 Subject-Yrs	1.88	0.0	0.0	0.36	0.0
	95% Confidence Interval	(0.05, 10.5)	(0.00; 2.55)	(0.0, 2.57)	(0.01, 1.99)	(0.00, 0.63)

Adapted from Summary of Clinical Safety Appendix A.57 and Table 29; p. 342-343 and 96-97.

7.6.2 Human Reproduction and Pregnancy Data

The study protocol for CNTO148ART3001 prohibited pregnant and breast feeding women from participating in these studies. Additionally, the study's entry criteria required women of reproductive potential to practice effective methods of contraception for the duration of the trial and regular screening by urine pregnancy testing. Discontinuation of study medication was also mandated by the protocol's withdrawal criteria if a subject became pregnant. Thus, no female subjects were reported to have become pregnant during this study. Two (2) pregnancies and 1 partner pregnancy were reported to have occurred in C0524T12 bringing the total number of pregnancies that occurred in subjects enrolled in golimumab studies or their partners to 78. The bulk of this pregnancy data from subjects and the partners of subjects was collected from studies conducted in support of the SC formulation of golimumab and was reviewed in support of its licensing application. (Refer to medical officer's review of BLA 125289 dated March 9, 2009 for additional information.) According to the Applicant, no congenital anomalies have been reported as an outcome among the pregnancies that occurred in either study subjects or their partners through the cut-off date March 30, 2012.

7.6.3 Pediatrics and Assessment of Effects on Growth

This application did not contain any data generated from assessments of IV golimumab's effect on growth since the Applicant has not conducted a study in children or adolescents.

Since IV golimumab represents a new formulation and a new route of administration, it triggers the Pediatric Research Equity Act (PREA). The Applicant has submitted a request for a partial waiver not to conduct a study in neonates and infants up to 1 year, 11 months since juvenile inflammatory arthritis (JIA) does not present at birth and the disease is not typically clinically evident before 1 year of age and as such patients are rare, and a deferral to conduct a study in children ages ≥ 2 through ≤ 17 years old with JIA since studies of IV golimumab in adult RA are completed and the application is ready for approval. Pursuant to this request, this submission contained a proposed pediatric development plan to evaluate the safety, efficacy, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of IV golimumab in 158 children between the ages 2 to 17 years and 11 months with polyarticular JIA despite standard therapy with methotrexate via a single, randomized withdrawal, controlled Phase 3 study of 52 weeks duration. The primary endpoint for the proposed study is the proportion of subjects with a disease flare between Week 20 and Week 52 (the double-blind, randomized-withdrawal portion of the study). Secondary endpoints include the ACR Pediatric 30 response rate at Weeks 20 and 52, the proportion of ACR Pediatric 30 responders who have inactive disease at Week 52, and the proportion of ACR Pediatric 30 responders at Week 20 who are in protocol defined clinical remission while on medication for JIA at Week 52. Clinical PK endpoints include serum golimumab concentrations over time. Safety variables include frequency of AEs, including AEs of interest such as tuberculosis and demyelinating disorders, infusion reactions, vascular events, pregnancies and malignancies, as well as changes in clinical lab tests and immunogenicity. Subjects will undergo efficacy and safety assessments at baseline and Week 2, then every 4 weeks until the study is completed (Week 52).

The Applicant plans to submit the pediatric protocol in the fourth quarter of 2013 with initiation of the study anticipated in the first quarter of 2014 and submission of the 52-week study report in the third quarter of 2017. Based on discussions held at the May 1, 2013 meeting of the Pediatric Review Committee (PeRC), it was agreed that the Applicant's proposed partial waiver for studies in neonates and infants up to 1 year, 11 months in age and deferral for pediatric studies in children ≥ 2 through ≤ 17 years of age was acceptable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Single IV doses of golimumab up to 10 mg/kg have been administered in a clinical study without any direct toxic effect. The Applicant stated in their submission there have been

no known occurrences of infusions of more than 10 mg/kg or known overdoses during any of the clinical studies in the IV golimumab program. Since golimumab is a monoclonal antibody which has to be administered via intravenous infusion and is associated with serious adverse events such as infections and malignancy, it is unlikely that this product will be abused. No formal studies on the withdrawal and rebound effects of golimumab were conducted in support of its safety.

7.7 Additional Submissions / Safety Issues

Additional safety information that was contained in the Applicant's 120-day safety update submitted on January 17, 2013 has been incorporated into the postmarketing and literature review subsections of this review.

8 Postmarket Experience

IV golimumab has not been approved for marketing in any country.

9 Appendices

9.1 Literature Review/References

In support of this licensing application for IV golimumab, the Applicant submitted eight publish citations as follows: 3 articles describing double-blind, placebo-controlled studies conducted with the SC formulation of golimumab in RA (2 studies) and psoriatic arthritis (1 study); 2 articles describing double-blind, placebo-controlled RA studies conducted with infliximab; 1 article discussing co-morbidity in RA, 1 article and 1 book chapter discussing early pregnancy loss. These citations were examined for clinical content and no new safety issues related to the use of IV golimumab as a treatment for RA were identified.

An updated literature search was conducted by this medical officer on June 4, 2013 using the search engine PubMed. A total of 15 citations were identified as follows: 1 article described the 52-week results from study CNTO148ART3001; 1 article was a review article that discussed the results from study CNTO148ART3001; 2 articles described the 48-week results from Study C0524T12, 4 articles described the results from various Phase 1 and 2 pharmacokinetic studies conducted with the IV and SC formulations of golimumab, 2 articles discussed the results from various studies conducted in patients with RA, ankylosing spondylitis and psoriatic arthritis treated with the SC formulation of golimumab; 2 articles were update reviews of biologic therapies for autoimmune diseases; and 4 articles discussed ongoing clinical trials which included studies evaluating the IV and SC formulations of golimumab. Examination of these 15 citations did not reveal any new potential safety signals associated with IV golimumab.

References:

1. Del Rincon, I et al. High Incidence of Cardiovascular Events in a Rheumatoid Arthritis Cohort Not Explained by Traditional Cardiac Risk Factors. *Arthritis and Rheumatism* 2001; 44 (12): 2737-2745.
2. Gonzalez, A et al. The Widening Mortality Gap between Rheumatoid Arthritis Patients and the General Population. *Arthritis and Rheumatism* 2007; 56(11): 3583-3587.
3. Listings, J et al. Infections in Patients with Rheumatoid Arthritis Treated with Biologic Agents. *Arthritis and Rheumatism* 2005; 52(11):3403-3412.
4. Dixon, WG et al. Serious Infection Following Anti-Tumor Necrosis Factor Alpha Therapy in Patients with Rheumatoid Arthritis. *Arthritis and Rheumatism* 2007; 56(9):2896-2904.

9.2 Labeling Recommendations

Based on review of the data submitted in support of this application, the following recommendations should be included in the product's label:

1. The tradename SIMPONI ARIA has been deemed acceptable by both DMETS and the Division

2. In view of the robust efficacy data supporting a radiographic inhibition claim for IV golimumab, this formulation should be licensed for marketing with a stand alone product label to distinguish it from the already marketed SC formulation which failed to demonstrate inhibition of radiographic progression
3. Safety information generated from Study C0524T12 should not be included in the IV golimumab label as this data may be misleading to health care prescribers since this study evaluated different doses and dosing regimens with and without MTX then the to-be-marketed dose and dosing regimen
4. Based on the safety database submitted in support of IV golimumab, no strengthening of the TNF inhibitor class labeling WARNINGS and PRECAUTIONS is warranted
5. Clarifying language needs to be included in the product's label alerting health care prescribers that increasing IV golimumab's dosing frequency may result in subtherapeutic effectiveness

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this application in view of the well documented safety profiles of the five other TNF inhibitors marketed in this country and the lack of any new or unexpected safety signal identified during the review of the safety database submitted in support of IV golimumab.

10 Individual Study Reviews

10.1 Individual Study Reports

Protocol C0524T12

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Golimumab, a Fully Human Anti-TNF- α Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate therapy.

Dates Conducted: This trial was started on Aug. 24, 2006 and completed on July 23, 2008. The long term extension of the study was completed on September 26, 2009.

Study Sites: A total of 85 centers in 15 countries worldwide: South America (Argentina, Peru, Mexico, Columbia), Europe (Germany, Hungary, Poland, Ukraine, Latvia, Lithuania, Malta), North America (US), and Asia-Pacific countries (Malaysia, New Zealand, Australia). Refer to Table 2 for additional information regarding study sites.

Objectives:

Primary Objective:

- Evaluate the clinical efficacy and safety of golimumab IV infusions every 12 weeks with and without methotrexate (MTX), compared it MTX alone, in subjects with active RA despite concurrent MTX treatment

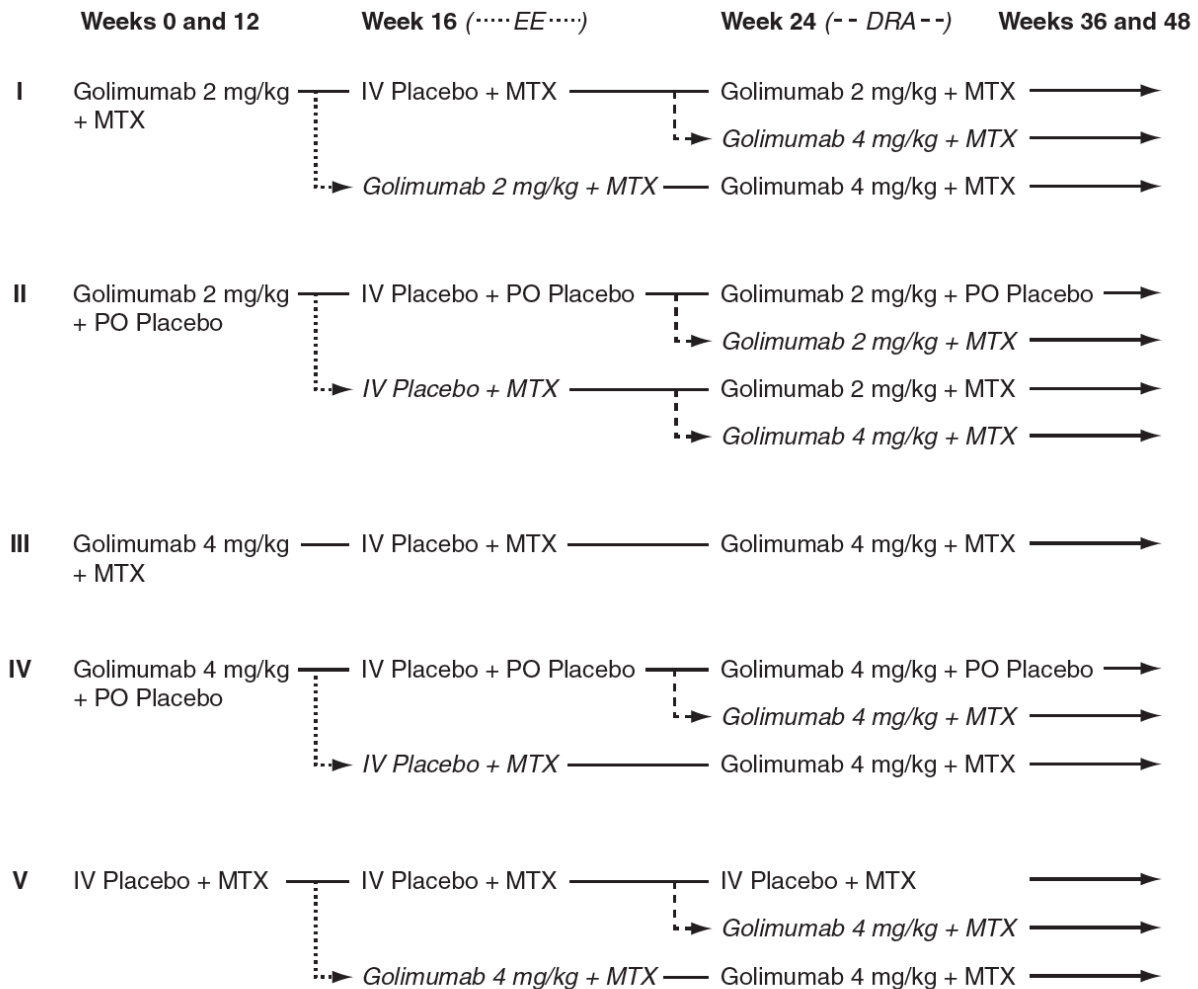
Secondary Objectives:

- Assess the effects on physical function and quality of life (QOL), the population PK of IV golimumab, and the pharmacodynamics of IV golimumab in subjects with active RA
- Assess the safety of SC golimumab after transition from IV golimumab

Overall Design:

This was to have been a randomized, double-blind, placebo-controlled, multicenter, 5-arm study of the efficacy and safety of IV administration of 2 mg or 4 mg golimumab (given with or without MTX over a period of 30 minutes every 12 weeks) for at least 48 weeks in 643 subjects with active RA despite concurrent MTX therapy. Eligible subjects were to have been randomized via 1:1:1:1:1 ratio to the five treatment groups shown in Figure 7 which depicts a schema of the trial. At Week 16 and Week 24, joint assessment results were to have been used to allow subjects to enter early escape (EE) and dose regimen adjustment (DRA), respectively, in a blinded fashion. (Note: EE and DRA methodologies are described in Figure 7.) All subjects were to have remained on the same assigned and blinded treatment that they had been receiving at Weeks 24, 36, and 48 were to have been followed for routine efficacy and safety assessments until database lock. No changes in concomitant medications for RA were to have been permitted. Treatment assignments were unblinded after the 48-week database lock. Within 3 months of the 48-week database lock, subjects were to have been given the option to enter the long-term extension and receive SC golimumab 50 mg every 4 weeks for 24 weeks of treatment designated by Week E-0 through Week E-24. A schema of the long-term extension study is displayed in Figure 8 below.

Figure 7 – Schema of Study C0524T12 Through Week 48

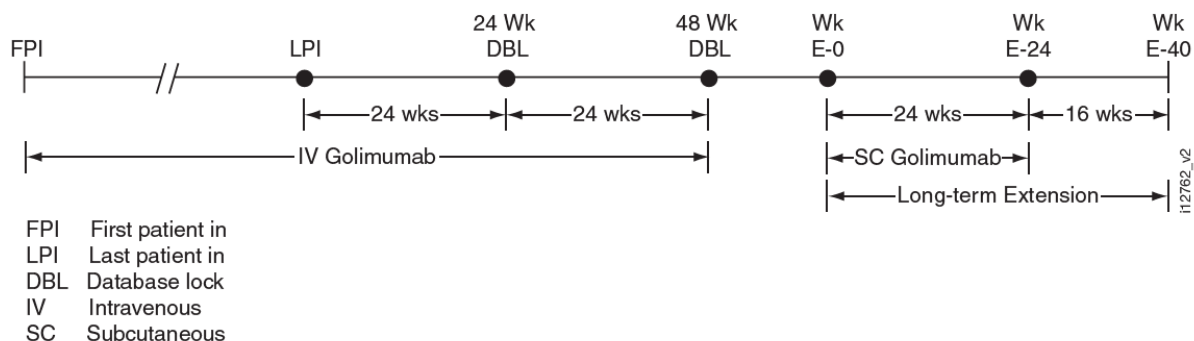


EE = Early escape (for subjects with < 20% improvement in both tender and swollen joint counts)
 DRA = Dose regimen adjustment. (Subjects in Group I-IV with < 20% improvement in both tender and swollen joint counts at Week 24 will enter DRA. Subjects in Group V who have not entered EE and have a total swollen and tender joint count of ≥ 4 at Week 24 will enter DRA.)
 MTX = Methotrexate PO Placebo = Oral placebo capsules (sham MTX) IV = Intravenous

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Adapted from 52-week study report Fig. 1; p.24

Figure 8 – Schema of Long Term Extension of Study C0524T12



Adapted from 52-week study report Fig. 2; p. 25.

Study Entry Criteria: This study utilized the same major inclusion and exclusion criteria as Protocol CNTO148ART3001 which are listed in the preceding Table 3.

Treatment: The same methods used in Study CNTO148ART3001 to administer IV golimumab were also used in this trial

Concomitant Medications: The same rules and prohibitions regarding the use of concomitant medications utilized in Study CNTO148ART3001 were applied in this study.

Study Procedures: The following Table 52 is a tabular flow chart of the scheduled study visits as well as protocol specified procedures and evaluations to have been performed over the course of the 48-weeks of the controlled portion of this study and the open-label extension. Visits during the open label extension were every 4 weeks and the assessments were similar to those employed in the 48-week study.

Table 52 – Study Schedule for Study C0524T12 Events Through Week 48

Assessments ^a	Screen	Wk 0	Wk 4	Wk 8	Wk 12	Wk 14 ^b	Wk 16	Wk 20	Wk 24	Wk 36	Wk 48
Randomization		X									
IVRS notification of tender & swollen joint counts		X					X		X		
Infusion		X			X		X		X	X	X
Efficacy evaluations ^e	X ^f	X	X	X	X	X	X	X	X	X	X
SF-36		X				X			X		X
HEcon		X		X			X		X		X
AE review ^{d,g}	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test ^h	X										
Routine laboratory analyses	X	X		X	X		X		X	X	X
CRP		X	X	X	X	X	X	X	X	X	X
ESR	X ⁱ	X ⁱ				X			X		X
Rheumatoid factor	X					X					
Anti-CCP antibodies	X					X					
Fasting glucose		X							X		X
ANA/anti-dsDNA antibodies		X							X		X

Assessments ^a	Screen	Wk 0	Wk 4	Wk 8	Wk 12	Wk 14 ^b	Wk 16	Wk 20	Wk 24	Wk 36	Wk 48
Golimumab concentrations		X ^j	X	X	X ^j	X	X ^k		X ^j	X ^k	X ^k
Population PK		X ^l									
Serum-based PD biomarkers ^m		X	X			X			X		X
Pharmacogenomics ⁿ		X									
Antibodies to golimumab		X							X		X
Serum lipid levels ^o		X							X		X
Cardiovascular markers		X				X			X		
Anemia markers		X				X					

Adapted from 48-week study report Attachment 1.1; p. 71-72.

Outcome Measures:

Primary Endpoint: This was to have been the proportion of subject who achieved an ACR 50 response at Week 14.

Major Secondary Endpoints: These were to have been as follows:

- Proportion of subjects achieving an ACR 50 response at Week 24
- Proportion of subjects achieving an ACR 20 response at Week 14
- Proportion of subjects with good or moderate Disease Activity Index Score 28 (DAS28) using CRP at Week 14
- Change from baseline in physical component summary (PCS) score of the SF-36 at week 14

Statistical Analysis: Chi-square tests (unstratified analyses) or Cochran-Mantel-Haenszel (CMH) tests (stratified analyses) were to have been used to compare the proportion of subjects achieving a specified endpoint between treatment groups. Continuous response parameters were to have been compared using ANOVA on the van der Waerden normal score. All statistical tests were 2-sided and performed at $\alpha=0.05$.

Study Conduct: There was one amendment to the protocol on December 19, 2007 that resulted in the following protocol changes: added a secondary objective; information on identification of the exact dose and time of golimumab SC dose to be administered during the long term extension of the study; information regarding the prefilled syringes; clarifications about the 24-week database lock, unblinding and initiation of SC administration after the 48-week database lock; updated primary analysis section, clarifications of the data review during the long term extension and introductory text to the major secondary analyses.

Results:

A total of 643 subjects were randomized, out of which 508 enrolled in the long term extension. A total of 39 subjects prematurely discontinued study treatment through Week 24 as follows: 15 patients due to adverse events (7 of which included worsening of RA), 11 patients due to unsatisfactory therapeutic effect, 8 patients due to other reasons, 3 due to lost to follow-up, and 2 due to discontinuation of oral study agent administration. Through Week 48, the number of subjects who prematurely withdrew from the study had increased to 73 patients and included 3 deaths. The pattern for study discontinuations through Week 48 was similar to the controlled portion of the study. Baseline demographics were generally comparable across treatment groups. Approximately 80% of the patients were female and 70% Caucasian. Median age was 51 years and median weight was approximately 70 kg. The ACR Core baseline disease characteristics of RA were consistent with a population with moderate to severe RA. Treatment for latent tuberculosis was initiated for approximately 14% of patients before dose administration with study agent. There was 1 subject who initially tested negative for TB that required treatment for TB after baseline.

Efficacy: Treatment with golimumab administered IV at 2 mg/kg (12.5%) and 4 mg/kg (19.4%) + MTX every 12 weeks trended but failed to capture the primary endpoint, the ACR 50 response rate at Week 14, as compared to placebo+MTX (13.2%; $p=0.051$).

Improvements were seen for the major secondary endpoints which included the ACR 20, DAS28, SF-36 responses at Week 14, and ACR 50 at Week 50. Treatment with golimumab alone when compared with placebo+MTX resulted in numerically greater improvements in the DAS28 and ACR response rates at Week 14, but with continued administration these improvements were not maintained through Week 24.

Immunogenicity: Treatment with golimumab resulted in the formation of anti-golimumab antibodies in approximately 5% and 7% of subjects after repeat IV infusions of golimumab every 12 weeks at Week 24 and Week 48, respectively. Patients treated with concomitant MTX tended to have lower rates of antibody formation.

Safety: The proportion of adverse events reported by subjects through Week 16 was similar between golimumab treated subjects and placebo + MTX subjects and the rates of adverse events increased with prolonged exposure. The most commonly reported adverse events during the controlled portion were URTI, nasopharyngitis, bronchitis, sinusitis and UTI. A higher rate of serious adverse events were reported by all golimumab treatment groups combined than in the placebo +MTX treatment group through Week 16 that were predominantly serious infections and increased with increasing exposure. No deaths, cases of tuberculosis, or serious opportunistic infections occurred through Week 24. There were a total of 6 deaths that occurred during the uncontrolled portion and long term open label extension as follows: 3 deaths due to cardiovascular events, 1 death due to unknown cause, 1 death due to septic shock, and 1 death due to respiratory insufficiency. These deaths did not appear to be dose-related. A total of 7 malignancies were reported through Week 48. Singular malignancies such as colon cancer, bladder cancer, thyroid cancer and lung cancer were observed in the golimumab 4 mg/kg + placebo and golimumab 4 mg/kg + MTX treatment groups while single cases of basal cell carcinoma and cervical carcinoma (Stage 0) were reported in the 2 mg/kg golimumab + MTX treatment group. The percentage of subjects with infusion reactions was similar between golimumab-treated subjects and placebo+MTX treated subjects through Week 16.

Conclusions: Although treatment with IV golimumab administered at doses and dosing regimens of 2 mg/kg and 4 mg/kg with and without MTX resulted in numerical improvements in the signs and symptoms of RA disease, C0524T12 is considered a failed study since it did not capture its primary endpoint, the ACR 50 response at Week 14. At the doses and dose regimens evaluated in this trial, treatment with IV golimumab appeared to be safe and well tolerated with no new or unexpected safety signals observed.

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/s/

ROSEMARIE NEUNER
06/14/2013

SUSAN L LIMB
06/14/2013

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125433	Brand Name	TRADENAME
OCP Division (I, II, III, IV, V)	II	Generic Name	Golimumab
Medical Division	570	Drug Class	Anti-TNFalpha
OCP Reviewer	Liang Zhao, Ph.D.	Indication(s)	RA
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	50 mg/4 mL vial
Pharmacometrics Reviewer	TBD	Dosing Regimen	2 mg/kg intravenous infusion at weeks 0, 4, and every 8 weeks
Date of Submission	September 18 th , 2012	Route of Administration	Intravenous infusion
Estimated Due Date of OCP Review	June 10 th , 2013	Sponsor	Jassen Biotech, Inc.
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	July 19 th 2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X			Referred to 3 phase I studies with the SC BLA submission (BLA#: 125289)
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	X	2	2	PopPK analysis and exposure-response analysis
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

___ Yes ___

This BLA submission (BLA125433) is fileable from a Clinical Pharmacology standpoint. Submission is supported by Phase III (efficacy and safety) trials. Please refer to the attached filing meeting slides for details.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement



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Bottomline Assessment

- **Fileable from Clin Pharm perspective**
 - Relevant datasets are included in submission
- **Mid-Cycle Deliverables:**
 - Evaluations of potential factors leading to PK variability
 - Evaluation of exposure-response analysis
 - Preliminary assessment of labeling language
 - DDI language
 - Immunogenicity
 - MOA

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Background

- Human monoclonal antibody that binds to both the soluble and transmembrane human TNF α
- Currently approved for the treatment of RA, PsA, AS
- Approved dosing regimen: 50 mg SC once a month, monotherapy or in combination with DMARDS
- Proposed dosing regimen: 2 mg/kg IV infusion at weeks 0 and 4, then every 8 weeks
- Separate BLA:
 - First BLA #: 125289 for SC
 - Current BLA #: 125433 for IV

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Summary of Prior PK in RA Patients

- Bioavailability in HV: 53%
- Tmax in RA population: 2-6 days
- Dose-proportional in RA patients (0.1-10 mg/kg IV)
- T1/2: 2 weeks in HV, patients with RA, PsA, or AS
- Time to reach SS with QM dosing: week 12
- Co-treatment with MTX
 - increases trough concentrations at SS
 - Decreases ADA from 7% to 2%
- Renal/hepatic impairment
 - No formal study of the effect of renal or hepatic impairment on the PK of golimumab was conducted.
- PopPK results regarding effects of important covariates
 - CL/F has no correlation with comed (ie, NSAIDS, corticosteroids, or sulfasalazine), gender for RA and PsA, age, and race
 - CL/F increase with increasing BW, (no meaningful observed clinical difference)
- IM+ patients generally had lower steady-state serum trough concentrations

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Clinical pharmacology studies in submission

- **Clinical pharmacology data available from**
 - **Three Phase I studies (i.e., C0466T01, C0524T14, and C0524T15, from SC submission BLA125289)**
 - C0466T01: FIH
 - C0524T14 and C0524T15: PK studies
 - **Two Phase III studies (i.e., C0524T12 and CNTO148ART3001, new information for this submission)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Summary of Clinical Pharmacology Related Studies

Study ID/Subject Population/Phase	Location of CSR in eCTD	Dose Regimen ^a	Route of Administration ^b	Number of PK Subjects ^c	Sampling Scheme ^d
C0466T01/RA Phase 1	24-Week SC submission, BLA, Sequence 0000	IV: 0.1, 0.3, 1.0, 3.0, 6.0 or 10.0 mg/kg single dose	IV	26	Intensive
C0524T14/RA Phase 1	52-Week/104-Week SC submission, sBLA, Sequence 0069	IV: 2 mg/kg Days 1 and 85 SC: 100 mg q4w through Week 20	IV/SC ^e	16 ^e	Intensive
C0524T15/HS Phase 1	52-Week/104-Week SC submission, sBLA, Sequence 0069	IV: 100 mg single dose or SC: 100 mg single dose	IV/SC ^e	22 ^e	Intensive
C0524T12/RA Phase 3	Current	IV: 2 mg/kg and 4 mg/kg q12w	IV	642	Sparse
CNT0148ART30 01/RA Phase 3	Current	IV: 2 mg/kg at Weeks 0, 4, and q8w thereafter	IV	463	Sparse

^a q12w = every 12 weeks, q8w = every 8 weeks

^b IV = intravenous

^c PK subjects (Non-compartmental analyses [NCA] for Phase 1, Population PK for Phase 3)

^d Intensive sampling schemes enable determination of the full PK profile using a non-compartmental analysis. Sparse sampling schemes require a model-based approach to characterize the pharmacokinetics adequately.

^e Although both IV and SC administrations were studied in C0524T14 and C0524T15, only IV data are presented in this document

Abbreviations: HS = healthy subjects; RA = subjects with active rheumatoid arthritis; PK = pharmacokinetics; BLA = biologics license

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Bioassay

- PK: enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescent immunoassays (ECLIA)
 - Studies using ELISA: C0466T01
 - Studies using MSD ECLIA: C0524T14, C0524T12 (LTE), CNT0148ART3001
 - Studies using ^{(b) (4)} ECLIA: C0524T12 (through week 48),
 - LOQs
 - ELISA: 0.078 mcg/mL in a sample with 1:10 dilution
 - ^{(b) (4)} ECLIA: 0.2 mcg/mL in a sample with 1:10 dilution
 - MSD ECLIA: 0.039 mcg/mL in a sample with 1:5 dilution
 - Assays are the same as used for SC application (BLA125289)
- IM: A validated enzyme immunoassay (EIA) method

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

PopPK analysis

- **Data derived from RA subjects after IV administration:**
 - Phase 1 study C0524T14: intensive PK sampling
 - Two Phase III studies C0524T12 and CNTO148ART3001: sparse sampling
 - why not to include studies from C0466T01 and C0524T15?
 - Drug source: C0466T01 was from an earlier cell line (C0466D)
 - Formulation: C0466T01 used a different formulation
 - Assay:
 - ELISA for C0466T01; ECLIA for in C0524T14, C0524T12, and CNTO148ART3001;
 - Population: C0524T15 in healthy subjects
 - Study design: the available covariate information from C0466T01 and C0524T15 were limited.
- **Demographics evaluated:**
 - Intrinsic factors: weight, age, gender, race, immune response (IR, ie, antibodies to golimumab), albumin, CRP, baseline swollen joint count, baseline tender joint count, diabetes status and white blood cell count (WBC)
 - Extrinsic factors: Smoking status and the use of concomitant MTX

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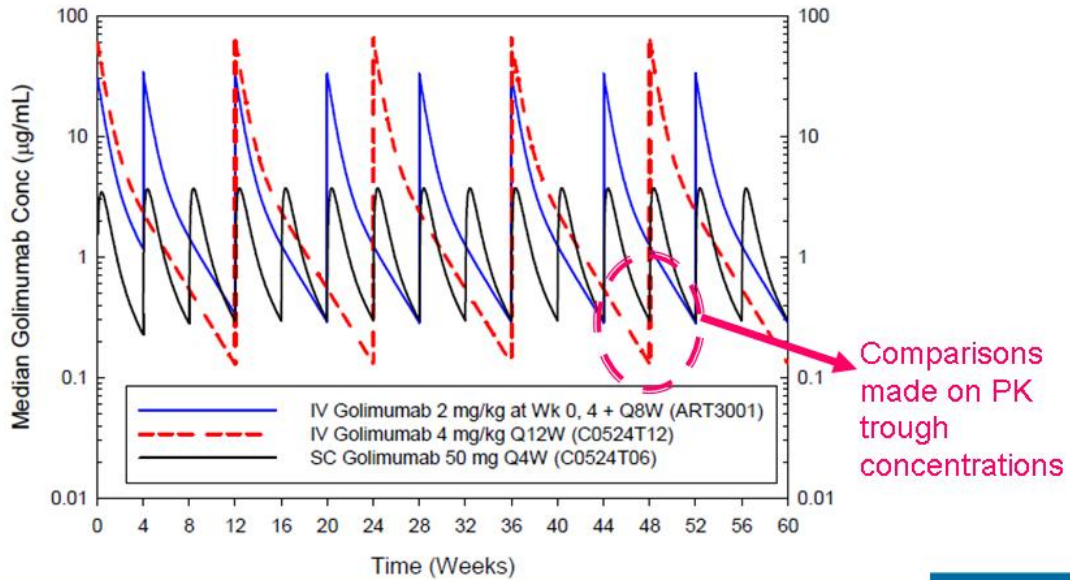
Pop PK Results

- Population PK analysis showed that body weight was a significant covariate on golimumab PK
 - When administered on a mg/kg (body weight) basis, higher concentrations with higher body weight
 - No substantial differences in golimumab PK profiles for subjects across different ranges of body weights
 - Consistent treatment benefit was seen for all subjects CSR, Section 5.1.3 and Attachment 2.4).
- Covariate analysis did NOT warrant dose adjustment based on
 - albumin level, CRP level, or concomitant use of MTX

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Sponsor's PK rationale for the proposed dosing regimen

Figure 7: Median Serum Golimumab Concentration-Time Profiles Following IV or SC Administration of Golimumab



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Exposure-response analysis

- Explored the relationship between ACR responses (ACR 20/ACR 50/ACR 70) and golimumab exposure
- Used data through Week 24 from studies CNT0148ART3001 and C0524T12
- Developed an indirect drug response model to simultaneously fit ACR 20/ACR 50/ACR 70 response rates through a latent variable approach

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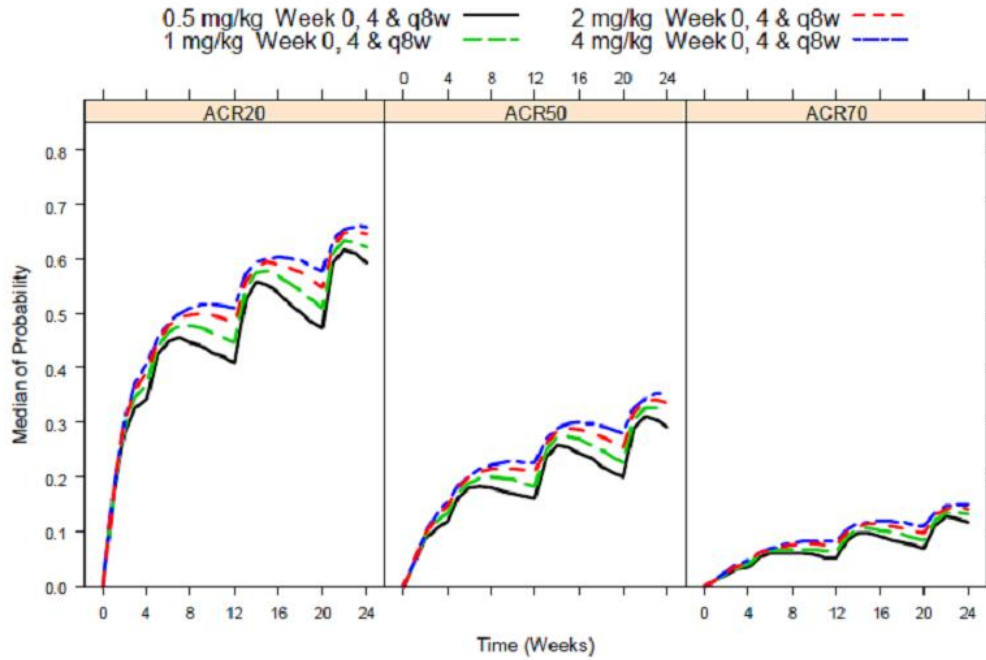
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Major Exposure-Response Modeling & Simulation Conclusions From Sponsor

- When ACR responses for IV golimumab 0.5 to 4 mg/kg given at Weeks 0, 4, and q8w + MTX were simulated, the 2 mg/kg dose level provided the desired ACR responses and increasing the dose to 4 mg/kg did not substantially increase ACR responses as compared with the 2 mg/kg at Weeks 0, 4, and q8w + MTX dosing regimen
- The proposed dosing regimen of golimumab 2 mg/kg administered IV at Weeks 0, 4, and q8w + MTX is well suited to achieve the desired ACR responses

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Figure 6: Comparison of Simulated Probability of Achieving ACR20, ACR50 and ACR70 between Dosing Regimens of Golimumab 0.5mg/kg, 1mg/kg, 2mg/kg and 4mg/kg at Week 0, 4 & Q8W



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Immunogenicity

- The combined antibody to golimumab incidence across all subjects treated in the two Phase 3 IV studies was 4.6% (26/560) and 7.0% (43/613) through weeks 48 and 52, respectively
- Through week 52, for subjects who did not receive MTX (golimumab monotherapy) the antibody to golimumab incidence was 12% (30/251) while the incidence was 4.2% (39/922) for subjects who were treated with golimumab + MTX
- For those subjects who were positive for antibodies to golimumab in CNT0148ART3001, 100% were positive for neutralizing antibodies
- IM+ → lower PK concentration

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/s/

LIANG ZHAO
11/07/2012

SURESH DODDAPANENI
11/08/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

MICROBIOLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 20 June 2013
To: Administrative File, STN 125433/0
From: Reyes Candau-Chacon, Ph.D., Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB
Subject: New Biologic License Application (BLA) Review Addendum
US License: 1864
Applicant: Janssen Biotech, Inc.
Facilities: Cilag AG, Hochstrasse 201, CH-8200 Schaffhausen, Switzerland (FEI #1018495)
Product: Simponi Aria FVP (IV) (golimumab)
Dosage: Sterile, single-use solution at a concentration of 12.5 mg/mL (50 mg/4 mL solution) in glass vials to be delivered by intravenous infusion at 2 mg/kg
Indication: Treatment of moderate to severely active Rheumatoid Arthritis (RA) in adults in combination with methotrexate
Due date: 19 July 2013

The purpose of this addendum is to report the submission of the Certificate of Analysis for the Rabbit Pyrogen Test performed in one commercial batch of Golimumab FVP (IV) DP. The sponsor submitted the CoA to the BLA on June 14, 2013 in amendment 0021. Results from the Rabbit Pyrogen Test for the two remaining batches will be submitted to the BLA as a post-marketing commitment.

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/s/

REYES CANDAU-CHACON
06/21/2013

PATRICIA F HUGHES TROOST
06/21/2013



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 21 May 2013
To: Administrative File, STN 125433/0
From: Reyes Candau-Chacon, Ph.D., Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB
Subject: New Biologic License Application (BLA)
US License: 1864
Applicant: Janssen Biotech, Inc.
Facilities: Cilag AG, Hochstrasse 201, CH-8200 Schaffhausen, Switzerland (FEI #1018495)
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Dosage: Sterile, single-use solution at a concentration of 12.5 mg/mL (50 mg/4 mL solution) in glass vials to be delivered by intravenous infusion at 2 mg/kg
Indication: Treatment of moderate to severely active Rheumatoid Arthritis (RA) in adults in combination with methotrexate
Due date: 19 July 2013

Recommendation for Approvability: BLA 125433 is recommended for approval from a microbial control, CMC sterility assurance and microbiology product quality perspective with the following post-marketing commitments:

1. Increase in-process control sample size (b) (4) and adjust acceptance criteria (b) (4)
(b) (4)
2. (b) (4). In addition, after production of 10 batches using the new bioburden sample size action and alert limits will be implemented. These changes will be submitted to the Agency in the Annual Report for BLA 125433, once approved.
(b) (4)
3. Perform the Rabbit Pyrogen Test in two additional batches of golimumab FVP (IV) DP and submit results to the Agency in a CBE-0 by September 2013.
4. Perform LAL spiking studies in undiluted golimumab FVP (IV) DP samples and test the samples after different hold times and submit the results to the Agency in the next Annual Report for BLA 125433 once approved.

Review Summary

Janssen Biotech, Inc. has submitted BLA 125433 to license golimumab for infusion and the associated drug product manufacturing process. This BLA cross-references the approved BLA 125289 golimumab (SIMPONI) for subcutaneous injection using a liquid prefilled syringe with autoinjector for the treatment for Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis. The DS manufacturing process for BLA 125433 is identical to that referenced in BLA 125289. Golimumab is a monoclonal antibody that binds to the trans-membrane bioactive forms of human tumor necrosis factor TNF α preventing the binding of TNF α to its receptor and inhibiting TNF α biological activity. Golimumab FVP (IV) is intended to be used in combination with methotrexate in adult patients with moderate to severely active Rheumatoid Arthritis.

BLA 125433 was submitted in eCTD on September 19, 2012. This review contains the assessment of the manufacturing process of golimumab FVP (IV) drug product form a sterility assurance and microbiology product quality perspective. The drug substance review is cross-referenced to BLA 125289.

Amendments Reviewed for Drug Product Quality Microbiology

Information Request date	Question numbers	Amendment sequence	Amendment date
04-Feb-2013	All (1-21) except 4e	0009	20-Feb-2013
02-Apr-2013	2d,4a,4b, 6a,6b,11f, 14b, 17c	0011	15-Apr-2013
17-Apr-2013	6a,6b,17c	0012	03-May-2013
18-April-2013	4e	0012	03-May-2013

Review Narrative

FDA Information Request 1

Information and validation of washing, depyrogenation, and sterilization processes of product-contact parts and equipment is included in the Appendix section. Amend the BLA to include that information in Module 3.

Sponsor Response in Amendment 0009

The sponsor will amend the BLA to include validation of washing, depyrogenation, and sterilization processes of product-contact parts and equipment in section 3.2.P.3.5.

Satisfactory

P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

Golimumab FVP (IV) DP is supplied as a sterile solution in a single-use 4 mL Type I glass vial sealed with an (b) (4) plastic flip-off cap. The final formulation contains 12.5 mg/mL golimumab (50

mg/4mL), 9.5 mM L-histidine (total), 4.5% (w/v) sorbitol, and 0.015% (w/v) polysorbate 80 (PS80), at pH 5.5.

Satisfactory

(b) (4)



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Conclusion

I. The Drug Product section of this BLA was reviewed from a CMC sterility assurance and microbiology product quality perspective and is recommended for approval with the following post-marketing commitments:

1. Increase in-process control sample size (b) (4) and adjust acceptance criteria (b) (4)

[Redacted]

In addition, after production of 10 batches using the new bioburden sample size action and alert limits will be implemented. These changes will be submitted to the Agency in the Annual Report for BLA 125433, once approved.

2. [Redacted] (b) (4)

[Redacted]

3. Perform the Rabbit Pyrogen Test in two additional batches of Golimumab FVP (IV) DP and submit results to the Agency in a CBE-0 by September 2013.
4. Perform LAL spiking studies in undiluted Golimumab FVP (IV) DP samples and test the samples after different hold times and submit the results to the Agency in the next Annual Report for BLA 125433 once approved.

II. The non-microbial aspects of the BLA should be reviewed by OBP/DMA.

III. An inspection waiver was issued for Cilag AG, Schaffhausen.

FDA Information Request for Golimumab FVP (IV), (b) (4)

IR1

Information and validation of washing, depyrogenation, and sterilization processes of product-contact parts and equipment is included in the Appendix section. Amend the BLA to include that information in Module 3.

IR2 - P.2.5 Microbial Attributes

- a. Clarify if the samples used in the container closure integrity tests (microbial and dye ingress) have been validated outside the normal operating range for crimping speed and crimping forces. Crimping speed and crimping forces should reflect worst-case operating conditions.
- b. Clarify if the microbial ingress test has been validated (b) (4).
- c. Include the (b) (4) test as part of your acceptance criteria for the microbial ingress test.
- d. Provide sensitivity (limit of detection) of both methods (microbial and dye ingress) correlated to breach size.
- e. Describe dye ingress controls and submit control results.

IR 3 - P.3.3 Description of Manufacturing Process and Process Controls

(b) (4)

IR 4 - P.3.4 Control of Critical Steps and Intermediates

- a. Justify your bioburden acceptance criteria (b) (4)
(b) (4) We recommend using a two tier system for microbial quality IPCs, with action limits based on impact to product quality and process understanding and alert limits based on historical trend data.
- b. Justify your IPC bioburden sample volume. We recommend increasing sample volumes to 100 mL.
- c. Indicate actions to be taken if acceptance criteria are exceeded.
- d. Indicate if (b) (4) are tested for integrity after use and provide acceptance criteria.

(b) (4)

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IR 14 - P.3.5.6 Shipping Validation

a. Indicate shipping routes and conditions of Golimumab FVP (IV) to the packaging and labeling site and to its final destination. b. Submit shipping validation protocol and shipping validation report. The shipping validation report should demonstrate the ability of the shipping containers to maintain controlled temperatures and to protect drug product and container closure integrity (b) (4) during shipping under worst-case conditions.

IR 15 - P.5.1 Specifications for Release and End of Shelf-life

Conduct container closure integrity in lieu of sterility as your end of shelf-life specification.

IR 16 - P.5.2 Analytical Procedures

- a. Submit description of the sterility test and indicate the number of DP vials used for the test.
- b. The endotoxin analytical method is referred to section 3.2.S.4.2 of the BLA. However this BLA does not have a Drug Substance section. Submit your endotoxin analytical method to the Agency and amend the BLA to include the method in section 3.2.P.5.2.

IR 17 - P.5.3 Validation of Analytical Procedures

- a. Describe the sterility suitability test, (b) (4)
- b. Clarify what “Placebo” stands for in the endotoxin interference test.
- c. Provide information and summary data for the rabbit pyrogen test of Golimumab FVP (IV) in conformance to 21CFR610.13 (b) or provide justification for not performing the test.

IR 18 - P.5.4 Batch Analysis

Submit in-process results related to microbial quality (endotoxin, bioburden, and sterility) for all DP batches manufactured to the current date.

IR 19 - P.8.2 Post-Approval Stability Protocol and Stability Commitment

Include container closure integrity in lieu of sterility as part of your stability program. Container closure integrity should be assessed annually and at expiry.

**Reviewer Comments to Sponsor Response to Information Request (Amendment 0009)
Comments to Sponsor Response to IR-2b**

Indicate how sensitivity of either method (microbial ingress and dye ingress) was determined. Sensitivity should be correlated to breach size using breached containers. Since the microbial and dye ingress validations were conducted with different pressure and time challenges, in order to assess if the dye ingress method is more sensitive than the microbial ingress method, sensitivity of both methods should be correlated to breach size. Otherwise, both methods should be validated using the same challenge conditions.

Comments to Sponsor Response to IR-4a and b

New sample size, new acceptance criteria, and reevaluation of alert and action limits should be submitted to the Agency in the next Annual Report.

(b) (4)

Comments to Sponsor Response to IR-17b

Non-endotoxin pyrogens will not be detected by the LAL test. Your response is adequate provided the rabbit pyrogen test was performed for the approved BLA 125289. Otherwise, the rabbit pyrogen test should be performed as per 21CFR610.13.b. In addition, the Agency has recently been informed that the LAL endotoxin assay may underestimate the amount of endotoxin in DP formulated with polysorbate.

(b) (4)

(b) (4)

Reviewer Comments to Sponsor Response Submitted on April 17, 2013

Comments to Sponsor Response to IR-6a and 6b

(b) (4)

Comments to Sponsor Response to IR-17c

Indicate when results from the Rabbit Pyrogen Test for two additional Golimumab FVP (IV) DP lots will be submitted to the Agency.

Reviewer Comments to Sponsor Response Submitted on April 18, 2013

IR 4 - P.3.4 Control of Critical Steps and Intermediates

- e) Please amend the BLA to include integrity test (b) (4) in section 3.2.P.3.4 “Control of Critical Steps and Intermediates”.

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/s/

REYES CANDAU-CHACON
05/22/2013

PATRICIA F HUGHES TROOST
05/23/2013

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA/NDA Number:
STN 125433/0
Established/Proper Name:
golimumab FVP (IV)

Applicant:
Janssen Biotech, Inc.
BLA/NDA Type:
52 week submission

Stamp Date:

January 14, 2013

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed ☐ including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: ☐ PI –non-annotated ☐ PI –annotated ☐ PI (electronic) ☐ Medication Guide ☐ Patient Insert ☐ package and container ☐ diluent ☐ other components ☐ established name (e.g. USAN) ☐ proprietary name (for review)	Y Y N Y N Y N Y N Y N Y N Y N Y N Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include: ☐ legible ☐ English (or translated into English) ☐ compatible file formats ☐ navigable hyper-links ☐ interpretable data tabulations (line listings) & graphical displays ☐ summary reports reference the location of individual data and records ☐ all electronic submission components usable (e.g. conforms to published guidance)	Y Y Y Y Y Y	
Companion application received if a shared or divided manufacturing arrangement	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	Table of contents in 2.3.P
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	Refer to STN 125289 already approved Defer to OBP Defer to OBP Comparability protocols: not applicable
☐ Drug Substance	N	
☐ Drug Product	Y	
☐ Facilities and Equipment	Y	
☐ Adventitious Agents Safety Evaluation	Y N	
☐ Novel Excipients	Y N	
☐ Executed Batch Records	Y	
☐ Method Validation Package	Y	
☐ Comparability Protocols	N	

CTD Module 3 Contents	Present ?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]	N	Refer to STN 125289 already approved
☐ general info		
☐ nomenclature		
☐ structure (e.g. sequence, glycosylation sites)		
☐ properties		
☐ manufacturers (names, locations, and responsibilities of all sites involved)		
☐ description of manufacturing process and process control		
☐ batch numbering and pooling scheme		
☐ cell culture and harvest		
☐ purification		
☐ filling, storage and shipping		
☐ control of materials		
☐ raw materials and reagents		
☐ biological source and starting materials		
☐ cell substrate: source, history, and generation		
☐ cell banking system, characterization, and testing		
☐ control of critical steps and intermediates		
☐ justification of specifications		
☐ stability		
☐ process validation (prospective		

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present ?	If not, justification, action & status
- plan, results, analysis, and conclusions) ☐ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) ☐ characterization of drug substance ☐ control of drug substance ☐ specifications ☐ justification of specs. ☐ analytical procedures ☐ analytical method validation ☐ batch analyses ☐ reference standards ☐ container closure system ☐ stability ☐ summary ☐ post-approval protocol and commitment ☐ pre-approval ☐ protocol ☐ results ☐ method validation		
Drug Product [3.2.P] [Dosage Form] ☐ description and composition ☐ pharmaceutical development ☐ preservative effectiveness ☐ container-closure integrity ☐ manufacturers (names, locations, and responsibilities of all sites involved) ☐ batch formula ☐ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ☐ controls of critical steps and intermediates	Y Y N Y Y Y Y Y	NA. FEI Numbers are missing OBP lead. Defer to OBP Microbial controls Microbial controls

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present ?	If not, justification, action & status
☐ process validation including aseptic processing & sterility assurance: ○ Filter validation ○ Component, container, closure depyrogenation and sterilization validation ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer validation ○ Other needed validation data (hold times)	Y	Sterility assurance
	N	Microbial retention test is in P.2.3.4. Validation of ^{(b) (4)} integrity test is missing. Addressed through IR.
	Y	This section is included in 3.2.A.1.
	Y	This section is included in 3.2.A.1
	Y N	NA – No lyophilizer used
	Y	Bioburden validation
☐ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	OBP lead. Defer to OBP
☐ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	Sterility and endotoxin
☐ reference standards or materials	Y N	NA- OBP lead. Defer to OBP
☐ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ○ administration device(s)	Y	
☐ stability ☐ summary ☐ post-approval protocol and commitment ☐ pre-approval ○ protocol ○ results ○ method validation	Y	Sterility and endotoxin

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present ?	If not, justification, action & status
Diluent (vials or filled syringes) [3.2P']	Y N	NA- No diluent included
☐ description and composition of diluent	Y N	
☐ pharmaceutical development	Y N	
☐ preservative effectiveness		
☐ container-closure integrity	Y N Y N	
☐ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
☐ batch formula		
☐ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N Y N Y N	
☐ controls of critical steps and intermediates		
☐ process validation including aseptic processing & sterility assurance:	Y N	
☐ Filter validation		
☐ Component, container, closure depyrogenation and sterilization validation	Y N	
☐ Validation of aseptic processing (media simulations)	Y N	
☐ Environmental Monitoring Program	Y N	
☐ Lyophilizer sterilization validation		
☐ Other needed validation data (hold times)	Y N	
☐ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
☐ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
☐ reference standards	Y N	
☐ container closure system		

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present ?	If not, justification, action & status
☐ specifications (vial, elastomer, drawings) ☐ availability of DMF & LOAs ☐ stability ☐ summary ☐ post-approval protocol and commitment ☐ pre-approval ☐ protocol ☐ results	Y N	
Other components to be marketed (full description and supporting data, as listed above): ☐ other devices ☐ other marketed chemicals (e.g. part of kit)	Y N Y N	NA
Appendices for Biotech Products [3.2.A] ☐ facilities and equipment ☐ manufacturing flow; adjacent areas ☐ other products in facility ☐ equipment dedication, preparation, sterilization and storage ☐ procedures and design features to prevent contamination and cross-contamination ☐ adventitious agents safety evaluation (viral and non-viral) e.g.: ☐ avoidance and control procedures ☐ cell line qualification ☐ other materials of biological origin ☐ viral testing of unprocessed bulk ☐ viral clearance studies ☐ testing at appropriate stages of production ☐ novel excipients	Y Y N Y N	OBP lead. Defer to OBP OBP lead. Defer to OBP
USA Regional Information [3.2.R] ☐ executed batch records	Y	OBP lead. Defer to OBP

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present ?	If not, justification, action & status
☐ method validation package	Y	Endotoxin and sterility.
☐ comparability protocols	Y N	NA
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	Defer to OBP
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	Defer to OBP
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	Defer to OBP
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	Microbial product quality tests.
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ☐ LAL instead of rabbit pyrogen ☐ mycoplasma ☐ sterility	Y N Y N Y	Rabbit pyrogen test missing and addressed through IR Defer to OBP
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	Defer to OBP
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reyes Candau-Chacon, PhD	January 14, 2013
Product Quality Reviewer	Date

Patricia Hughes, PhD	January 14, 2013
Team Leader	Date

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/s/

REYES CANDAU-CHACON
01/14/2013

PATRICIA F HUGHES TROOST
02/11/2013

PRODUCT QUALITY (Biotechnology)

FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number:

Applicant:

Stamp Date:

125433

Janssen

Sept 18, 2012

Established/Proper Name:

BLA/NDA Type:

golimumab

BLA

On initial overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	☒ Y ☐ N	
Form 356h completed	☒ Y ☐ N	Form 3674 present
☐ including list of all establishment sites and their registration numbers	☒ Y ☐ N	
Comprehensive Table of Contents	☒ Y ☐ N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	☒ Y ☐ N	
Labeling:	☐ Y ☐ N	
☐ PI –non-annotated	☒ Y ☐ N	
☐ PI –annotated	☒ Y ☐ N	
☐ PI (electronic)	☒ Y ☐ N	
☐ Medication Guide	☒ Y ☐ N	
☐ Patient Insert	☐ Y ☐ N	N/A
☐ package and container	☒ Y ☐ N	
☐ diluent	☐ Y ☐ N	N/A
☐ other components	☐ Y ☐ N	N/A
☐ established name (e.g. USAN)	☒ Y ☐ N	
☐ proprietary name (for review)	☒ Y ☐ N	In follow-up submitted at 10-22-2012

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	☒ Y ☐ N	
☐ legible	☐ Y ☐ N	
☐ English (or translated into English)	☐ Y ☐ N	
☐ compatible file formats	☐ Y ☐ N	
☐ navigable hyper-links	☐ Y ☐ N	
☐ interpretable data tabulations (line listings) & graphical displays	☐ Y ☐ N	
☐ summary reports reference the location of individual data and records	☐ Y ☐ N	
☐ all electronic submission components usable (e.g. conforms to published guidance)	☐ Y ☐ N	
Companion application received if a shared or divided manufacturing arrangement	☐ Y ☐ N	N/A

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	☒ Y N	
Introduction to the summary documents (1 page) [2.2]	☒ Y N	
Quality overall summary [2.3]	☒ Y N	
☐ Drug Substance	☒ Y N	
☐ Drug Product	☒ Y N	
☐ Facilities and Equipment	☒ Y N	
☐ Adventitious Agents Safety Evaluation	☒ Y N	
☐ Novel Excipients	☒ Y N	
☐ Executed Batch Records	Y N	N/A
☐ Method Validation Package	Y N	N/A
☐ Comparability Protocols	Y N	N/A

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	☒ Y N	
Drug Substance [3.2.S]		Not applicable, cross-references original Simponi BLA (125289)
Drug Product [3.2.P] [Dosage Form]		
☐ description and composition	☒ Y N	
☐ pharmaceutical development	☒ Y N	
☐ preservative effectiveness	Y N	NA, the product is single use w/o preservative
☐ container-closure integrity	☒ Y N	
☐ manufacturers (names, locations, and responsibilities of all sites involved)	☒ Y N	
☐ batch formula	☒ Y N	
☐ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	☒ Y N	
☐ controls of critical steps and intermediates	☒ Y N	
☐ process validation including aseptic processing & sterility assurance:	☒ Y N	
☐ Filter validation		
☐ Component, container, closure depyrogenation and sterilization validation		

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
☐ Validation of aseptic processing (media simulations) ☐ Environmental Monitoring Program ☐ Lyophilizer validation ☐ Other needed validation data (hold times) ☐ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin) ☐ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities) ☐ reference standards or materials ☐ container closure system [3.2.P.7] ☐ specifications (vial, elastomer, drawings) ☐ availability of DMF & LOAs ☐ administration device(s) ☐ stability ☐ summary ☐ post-approval protocol and commitment ☐ pre-approval ☐ protocol ☐ results ☐ method validation	☒ Y N ☒ Y N ☒ Y N ☒ Y N ☒ Y N	
Diluent (vials or filled syringes) [3.2P']		N/A there is no diluent
Other components to be marketed (full description and supporting data, as listed above):		N/A, there are no other components
Appendices for Biotech Products [3.2.A] ☐ facilities and equipment ☐ manufacturing flow; adjacent areas ☐ other products in facility ☐ equipment dedication, preparation, sterilization and storage ☐ procedures and design features	☒ Y N	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
to prevent contamination and cross-contamination ☐ adventitious agents safety evaluation (viral and non-viral) e.g.: ☐ avoidance and control procedures ☐ cell line qualification ☐ other materials of biological origin ☐ viral testing of unprocessed bulk ☐ viral clearance studies ☐ testing at appropriate stages of production ☐ novel excipients	Y N	N/A This is performed on drug substance. Drug substance information was submitted in BLA 125289
	Y N	
USA Regional Information [3.2.R] ☐ executed batch records ☐ method validation package ☐ comparability protocols	☒ N ☒ N Y N	N/A There are no CPs
Literature references and copies [3.3]	☒ N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	☒ N	
Includes data demonstrating consistency of manufacture	☒ N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	☒ N	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	☒ N	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	☒ N	
Certification that all facilities are ready for inspection	Y N	N/A Ciling Ab is licensed to produce other products & inspected in past
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test	☒ N	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?		If not, justification, action & status
methods used and time intervals for product assessment.			
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ☐ LAL instead of rabbit pyrogen ☐ mycoplasma ☐ sterility	Y	N	N/A, Janssen used Compendial methods
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	N	N/A, this product is exempt from PPA lot testing
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	☒	N	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	☒	N	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?

Yes No

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

[Signature]

Oct 31 2012

Product Quality Reviewer(s)

Date

[Signature]

31 Oct 2012

Branch Chief/Team Leader/Supervisor

Date

[Signature]

10/31/2012

Division Director

Date

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/s/

KURT A BRORSON
11/28/2012

DAVID M FRUCHT
11/29/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

PROPRIETARY NAME REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Proprietary Name Review—Final

Date: June 6, 2013

Reviewer: Teresa McMillan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Drug Name(s): Simponi Aria (Golimumab)
Injection

Strengths: 50 mg/4 mL

Application Type/Number: BLA 125433

Applicant/Sponsor: Jansen Biotech, Inc

OSE RCM #: 2013-839

*** This document contains proprietary and confidential information that should not be released to the public.***

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4	REFERENCES.....	4

1 INTRODUCTION

This re-assessment of the proposed proprietary name, Simponi Aria is written in response to the anticipated approval of this BLA within 90 days from the date of this review. DMEPA found the proposed name, Simponi Aria, acceptable in OSE Review #2013-106 dated April 2, 2013.

2 METHODS AND DISCUSSION

For re-assessments of proposed proprietary names, DMEPA searches a standard set of databases and information sources (see section 4) to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review. For this review we used the same search criteria described in OSE Review #2013-106. We note that none of the proposed product characteristics were altered. However, we evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. The searches of the databases yielded no new names, thought to look or sound similar to Simponi Aria and represent a potential source of drug name confusion.

Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. The Safety Evaluator did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of June 5, 2013.

3 CONCLUSIONS

The re-evaluation of the proposed proprietary name, Simponi Aria, did not identify any vulnerability that would result in medication errors with any additional names noted in this review. Thus, DMEPA has no objection to the proprietary name, Simponi Aria, for this product at this time.

DMEPA considers this a final review; however, if approval of the BLA is delayed beyond 90 days from the date of this review, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

If you have further questions or need clarifications, please contact Nichelle Rashid, OSE project manager, at 301-796-3904.

4 REFERENCES

1. OSE Reviews

2. *Drugs@FDA* (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved [brand name](#), [generic drugs](#), [therapeutic biological products](#), [prescription](#) and [over-the-counter](#) human drugs and [discontinued drugs](#) and “[Chemical Type 6](#)” approvals.

3. *USAN Stems* (<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page?>)

USAN Stems List contains all the recognized USAN stems.

4. *Division of Medication Error Prevention and Analysis Proprietary Name Consultation Request*

Compiled list of proposed proprietary names submitted to the Division of Medication Error Prevention and Analysis for review. The list is generated on a weekly basis from the Access database/tracking system.

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

/s/

TERESA S MCMILLAN
06/06/2013

LUBNA A MERCHANT
06/06/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Proprietary Name Review

Date: April 2, 2013

Reviewer: Teresa McMillan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, PharmD, MPH
Division of Medication Error Prevention & Analysis

Division Director: Carol Holquist, RPh,
Division of Medication Error Prevention & Analysis

Drug Name(s): Simponi Aria (Golimumab)
Injection

Strengths: 50 mg/4 mL

Application Type/Number: BLA 125433

Applicant/Sponsor: Jansen Biotech, Inc

OSE RCM #: 2013-106

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Simponi Aria, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

This Biologic License Application is currently under review with the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). The first and second proposed proprietary names, [REDACTED]^{(b) (4)} were found unacceptable by DMEPA in OSE Reviews #2011-4198, and 2012-2551 respectively.

On January 2, 2013, Jansen Biotech, Inc submitted a request to the Agency for an assessment of the proposed proprietary name under BLA 125433.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission.

- Active Ingredient: Golimumab
- Indication of Use: In combination with methotrexate is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis
- Route of Administration: Intravenous
- Dosage Form: Injection
- Strength: 50 mg/4 mL (12.5 mg/mL)
- Dose and Frequency: 2 mg/kg administered intravenously at weeks 0, 4 and every 8 weeks thereafter over 30 minutes
- How Supplied: Available in packs of 1 vial (50 mg/4 mL vial) in each carton
- Storage: Refrigerated at 2°C to 8°C and protect from light

2. RESULTS

The following sections provide the information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion OPDP determined the proposed name is acceptable from a promotional perspective. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) indicated that the use of the modifier ‘Aria’ was promotional given that arias are beautiful or expressive melodies. In addition, DPARP stated that the intravenous and subcutaneous formulations are different products with different efficacy profiles. DPARP expressed concerns that there may be a greater chance that people will assume that both formulations work the same with the same root name, especially since the subcutaneous formulation has no modifier. DPARP’s preference would be a unique name that is evocative of “Simponi”, so people know that they were

both golimumab, but still different. DPARP also noted that this was not a formal objection.

OPDP reevaluated the name, taking into consideration DPARP’s concerns and maintained their position. Neither DPARP or DMEPA objected to OPDP’s final decision regarding the promotional aspect of the name, Simponi Aria.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) SEARCH

The January 8, 2013 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The proprietary name is comprised of two words, the root name ‘Simponi’ and the modifier ‘Aria’. The Applicant did not indicate in their submission an intended meaning or derivation for the modifier ‘Aria’. Also, the Applicant did not provide data to support that the modifier is not error prone or a source of confusion. This product will be added to the existing “Simponi” product line that is comprised of a prefilled syringe and an autoinjector, both of which are administered subcutaneously. This product is administered intravenously. Therefore, we have evaluated whether or not the proposed name requires the modifier, evaluated the appropriateness of the chosen modifier ‘Aria’, and considered if this product should utilize a totally different proprietary name to help differentiate the route of administration and the product presentation from the existing product line. Our evaluation of these issues is discussed in Section 2.2.7.

2.2.3 Medication Error Data Selection of Cases

DMEPA searched the AERS database for medication errors involving Simponi which would be relevant for this review using the search strategy in Table 1.

Table 1: AERS Search Strategy	
Date: January 31, 2013	Date range- May 24, 2011- January 31, 2013 (the search was limited to the last date of our AERS search in OSE RCM #2011-1133 and 2011-1412)
Drug Names	Active Ingredient- *GOLIMUMAB* Product Name Name-*SIMPONI*
MedDRA Search Strategy	Medication Errors HLT Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

This search strategy yielded 133 cases. Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case.

The search yielded no cases of name confusion relevant to this review.

2.2.4 FDA Name Simulation Studies

Seventy-eight practitioners participated in DMEPA’s prescription studies. One participant identified the currently marketed product “Simponi”. Eight participants interpreted the name correctly as “Simponi Aria”. The remaining participants provided incorrect responses. The remaining misinterpretations from all responses occurred with the letter ‘S’ being misinterpreted for the letters ‘L’, ‘Z’, and ‘C’, the letter ‘i’ for the letter ‘e’ and ‘y’, the letter ‘m’ for the letter ‘n’, the letter ‘p’ for the letters ‘c’ and ‘t’, the letter ‘o’ for the letters ‘a’, ‘e’, ‘i’, the letter ‘n’ for the letters ‘u’, ‘r’, ‘v’, and the letter strings ‘in’ and ‘nm’, the letter ‘i’ for the letters ‘r’ and ‘y’ and the letter string ‘ee’, the letter ‘A’ for the letters ‘R’, ‘S’, ‘E’, the letter ‘r’ for the letters ‘e’ and the letter string ‘ir’, the letter ‘i’ for the letters ‘r’, and ‘e’, and the letter ‘a’ for the letter ‘s’, ‘q’, ‘f’, and letter strings ‘ap’, ‘ate’, ‘eat’ and ‘ya’. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines at Initial Review

See comments provided by DPARP in Section 2.1.

2.2.6 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Simponi Aria. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Simponi Aria identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, and External Name Study)

Look Similar					
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Sumycin	FDA	Arava	FDA	Sinequan	FDA
Semprex-D	FDA	Sensipar	FDA	Ara-C	FDA
Axid	FDA	Auro	FDA	Auvi-Q	FDA
AVC	FDA	Avar	FDA		
Look and Sound Similar					
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Simponi	FDA				

Our analysis of the 12 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined 11 names will not pose a risk for confusion as described in Appendices D through E. One name, Simponi, poses some risk for confusion and this risk is described further in Section 2.2.7.

2.2.7 FMEA of the Modifier Aria for this product

The Applicant proposes to use the modifier ‘Aria’ to differentiate the intravenous injectable vial formulation from the currently marketed, Simponi (Golimumab) pre-filled syringe and autoinjector subcutaneous formulations.

There are several differences between the proposed formulation and the current marketed formulations. These differences are listed in Table 2 below.

Table 2.

	Simponi Aria	Simponi
Indication of Use	Treatment of Rheumatoid Arthritis	Treatment of Rheumatoid Arthritis, Active Psoriatic Arthritis, and Active Ankylosing Spondylitis
Route of Administration	Intravenous	Subcutaneous
Strength	50 mg/4 mL (12.5 mg/mL)	50 mg/0.5 mL
Dose and Frequency	2 mg/kg administered at weeks 0, 4, and every 8 weeks thereafter	50 mg once monthly
How Supplied	50 mg/4 mL vial, each in a carton	50 mg/0.5 mL single dose prefilled SmartJect autoinjector, 50 mg/0.5 mL in a single dose prefilled syringe

In addition, the proposed formulation’s efficacy profile appears to differ from the currently marketed product, Simponi (Golimumab), although review is still ongoing. At the time of this review, the safety profile of the proposed product was undetermined by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP).

Due to the differences among these products we concluded that it would not be appropriate to use the same name (i.e. market both formulations simply as Simponi). Given the need to distinguish the proprietary nomenclature of these products and the Applicant’s proposal to use the Simponi name with the addition of a modifier, we considered the following: (1) whether a modifier could adequately distinguish the two products and whether the modifier proposed is appropriate and (2) if a modifier is insufficient to distinguish the currently marketed product whether marketing the product under a unique name be appropriate.

2.2.7.1 Safety assessment of the modifier

Some proprietary names are constructed of a root name and more than one word or component. The addition of words or components are referred to as the modifier portion of the proprietary name, The modifier portion of a proprietary drug name may be a letter, number, word, or combination of letters, numbers, and words attached to the beginning, middle or end of a root proprietary drug name There is an existing practice of naming drug products within a product line with the same root proprietary name (existing

name marketed) and a modifier to distinguish various products marketed under the same root name.

Generally speaking, drug manufacturers name employ modifiers that convey characteristics about the drug such as ODT for orally-disintegrating tablets, or XR to signal the product is extended-release. In these circumstances, the lack of standardization of these proprietary drug name modifiers has led to misinterpretation of the intended meaning of the modifier resulting in confusion and errors in dispensing and administering the wrong drug, wrong formulation, wrong dose, wrong strength, and wrong frequency of administration. Additionally, the omission or oversight of modifiers in prescribing, dispensing, and administration has been cited as a source of error, particularly for those drugs that use modifiers to distinguish between members of the same product line.

Less commonly, modifiers are used to denote a specific formulation or packaging configuration (e.g., Zyprexa Relprevv and Nicoderm CQ.). In some circumstances, these modifiers do not have any intended meaning or derivation and may not explicitly communicate or relate to the difference between the products. In other words, these modifiers serve only to indicate there is a difference between two products (e.g. Zyprexa Relprev differs in some way from Zyprexa) but does not communicate the nature of the difference. We note that the modifier “Aria” is this sort of modifier, and does not have any proposed meaning and no data was submitted by the Applicant to support that the modifier communicates a meaning (intended or otherwise).

Due to the errors identified with drug name modifiers the Institute of Medicine and the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) requested FDA develop standards around drug name modifiers. The IOM also recommended that FDA and industry collaborate to develop a common drug nomenclature that standardizes abbreviations, acronyms, and terms, to the extent possible.¹ Additionally, NCC MERP requested FDA and the pharmaceutical industry evaluate the proprietary name modifier to determine the potential for errors that could occur in any phase of the medication use process before marketing.²

Whenever manufacturers decide to use a modifier as part of their proprietary name, given the recommendations put forward by the IOM, FDA strongly encourages the use of an existing modifier with an established meaning. However, there are no consistent terms used to represent the proposed differences in the Simponi and Simponi Aria product characteristics listed in Table 2 of Section 2.2.7, and we cannot envision a modifier that would safely relay the differences³. Therefore, we conclude that using a novel modifier

¹ Preventing Medication Errors: Quality Chasm Series, July 2006, Ch. 6, Page 274.

² Promoting the Safe Use of Suffixes in Prescription Drug Names, December 2007, <http://www.nccmerp.org/council/council2008-08-01.html>

³ (b) (4) was previously proposed to convey the difference in the route of administration between the two products. However, we identified a number of safety issues related to the use (b) (4) and ultimately found the name unacceptable in OSE Review #2011-4198.

that does not relate to the product characteristics is the only viable option for this firm if a modifier is to be employed.

Given the applicant's proposal to use a modifier, we evaluated the potential risk of confusion within the Simponi product line. Our search of the AERS database did not identify any confusion with the existing Simponi product. We note that by adding a modifier to 'Simponi, the two existing packaging configurations, a pre-filled syringe and autoinjector, are further differentiated from the intravenous formulation. If a prescription is written for 'Simponi Aria', it is unlikely a prefilled syringe or autoinjector will be dispensed. Thus, the name offers a distinguishing factor that is not currently seen within the current product line.

However, we also note that omission and oversight of a modifier is cited in literature⁴ as a common cause of medication error. Postmarketing experience shows that the introduction of product line extensions result in medication errors if the modifier is omitted and the product characteristics are similar or overlap. Although there are several differences in the product characteristics, omission and oversight of the modifier was still evident in our name simulation studies in which one participant omitted the modifier. We considered the potential safety implications of this error. We asked DPARP to opine on the potential safety concerns, and the clinical staff noted that there are no significant clinical concerns if the approved subcutaneous formulation of golimumab is administered intravenously or if the proposed intravenous formulation of golimumab is administered subcutaneously. The only exception is a painful injection may occur if the proposed 4 mL intravenous formulation is administered subcutaneously given the volume. We also note there is a possibility of wrong dose errors if the modifier is omitted. The Simponi prefilled syringe and autoinjector is available in 50 mg only. Thus, if a Simponi Aria prescription is misinterpreted as Simponi there is a possibility that wrong dose errors may occur.

Finally, we considered whether Aria itself is a suitable modifier from a safety perspective. We found that Aria is not a medical abbreviation, does not contain a USAN stem, and does not appear to present any overt safety concerns from a look or sound alike perspective.

2.2.7.2 Safety of using a unique name to market this product

An alternative to using a modifier to distinguish this product from the currently marketed products is to use a totally different root name. However, introducing a total new proprietary name for this product also carries a risk of medication errors. Specifically, marketing the new product under a unique name may lead to additional medication errors such as therapeutic duplication and overdoses. These errors may have greater associated safety risks than the omission or oversight of the modifier as discussed in Section 2.2.7.1. Therefore, for the aforementioned reasons listed in Sections 2.2.7.1, and 2.2.7.2. DMEPA finds that the proprietary name 'Simponi Aria,' although not free from the risk of error, offers a safer approach to naming this product.

⁴ Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

2.2.8 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) via e-mail on March 25, 2013. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on March 25, 2013, they stated no additional concerns with the proposed proprietary name, Simponi Aria.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

If you have further questions or need clarifications, please contact Nichelle Rashid, OSE project manager, at 301-796-3904.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Simponi Aria, and have concluded that this name is acceptable. The proposed proprietary name will be re-reviewed 90 days prior to approval of the NDA. The results are subject to change. If any of the proposed product characteristics as stated in your submission are altered, the name must be resubmitted for review.

4 REFERENCES

1. ***Micromedex Integrated Index*** (<http://csi.micromedex.com>)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO***
(<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

7. ***U.S. Patent and Trademark Office*** (<http://www.uspto.gov>)

USPTO provides information regarding patent and trademarks.

8. ***Clinical Pharmacology Online*** (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common,

combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

10. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

11. Access Medicine (www.accessmedicine.com)

Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. USAN Stems (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)

USAN Stems List contains all the recognized USAN stems.

13. Red Book (www.thomsonhc.com/home/dispatch)

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

14. Lexi-Comp (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

15. Medical Abbreviations (www.medilexicon.com)

Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

16. CVS/Pharmacy (www.CVS.com)

This database contains commonly used over the counter products not usually identified in other databases.

17. Walgreens (www.walgreens.com)

This database contains commonly used over the counter products not usually identified in other databases.

18. Rx List (www.rxlist.com)

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. Dogpile (www.dogpile.com)

Dogpile is a [Metasearch](#) engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

20. Natural Standard (<http://www.naturalstandard.com>)

Natural Standard is a resource that aggregates and synthesizes data on complementary and alternative medicine.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.⁵

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

⁵ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.⁶

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

⁶ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	Considerations when Searching the Databases		
	<i>Potential Causes of Drug Name Similarity</i>	<i>Attributes Examined to Identify Similar Drug Names</i>	<i>Potential Effects</i>
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	- Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication - Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the

safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically

scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁷ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product

⁷ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And are there any components of the name that may function as a source of error beyond sound/look-alike?”

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

- a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

APPEARS THIS WAY ON ORIGINAL

Appendix B: Letters and Letter Strings with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Simponi	Scripted May Appear as	Spoken May Be Interpreted as
Capital 'S'	G, 5, L, Z	'C', 'Z', S
lower case 's'	a, n, r, G, g,	'c', 'z', 'x'
lower case 'i'	c, e, j, l,r	any vowel, ee, y
lower case 'm'	n, v, z, w, wi, vi, onc, m, mn,	'n'
lower case 'p'	g, j, l, q, yn, ys	'b', 'c', 't'
lower case 'o'	a, c, e, .i, u	any vowel, 'oh'
lower case 'n'	m, u, x, r, h, s,v	'm', 'mn'
Letters in Modifier, Aria	Scripted May Appear as	Spoken May Be Interpreted as
Capital 'A'	FL, H, Ci, O, S	Any vowel,
lower case 'a'	el, ci, cl, d, o, u, c, e,q	Any vowel
lower case 'r'	e, n, s, v	'w', 'wr'
Letter Strings	Scripted May Appear as	Spoken May Be Interpreted as
ri	w	
ra	u	
ia		'f', 'ap', 'ate', 'eat', 'ya'

Appendix C: Prescription Simulation Samples and Results

Figure 1. Simponi Aria (Conducted on 1/17/2013)

Handwritten Requisition Medication Order	Verbal Prescription
<u>Medication Order:</u> Simponi Aria 130mg IV over 30 minutes	Simponi Aria Bring to infusion clinic #3
<u>Outpatient Prescription:</u> Simponi Aria Sig: Bring to infusion clinic Disp: #3	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

Study Name: Simponi Aria

As of Date 2/13/2013

192 People Received Study

78 People Responded

Study Name: Simponi Aria

	Total	30	25	23
INTERPRETATION	INPATIENT	VOICE	OUTPATIENT	TOTAL
?	0	1	0	1
CINTONI RES	0	1	0	1
LINPONI SEIA	1	0	0	1
SEMPEUR ARIA	0	0	1	1
SENPOINI SEIA	1	0	0	1
SENPONI SERA	1	0	0	1
SIMPANI ARIA	0	0	1	1
SIMPARI ARIA	0	0	2	2
SIMPENI ARIA	0	0	3	3
SIMPERI	0	0	1	1
SIMPERI ARIA	0	0	1	1
SIMPERI ARIQ	0	0	1	1
SIMPEUI ARIA	0	0	1	1
SIMPEUR ARIA	0	0	1	1
SIMPINI ARIA	0	0	1	1
SIMPIONI ARIA	0	0	1	1

SIMPONI	0	1	0	1
SIMPONI AIRIA	0	0	1	1
SIMPONI AREA	0	1	0	1
SIMPONI ARIA	0	1	7	8
SIMPONI EREAP	0	1	0	1
SIMPONI ERIA	0	1	0	1
SIMPONI RES	0	2	0	2
SIMPONI SEIA	1	0	0	1
SIMPONI SERA	7	0	0	7
SIMPONI SIRA	6	0	0	6
SIMPORI SIRA	1	0	0	1
SIMPOVI ARIA	0	0	1	1
SINCONNEE REF	0	1	0	1
SINPONI RES	0	2	0	2
SINPONI SEIA	2	0	0	2
SINPONI SERA	6	0	0	6
SINPONI SIRA	2	0	0	2
SINPONIARIA	0	1	0	1
SINPORI SERA	1	0	0	1
SINPOUI SIRA	1	0	0	1
SINTONI	0	1	0	1
SYMPONI	0	1	0	1
SYMPONI AREA	0	1	0	1
SYMPONI ARIA	0	1	0	1
SYMPONI ARIATE	0	2	0	2
SYMPONI RES	0	1	0	1

SYMPONY AREA	0	1	0	1
SYMPONY AREAT	0	1	0	1
SYMPONY ARIA	0	1	0	1
SYMPONY ERIYA	0	1	0	1
ZINPONI ARIA	0	1	0	1

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name		Active Ingredient	Similarity to Simponi Aria	Failure preventions
1	Sinequan	Doxepin	Look alike	The name was evaluated in OSE Simponi Proprietary Name Review #2008-1069 as a potential look alike. To date, there has been no name confusion identified with Simponi.
2	Semprex D	Acrivastine; Pseudoephedrine	Look alike	The name was evaluated in OSE Simponi Proprietary Name Review #2008-1069 as a potential look alike. To date, there has been no name confusion identified with Simponi.
3	Sensipar	Cinacalcet	Look alike	The name was evaluated in OSE Simponi Proprietary Name Review #2008-1069 as a potential look alike. To date, there has been no name confusion identified with Simponi.

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

Proposed name: Simponi Aria (Golimumab) Dosage form(s): Solution for Injection Strength(s): 50 mg/4 mL (12.5 mg/mL) Usual dose: 2 mg/kg administered intravenously at weeks 0, 4 and every 8 weeks thereafter over 30 minutes	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names	
1	Sumycin (Tetracycline)-discontinued <u>Capsules</u> 500 mg <u>Oral Suspension/Syrup</u> 125 mg/5mL <u>Tablets</u> 250 mg, 500 mg <u>Usual Dose</u> 250 mg-1000 mg given in 2-4 divided doses. Max dose 4 grams/day.	<u>Similarities</u> <u>Orthographics</u> The letter string ‘Summy’ when scripted appears similar to the letter string ‘Simp’.	<u>Differences</u> <u>Strength</u> Simponi Aria is available as a single strength which does not require a strength to be written on the prescription vs. Sumcyin is available in multiple strengths (i.125 mg/ 5mL, 250 mg, 500 mg) which would require a strength on a prescription. <u>Usual Dose</u> 1 -2 tablet, 2-4 teaspoonfuls vs. 2 mg/kg <u>Frequency of Administration</u> 2-4 times daily vs. Once at weeks 0 and 4, then every 8 weeks

Proposed name: Simponi Aria (Golimumab) Dosage form(s): Solution for Injection Strength(s): 50 mg/4 mL (12.5 mg/mL) Usual dose: 2 mg/kg administered intravenously at weeks 0, 4 and every 8 weeks thereafter over 30 minutes	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names	
2	Arava (leflunomide) <u>Tablet</u> 10 mg, 20 mg, 100 mg <u>Usual Dose</u> Loading dose- 100 mg once daily for 3 days Maintenance dose- 20 mg once daily. Max dose- 20 mg/day	<u>Similarities</u> <u>Orthographics</u> Both names begin with the letter string 'Ar' and end with the letter 'a'. The letter string 'va' when scripted appears similar to the letter string 'ia'. <u>Usual Dose and Strength (achievable)</u> 100 mg	<u>Differences</u> <u>Orthographics</u> The infix letter 'a' in the name Arava provides sufficient differentiation between the modifier Aria by elongating the name Arava. <u>Frequency of Administration</u> Once at weeks 0 and 4, then every 8 weeks vs. Once daily

Proposed name: Simponi Aria (Golimumab) Dosage form(s): Solution for Injection Strength(s): 50 mg/4 mL (12.5 mg/mL) Usual dose: 2 mg/kg administered intravenously at weeks 0, 4 and every 8 weeks thereafter over 30 minutes	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names	
3	ARA-C (synonym for Cytarabine) <u>Suspension for Injection</u> 50 mg/5 mL <u>Usual Dose</u> 50 mg intrathecally (intraventricular or lumbar puncture) over 1—5 minutes every 14 days during induction and consolidation weeks 1, 3, 5, 7, and 9; give an additional 50 mg intrathecally at week 13. For maintenance therapy, 50 mg intrathecally every 28 days for 4 doses on weeks 17, 21, 25, and 29.	<u>Similarities</u> <u>Orthographics</u> Both names begin with the letter string ‘Ar’. The letter ‘c’ when scripted appears similar to the letter ‘a’. <u>Strength (similarity)</u> 50 mg/4 mL vs. 50 mg/5 mL	<u>Differences</u> <u>Usual Dose</u> 50 mg vs. 2 mg/kg <u>Frequency of Administration</u> Every 14 days during induction and consolidation weeks 1, 3, 5, 7, and 9 or every 28 days for 4 doses on weeks 17, 21, 25, and 29 vs. Once at weeks 0 and 4, then every 8 weeks

Proposed name: Simponi Aria (Golimumab) Dosage form(s): Solution for Injection Strength(s): 50 mg/4 mL (12.5 mg/mL) Usual dose: 2 mg/kg administered intravenously at weeks 0, 4 and every 8 weeks thereafter over 30 minutes	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
4 Axid (nizatidine)- capsules discontinued <u>Capsules</u> 150 mg, 300 mg <u>Oral Solution</u> 15 mg/mL <u>Usual Dose</u> 150 mg PO twice daily or 300 mg once daily	<u>Similarities</u> <u>Orthographics</u> The letter string ‘Ax’ when scripted appears similar to the letter string ‘Ar’. The letter string ‘id’ when scripted appears similar to the letter string ‘ia’. <u>Strength (achievable)</u> 50 mg/4 mL vs. 150 mg, 300 mg <u>Usual Dose</u> 150 mg	<u>Differences</u> <u>Orthographics</u> The name Axid contains two upstrokes (‘A’, ‘d’) vs. the name Aria contains one upstroke (‘A’) giving them different shapes when scripted. <u>Frequency of Administration</u> 1-2 times daily vs. Once at weeks 0 and 4, then every 8 weeks

Proposed name: Simponi Aria (Golimumab) Dosage form(s): Solution for Injection Strength(s): 50 mg/4 mL (12.5 mg/mL) Usual dose: 2 mg/kg administered intravenously at weeks 0, 4 and every 8 weeks thereafter over 30 minutes	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names	
5	Auro Ear Drops or Auro Earache Relief (carbamide peroxide) discontinued <u>Solution</u> 6.5% <u>Usual Dose</u> Instill 5—10 drops twice daily in the affected ear(s) for up to 4 days. Keep drops in ear for 5 minutes by keeping head tilted or placing cotton in ear. Do not use for more than 4 days.	<u>Similarities</u> <u>Orthographics</u> The letter string ‘Au’ when scripted appears similar to the letter string ‘Ar’. The letter string ‘ro’ when scripted appears similar to the letter string ‘ia’. <u>Strength</u> Both are available as a single strength which does not require a strength to be written on the prescription.	<u>Differences</u> <u>Usual Dose</u> 5-10 drops/instillation vs. 2 mg/kg <u>Frequency of Administration</u> Twice daily vs. Once at weeks 0 and 4, then every 8 weeks

Proposed name: Simponi Aria (Golimumab) Dosage form(s): Solution for Injection Strength(s): 50 mg/4 mL (12.5 mg/mL) Usual dose: 2 mg/kg administered intravenously at weeks 0, 4 and every 8 weeks thereafter over 30 minutes	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
6 Auvi-Q (epinephrine) <u>Solution for Injection (autoinjector)</u> 0.15 mg/0.15 mL 0.3 mg/0.3 mL <u>Usual Dose</u> 0.15 mg-0.3 mg intramuscularly for one dose	<u>Similarities</u> <u>Orthographics</u> The letter string ‘Au’ when scripted appears similar to the letter string ‘Ar’. The letter string ‘vi’ when scripted appears similar to the letter string ‘ia’	<u>Differences</u> <u>Orthographics</u> The name Auvi-Q contains one upstroke (‘A’) and one downstroke (‘q’) vs. the modifier Aria contains one upstroke (‘A’) and no downstroke (‘p’) giving them different shapes when scripted. <u>Strength</u> Simponi Aria is available as a single strength which does not require a strength to be written on the prescription vs. Auvi-Q is available in multiple strengths (i.e. 0.15 mg/0.15 mL , 0.3 mg/0.3 mL which would require a strength on a prescription. <u>Usual Dose</u> 0.15 mg -0.3 mg vs. 2 mg/kg <u>Frequency of Administration</u> Once vs. Once at weeks 0 and 4, then every 8 weeks

Proposed name: Simponi Aria (Golimumab) Dosage form(s): Solution for Injection Strength(s): 50 mg/4 mL (12.5 mg/mL) Usual dose: 2 mg/kg administered intravenously at weeks 0, 4 and every 8 weeks thereafter over 30 minutes	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names	
7	AVC (sulfanilamide) <u>Vaginal cream</u> 15 % <u>Usual Dose</u> Use 1 applicatorful vaginally once or twice daily for 30 days.	<u>Similarities</u> <u>Orthographics</u> The letter string ‘Av’ when scripted appears similar to the letter string ‘Ar’. The letter ‘c’ when scripted appears similar to the letter s ‘a’. <u>Strength</u> Both are available as a single strength which does not require a strength to be written on the prescription.	<u>Differences</u> <u>Usual Dose</u> 1 applicatorful vs. 2 mg/kg <u>Frequency of Administration</u> Once-Twice daily vs. Once at weeks 0 and 4, then every 8 weeks

Proposed name: Simponi Aria (Golimumab) Dosage form(s): Solution for Injection Strength(s): 50 mg/4 mL (12.5 mg/mL) Usual dose: 2 mg/kg administered intravenously at weeks 0, 4 and every 8 weeks thereafter over 30 minutes	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names	
8	Avar (Sulfacetamide;sulfur) <u>Topical suspension (cleanser)</u> 10%-5% <u>Usual Dose</u> Wash affected area(s) as directed for 10 to 20 seconds once or twice per day.	<u>Similarities</u> <u>Orthographics</u> The letter string ‘Av’ when scripted appears similar to the letter string ‘Ar’. The letter string ‘ar’ when scripted appears similar to the letter string ‘ia’. <u>Strength</u> Both are available as a single strength which does not require a strength to be written on the prescription.	<u>Differences</u> <u>Usual Dose</u> Affected areas vs.2 mg/kg <u>Frequency of Administration</u> Once-Twice daily vs. Once at weeks 0 and 4, then every 8 weeks

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/s/

TERESA S MCMILLAN
04/02/2013

LUBNA A MERCHANT
04/02/2013

KELLIE A TAYLOR
04/02/2013

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
04/02/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

OFFICER/EMPLOYEE LIST

Officer/Employee List

Application: BLA 125433 Simponi Aria

The following officers or employees of FDA participated in the decision to approve this application *and* consented to be identified on this list:

Barnes, Sandy L.
Brorson, Kurt
Buenconsejo, Joan
Burke, Laurie B.
Candauchacon, Maria

Chung, Christine
Donohoe, Elizabeth A.
Duer, Robin
Griffiths, LaShawn
Hulett, Melissa

Hughes, Patricia
Limb, Susan
Merchant, Lubna
Neuner, Rosemarie
Pohlman, Janice

Prabhakara, Ranjani
Rains, Kimberly E.
Read, Erik
Robison, Timothy W.
Scales, Twanda

Seymour, Sally
Szydlo, Roberta
Yim, Sarah
Zhao, Liang

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) or microbiologist (BMAB) and included for each type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	125433	
Product Name:	Simponi Aria FVP (IV) (golimumab)	
PMC #4 Description:	Perform LAL spiking studies in undiluted golimumab FVP (IV) DP samples and test the samples after different hold times	
PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>07/20/2014</u>
	Other:	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAIA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Sponsor will conduct endotoxin recovery studies of undiluted golimumab FVP (IV) spiked with endotoxin and held for different times.

2. Describe the particular review issue and the goal of the study.

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Some formulations containing polysorbate have resulted in low endotoxin recovery in non-diluted samples over time. The study will assess endotoxin recovery of non-diluted samples to verify the adequacy of the endotoxin test method.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Endotoxin recovery from non-diluted drug product samples spiked with endotoxin.

5. To be completed by ONDQA/OBP/BMAB Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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SALLY M SEYMOUR
07/16/2013

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) or microbiologist (BMAB) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125433
Product Name: Simponi Aria FVP (IV) (golimumab)

PMC #3 Description: Perform the Rabbit Pyrogen Test on two batches of Golimumab FVP (IV) DP. Submit the results as a CBE-0 Supplement.

PMC Schedule Milestones:

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>MM/DD/YYYY</u>
Final Report Submission:	<u>09/30/2013</u>
Other:	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA AA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Sponsor will conduct the rabbit pyrogen test on two batches of golimumab FVP (IV) drug product per 21CFR610.13. The sponsor has submitted rabbit pyrogen test results from one batch during the first BLA review cycle, therefore additional rabbit pyrogen tests can be performed post-approval.

2. Describe the particular review issue and the goal of the study.

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The rabbit pyrogen test is an *in vivo* test to determine the presence of pyrogenic substances. Rabbit pyrogen test results were not included in the original BLA. The sponsor will perform the test in triplicate on three different batches. The results of the first batch were submitted within the first review cycle and the results of the other two batches will be submitted as a post-marketing commitment.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Rabbit pyrogen test

5. To be completed by ONDQA/OBP/BMAB Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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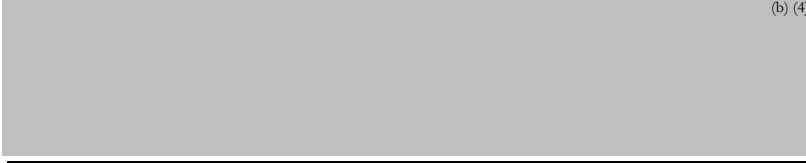
/s/

SALLY M SEYMOUR
07/16/2013

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) or microbiologist (BMAB) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125433
Product Name: Simponi Aria FVP (IV) (golimumab)

PMC #2 Description:  (b) (4)

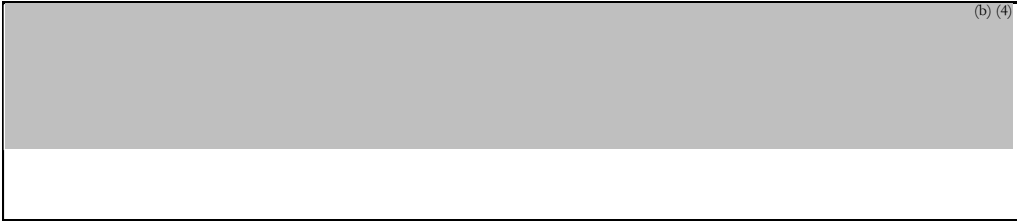
PMC Schedule Milestones:

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>MM/DD/YYYY</u>
Final Report Submission:	<u>07/20/2014</u>
Other: _____	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA A OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

 (b) (4)

2. Describe the particular review issue and the goal of the study.

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(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

(b) (4)

5. To be completed by ONDQA/OBP/BMAB Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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SALLY M SEYMOUR
07/16/2013

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) or microbiologist (BMAB) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125433
Product Name: Simponi Aria FVP (IV) (golimumab)

PMC #1 Description: Increase in-process control sample size (b) (4) and adjust acceptance criteria (b) (4).
(b) (4)
In addition, implement the new bioburden sample size action and alert limits after production of 10 batches. The Final Report Submission should include the new in-process limits.

PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 07/20/2014
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The sponsor has initiated the requalification of the bioburden assay (b) (4). This requalification is necessary to implement the new bioburden limits; therefore the new in-process bioburden limits can be submitted post-approval once requalification is complete.

2. Describe the particular review issue and the goal of the study.

Bioburden limits for in-process controls will (b) (4). The qualification study will assess if (b) (4) impact the bioburden results of in-process controls.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
 Assay
 Sterility
 Potency
 Product delivery
 Drug substance characterization
 Intermediates characterization
 Impurity characterization
 Reformulation
 Manufacturing process issues
 Other

Describe the agreed-upon study:

Requalification of bioburden assay

5. To be completed by ONDQA/OBP/BMAB Manager:

- Does the study meet criteria for PMCs?
 Are the objectives clear from the description of the PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

SALLY M SEYMOUR
07/16/2013

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #

Product Name: BLA 125433 Intravenous (IV) Golimumab (Simponi Aria®)

PMR/PMC Description: To conduct a trial that will evaluate the safety, efficacy, PK/PD and immunogenicity of IV golimumab in pediatric patients between the ages 2 to 17 years and 11 months with active Juvenile idiopathic arthritis (JIA) despite standard therapy with methotrexate.

PMR/PMC Schedule Milestones: Final Protocol Submission: 12/31/2013
Study/Trial Completion: (b) (4)
Final Report Submission: 12/31/2018
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Efficacy and safety in patients 18 years and older have been established.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The trial is a PREA requirement.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The proposed trial will evaluate the safety, efficacy, PK/PD and immunogenicity of IV golimumab in the pediatric population via a 52-week, randomized, withdrawal controlled Phase 3 trial in children ages 2 to 17 years and 11 months old with active JIA despite standard therapy with methotrexate (MTX). All subjects who complete the proposed trial will have the opportunity to participate in an open-label extension in addition to undergoing long term safety follow-up in order to determine the safety risks associated with long term exposure to IV golimumab.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

SALLY M SEYMOUR
07/16/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	SIMPONI ARIA (golimumab) injection, for intravenous use
Applicant	Janssen Biotech, Inc.
Application/Supplement Number	BLA 125433
Type of Application	Original
Indication(s)	Treatment of adult patients with moderately to severely active Rheumatoid Arthritis in combination with methotrexate
Established Pharmacologic Class ¹	Tumor Necrosis Factor Blocker
Office/Division	ODE II/DPARP
Division Project Manager	Christine Chung
Date FDA Received Application	September 18, 2012
Goal Date	July 18, 2013
Date PI Received by SEALD	July 15, 2013
SEALD Review Date	July 15, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*

Selected Requirements of Prescribing Information

• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment: *The proper name "(golimumab)" should be removed; only the drug product name "SIMPONI ARIA" should be in the HL Limitation Statement.*

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES

12. All text must be **bolded**.

Comment:

YES

13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Selected Requirements of Prescribing Information

Comment:

- NO** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment: *The statement is not centered; the Final Implementation guidance recommends that this statement be centered within the box.*

YES

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

YES

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A

17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

N/A

22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES

23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Selected Requirements of Prescribing Information

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Selected Requirements of Prescribing Information

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- NO** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

Selected Requirements of Prescribing Information

12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: The title of subsection 13.1 includes an "and" after "Mutagenesis"; the required title is: "Carcinogenesis, Mutagenesis, Impairment of Fertility".

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment: The entire cross reference should be in italics, including the outer brackets. Cross-references in 2.2, 5.1, 5.5, 5.6, 6, 6.1, 6.2, 7.1, 7.2, 7.3 and 8.1 have outer brackets that are not italicized.

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- NO** 42. All text is **bolded**.

Comment: The cross-references within the boxed warning are not bolded; the LRT and the W&P, Contraindications and BW guidance recommend that all text in the BW be bolded.

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

ELIZABETH A DONOHOE
07/15/2013

LAURIE B BURKE
07/15/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
BLA# 125433	BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name:	proposed (b) (4)	
Established/Proper Name:	golimumab for infusion	
Dosage Form:	sterile solution in vial	
Strengths:	50 mg/ 4 mL	
Applicant:	Janssen	
Agent for Applicant (if applicable):		
Date of Application:	9/18/12	
Date of Receipt:	9/18/12	
Date clock started after UN:		
PDUFA Goal Date:	7/18/13	Action Goal Date (if different):
Filing Date:	11/17/12	Date of Filing Meeting: 10/29/12
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): treatment of moderately to severely active Rheumatoid Arthritis (RA) in adults, in combination with methotrexate		
Type of Original BLA: AND (if applicable)	☐ 505(b)(1)	☐ 505(b)(2)
Type of NDA Supplement:	☐ 505(b)(1)	☐ 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	☒ Standard	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>	☐ Priority	
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): INDs 9925, 12723, 12729				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required																			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears																			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm		✓																		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			N/A	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>			N/A	BLA
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:				

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			✓	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?				
If yes, were all of them submitted on time?				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?				
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?				
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			

<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	✓			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	✓			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>				
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>				
Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	✓			
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	✓			
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>				
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	✓			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		✓		
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)			✓	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 5/18/2009	✓			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 9/23/2011	✓			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):				
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/17/12

BLA/NDA/Supp #: BLA 125433

PROPRIETARY NAME: proposed (b) (4)

ESTABLISHED: golimumab for infusion

DOSAGE FORM/STRENGTH: 50 mg/4 mL vial

APPLICANT: Janssen Biotech, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Rheumatoid Arthritis

BACKGROUND:

Filing/Planning meeting scheduled 10/30/12 was cancelled due to Hurricane Sandy. All disciplines indicated BLA is filable and concurred with Standard review timeclock. Review issues identified have been included in the 74-day letter. Planning meeting is scheduled for 11/29/12 at which any review concerns or needs will be discussed.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christine Chung	
	CPMS/TL:	Sandy Barnes	
Cross-Discipline Team Leader (CDTL)	Susan Limb		
Clinical	Reviewer:	Rosemarie Neuner	
	TL:	Susan Limb	
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Liang Zhao	
	TL:	Suresh Doddapaneni	
Biostatistics	Reviewer:	Ruthanna Davi	
	TL:	Joan Buenconsejo	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mamata De	
	TL:	Timothy Robison	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Kurt Brorson	
	TL:	David Frucht	
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:	Kimberly Rains	
	TL:		
Facility Review/Inspection	Reviewer:	Maria Candauchacon	
	TL:	Patricia Hughes	
OSE/DMEPA (proprietary name)	Reviewer:	Teresa Mcmillan	
	TL:	Lubna Merchant	
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	
	TL:	Janice Pohlman	
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees:			

FILING MEETING DISCUSSION:

No filing meeting held. See background above. Comments provided by email.

GENERAL 505(b)(2) filing issues? If yes, list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments: None	☐ Not Applicable
CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason: New BLA but not new entity

○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	
• Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology (for sterile products)</u> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	☐ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Badrul Chowdhury, Director, DPARP	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. See letter in DARRTS <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
☒	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

CHRISTINE H CHUNG
07/12/2013

SANDRA L BARNES
07/12/2013



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date: July 11, 2013

Reviewer: Kimberly Rains, Pharm.D.
Office of Biotechnology Products

Through: Erik Read, Ph.D.
Division of Monoclonal Antibodies

Kurt Brorson, Ph.D.
Division of Monoclonal Antibodies

Application: BLA 125433/0

Product: Simponi[®] Aria (golimumab)[™]

Applicant: Janssen Biotech, Inc.

Submission Date(s): September 18, 2012, May 7, 2013, June 26, 2013, July 10, 2013

Executive Summary

The carton and container labels for Simponi[®] Aria (golimumab)[™] were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, USP 36/ NF 31 (5/1/13-12/31/13). Labeling deficiencies were identified, mitigated, and revised. Comments are listed in the conclusions section. The labels are acceptable.

Background and Summary Description

Simponi[®] (golimumab) was approved in 2009 for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and ulcerative colitis by subcutaneous injection. The product is supplied as a 50 mg/0.5 mL or 100 mg/mL prefilled syringe or Autoinjector. Janssen Biotech has submitted an original BLA 125433, for severely active Rheumatoid Arthritis

(RA) in adults, in combination with methotrexate by intravenous infusion. The product is supplied as 50 mg/4 mL vial.

Materials Reviewed:

<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6810cb0e6>

Sequence: 0000, 0014, 0022, 0025 * Labels displayed are for sequence 0000.

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions



End of Sponsor Material

Conclusions

The comments below were submitted to the applicant. Revisions were provided in amendment 0022 dated June 26, 2013 to address the comments below. The revised carton and container labels are acceptable. Additional comments were provided to the applicant from the Division of Medication Error Prevention and Analysis and generated revised labels that were submitted July 10, 2013. The labels are acceptable.

1. Container

- a. Indicate how the label is affixed to the vial and where the visual area of inspection is located as per 21 CFR 610.60 (e). Information provided.
Acceptable.

2. Carton

- a. Replace the statement, (b) (4) with the statement, "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide" in bold on all carton and container labels per 21 CFR 610.60, 21(7) and 21 CFR 208.24(d). Applicant will retain proposed statement. **Acceptable.** Medication guides primarily applies to outpatient medications.

- b. Replace the statement, [REDACTED] ^{(b) (4)} with the statement, “See package insert for dilution, dosage, and administration.” Applicant will retain proposed statement. **Acceptable**

3. Container and Carton

- a. Revise the statement, “Single-Use Vial-Discard unused portion” with the statement, “Single-Dose Vial-Discard unused portion.” and move the statement below the route of administration. **See recommended format below. Discard statement moved and Single-Use statement retained. Guidance to Industry regarding package type terminology (Single-Use vs. Single Dose) has not been finalized. The agency has no regulatory authority to enforce. **Acceptable**
- b. Move the route of administration adjacent to the proper name, “golimumab” on the line below. The agency has been working to establish a consistent presentation for the proper name, dosage form and route of administration. *See recommended format below. **Change made and acceptable**
- c. Please revise the strength presentation, “50 mg/4 mL” to include in close proximity the volume per mL (12.5 mg/mL) to comply with the United States Pharmacopeia, 5/1/13-7/31/13, USP 36/NF 31, General Chapter, Injection <1>, “STRENGTH AND TOTAL VOLUME FOR SINGLE- AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS”. *See recommended format below. **Change made and acceptable**
- d. Remove the statement, [REDACTED] ^{(b) (4)} to allow for the statements requested in 3(a). **Change made and acceptable**

4. Ferrule and cap overseal

- a. Please comment on if there is any text on the ferrule and cap overseal. A revised USP standard will go into effect on December 1, 2013. We refer you to the following information:
http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1La_beling.pdf
Information provided. **Acceptable.**

* Recommended format:

Simponi® Aria™
(golimumab)

50 mg/4 mL
(12.5mg/mL)

For Infusion only

Single-dose vial
Discard unused portion

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

/s/

KIMBERLY M RAINS
07/11/2013

ERIK K READ
07/12/2013

SARAH B KENNETT on behalf of KATHLEEN A CLOUSE STREBEL
07/12/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 1, 2013

To: Badrul A. Chowdhury, MD, PhD
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Roberta Szydlo, RPh, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): SIMPONI ARIA (golimumab)

Dosage Form and Route: Intravenous (IV)

Application Type/Number: BLA 125433

Applicant: Janssen Biotech, Inc.

INTRODUCTION

On September 18, 2012, Janssen Biotech, Inc. (Janssen) submitted for the Agency's review a new Biologics License Application (BLA) for golimumab intravenous (IV) indicated for the treatment of adult patients with moderately to severely active Rheumatoid Arthritis in combination with methotrexate. On January 2, 2013, Janssen submitted a Proprietary Name Review for SIMPONI ARIA. On May 8, 2013, the Agency found the tradename SIMPONI ARIA acceptable.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) on November 29, 2012 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SIMPONI ARIA (golimumab) For Infusion.

MATERIAL REVIEWED

- Draft SIMPONI ARIA (golimumab) For Infusion MG received on September 18, 2012 and received by DMPP on June 20, 2013
- Draft SIMPONI ARIA (golimumab) For Infusion MG received on September 18, 2012 and received by OPDP on June 21, 2013.
- Draft SIMPONI ARIA (golimumab) For Infusion Prescribing Information (PI) received on September 18, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on June 20, 2013
- Draft SIMPONI ARIA (golimumab) For Infusion Prescribing Information (PI) received on September 18, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on June 21, 2013.
- Approved Simponi (golimumab) injection, for subcutaneous use comparator labeling dated May 15, 2013.

REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

CONCLUSIONS

The MG is acceptable with our recommended changes.

RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
07/01/2013

ROBERTA T SZYDLO
07/01/2013

ROBIN E DUER
07/01/2013

LASHAWN M GRIFFITHS
07/01/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 28, 2013

To: Christine Chung, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer, Office of Prescription
Drug Promotion (OPDP)

CC: Kathleen Klemm, Acting Group Leader, OPDP

Subject: BLA 125433
OPDP labeling comments for SIMPONI ARIA (golimumab) For
Infusion

OPDP has reviewed the proposed Package Insert (PI) and Carton and Container Labeling for SIMPONI ARIA (golimumab) For Infusion (Simponi Aria) submitted for consult on November 29, 2012, and offers the following comments. OPDP's comments regarding the proposed Medication Guide will be incorporated into a collaborative review by the Division of Medical Policy Programs (DMPP) and OPDP and will follow under separate cover.

OPDP's comments on the PI are based on the proposed draft labeling titled "125433 labeling eroom 6-20-13 clean.doc" that was sent via email from DPARP to OPDP on June 21, 2013. OPDP's comments on the PI are provided directly in the marked-up document attached (see below).

OPDP has reviewed the proposed carton and container labeling submitted by the sponsor on September 18, 2012, and located in the EDR at:

- [\\cbsap58\M\CTD_Submissions\STN125433\0000\m1\us\vial-carton.pdf](\\cbsap58\M\CTD_Submissions\STN125433\0000\m1\us\vial-carton.pdf)
- [\\cbsap58\M\CTD_Submissions\STN125433\0000\m1\us\vial-carton-sample.pdf](\\cbsap58\M\CTD_Submissions\STN125433\0000\m1\us\vial-carton-sample.pdf)
- [\\cbsap58\M\CTD_Submissions\STN125433\0000\m1\us\vial-label.pdf](\\cbsap58\M\CTD_Submissions\STN125433\0000\m1\us\vial-label.pdf)

- [\\cbsap58\M\leCTD_Submissions\STN125433\0000\m1\us\vial-label-sample.pdf](\\cbsap58\M\leCTD_Submissions\STN125433\0000\m1\us\vial-label-sample.pdf)

OPDP has no comments at this time on the proposed carton and container labeling.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

19 Pages of Draft Labeling have been
Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

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/s/

ROBERTA T SZYDLO
06/28/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, and Packaging Review

Date: June 14, 2013

Reviewer: Teresa McMillan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention & Analysis

Drug Name(s): Simponi Aria (Golimumab)
Injection

Strengths: 50 mg/4mL

Application Type/Number: BLA 125433

Applicant/Sponsor: Janssen Biotech, Inc

OSE RCM #: 2012-2865

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container labels, carton labeling, insert labeling and medication guide for Simponi Aria, BLA 125433 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

On September 18, 2012, the Applicant submitted container labels, carton labeling, and insert labeling for BLA 125433. The proprietary name, Simponi Aria was granted conditionally acceptable on April 2, 2013 for this product. Thus, the applicant submitted revised container labels, carton labeling, insert labeling, and medication guide for BLA 125433 to reflect the proprietary name on May 8, 2013 and May 10, 2013 respectively.

1.2 PRODUCT INFORMATION

The following product information is provided in the May 10, 2013 submission.

- Active Ingredient: Golimumab
- Indication of Use: In combination with methotrexate is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis
- Route of Administration: Intravenous
- Dosage Form: Injection
- Strength: 50 mg/4 mL (12.5 mg/mL)
- Dose and Frequency: 2 mg/kg administered intravenously at weeks 0, 4 and every 8 weeks thereafter over 30 minutes
- How Supplied: Available in packs of 1 vial (50 mg/4 mL vial) in each carton
- Storage: Refrigerated at 2°C to 8°C and protect from light

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Simponi medication error reports. We also reviewed the Simponi Aria labels, package insert labeling, and medication guide submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES AND LITERATURE SEARCH

We used the FAERS search results and literature search documented in OSE Review #2012-2173 Label, Labeling, and Packaging Review dated April 25, 2013. In addition, the PubMed and the ISMP publications literature search documented in OSE Review #2012-2173 did not identify any additional cases.

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels and Carton Labeling submitted on May 8, 2013(Appendix B and C)
- Insert Labeling and Medication Guide submitted on May 10, 2013 (no image)
- Currently approved 50 mg/0.5 mL Prefilled Syringe and Autoinjector Labels and Carton Labeling (See Appendix D and E for images of Container Labels and Carton Labeling)

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Simponi in OSE Label, Labeling, and Packaging Review #2012-2173 dated April 25, 2013. We considered the errors retrieved in the previous review to assess if any of the cases retrieved and the medication error risk assessment issues identified is relevant to our current assessment. These cases are discussed in section 3.1.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the associated labels and labeling.

3.1 MEDICATION ERROR CASES

DMEPA previously identified two foreign cases of wrong route of administration medication errors in OSE Review #2012-2173. These cases involved golimumab that was administered intravenously instead of subcutaneously. Both cases state that this error resulted in the patients receiving an overdose. However, no root cause, dose, or outcome was reported. We note that the labels and labeling for the currently approved subcutaneous Simponi formulations adequately states the route of administration. However, the proposed labels and labeling for Simponi Aria can be improved to increase the readability and prominence of the route of administration on the labels and labeling to help mitigate these errors. This mitigation is discussed further in Section 3.2.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

This product is the first intravenous formulation of the currently marketed product Golimumab. We note that there are subcutaneous (prefilled syringe and autoinjector) formulations of Golimumab. The subcutaneous formulations are available in a 50 mg per 0.5 mL strength and administered at 50 mg once monthly. There is a risk for

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

selection errors and wrong route of administration errors because this product contains the same active ingredient, Golimumab, as Simponi and is available in 50 mg.

We previously identified cases of wrong route of administration. It is important to adequately differentiate the labels and labeling of the subcutaneous and intravenous formulations. The Applicant has included the route of administration throughout the labels and labeling. However, this information can be more prominent to help further mitigate wrong route of administration errors. In regards to potential selection errors, it is very important that the labels and labeling for this product are adequately differentiated from the currently approved Simponi line. We provide recommendations for the labels and labeling in Section 5.2 Comments to the Applicant.

In addition, we note that the insert labeling as well as the carton labeling and container labels do not express the strength per milliliter. This can be misleading and potentially result in wrong dose errors. However, this risk can be mitigated by adequately displaying the total drug content per total volume and strength per milliliter throughout the labels and labeling. We also note the general considerations for administration section of the insert labeling is unclear and does not state how long and at what temperature this product can be stored once diluted. The storage requirements after dilution are important for safe use of this product. The insert labeling also uses dangerous abbreviations such as “IV” and “SC”. The Agency discourages the use of these dangerous abbreviations because they may be interpreted as “four”, “ill” or “intravertebral” and “SL” or “sublingual”. We provide recommendations for the insert labeling as well as the labels and labeling in Section 5.1 Comment to the Division and 5.2 Comments to the Applicant.

An assessment of the medication guide indicates the proposed revisions are acceptable. However, we note the proposed container labels, carton labeling and insert labeling can be further improved to clarify important information for the healthcare practitioner.

4 CONCLUSIONS

DMEPA concludes the proposed revisions in the medication guide are acceptable. However the proposed container labels, carton labeling and insert labeling can be improved to increase the readability and prominence of important information and to clarify information on the label to mitigate any confusion.

5 RECOMMENDATIONS

DMEPA provides the following comments for consideration prior to approval of this BLA:

5.1 COMMENTS TO THE DIVISION

A. Insert Labeling

- 1 Revise Section 2.3 (b) (4) section of the insert labeling as follows:

Simponi Aria injection should be diluted to prepare an infusion solution for intravenous administration by a healthcare professional using an aseptic technique as follows:

1. Calculate the 2 mg/kg dose.
Patient's weight (kg) x 2 mg/kg of SIMPONI ARIA=Dose (mg)
2. Calculate the volume of SIMPONI ARIA needed.
Dose (mg) ÷ 12.5 mg/mL= volume of SIMPONI ARIA (mL)
3. Check that the solution is colorless to light yellow and opalescent. The solution may develop a few fine translucent particles as golimumab is a protein. Do not use if opaque particles, discoloration or other foreign particles are present.
4. Dilute the total volume of SIMPONI ARIA injection with 100 mL 0.9% Sodium Chloride Injection, USP. For example, this can be accomplished by withdrawing a volume of the 0.9% Sodium Chloride Injection, USP from the 100 mL infusion bag or bottle equal to the volume of Simponi Aria required for the dose. Slowly add the total volume of SIMPONI ARIA injection to the 100 mL infusion bag or bottle. Gently mix.
5. Prior to infusion, visually inspect the diluted SIMPONI ARIA infusion solution for particulate matter or discoloration. Do not use if these exist.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.22 micrometer or less). Do not store any unused portion of the infusion solution for reuse.
7. Do not infuse the diluted SIMPONI ARIA solution concomitantly in the same intravenous line with other agents. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of diluted Simponi ARIA solution with other agents.
8. Infuse the diluted solution over 30 minutes.

- 2 In Section 2.3, General Considerations for Administration add a statement which includes the length of time and at what temperature this product can be stored once diluted.
- 3 Revise all instances of the abbreviations "SC", and "IV" throughout the Prescribing Information and the Instructions for Use. Revise to read subcutaneously, and intravenously respectively². The abbreviation "SC"

² Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org

can be interpreted as SL or sublingual. The abbreviation IV can also be interpreted as “four”, “ill” or “intravertebral”. As part of a national campaign to prevent the use of error-prone abbreviations, FDA agreed not to approve error-prone abbreviations in labeling because they are carried to the prescribing practice.

- 4 Consider revising Section 3, Dosage Forms and Strengths to the following:

Injection, [50 mg/ mL (12.5 mg/mL)]

- 5 Revise the “How Supplied” portion of Section 16 to the following:

Simponi Aria is supplied in a single-dose vial. Each vial contains 50 mg of golimumab per 4 mL of solution (12.5 mg of golimumab per mL).

5.2 COMMENTS TO THE APPLICANT

A. General Comments [Container labels and Carton labeling]

1. The strength is listed as 50 mg/4 mL throughout the labels and labeling and does not include the strength per milliliter. Increase the prominence and bold the strength statement and revise to the following wherever presented:

50 mg/4 mL

(12.5 mg/mL)

2. Reduce the size of the colored bar that appears beneath the “For Infusion” statement. As presented, it detracts from the proprietary and established names as well as the strength.
 3. Remove the ^{(b) (4)} that appears above the proprietary name. As presented, it detracts from the proprietary and established names as well as the strength.
 4. Remove the ^{(b) (4)} statement after the proper name.
 5. Revise and increase the prominence of the route of administration to the following:
For Intravenous Infusion
 6. Delete ^{(b) (4)} because the net quantity is displayed in the strength statement.
 7. Revise the statement “Single Use Vial-Discard Unused Portion” to “Single Dose Vial-Discard Unused Portion” and relocate this statement below the route of administration.
-

B. General Comments [Professional Sample Container labels and Carton labeling]

1. Delete the phrase (b) (4) from the professional sample label and labeling.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Appendix B: Container Labels



(b) (4)

Appendix C: Carton Labeling



(b) (4)

Sample Carton Labeling

(b) (4)



Appendix D: Approved Simponi Prefilled Syringe and Autoinjector Labels

*Approved 50 mg/0.5 mL Prefilled Syringe-Trade (Note: The plain white label is the current trade label. The colors on the colored labeled cannot be seen unless held under light. This is used for security purposes to prevent counterfeiting.)

(b) (4)



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Approved 50 mg/0.5 mL Autoinjector -Trade

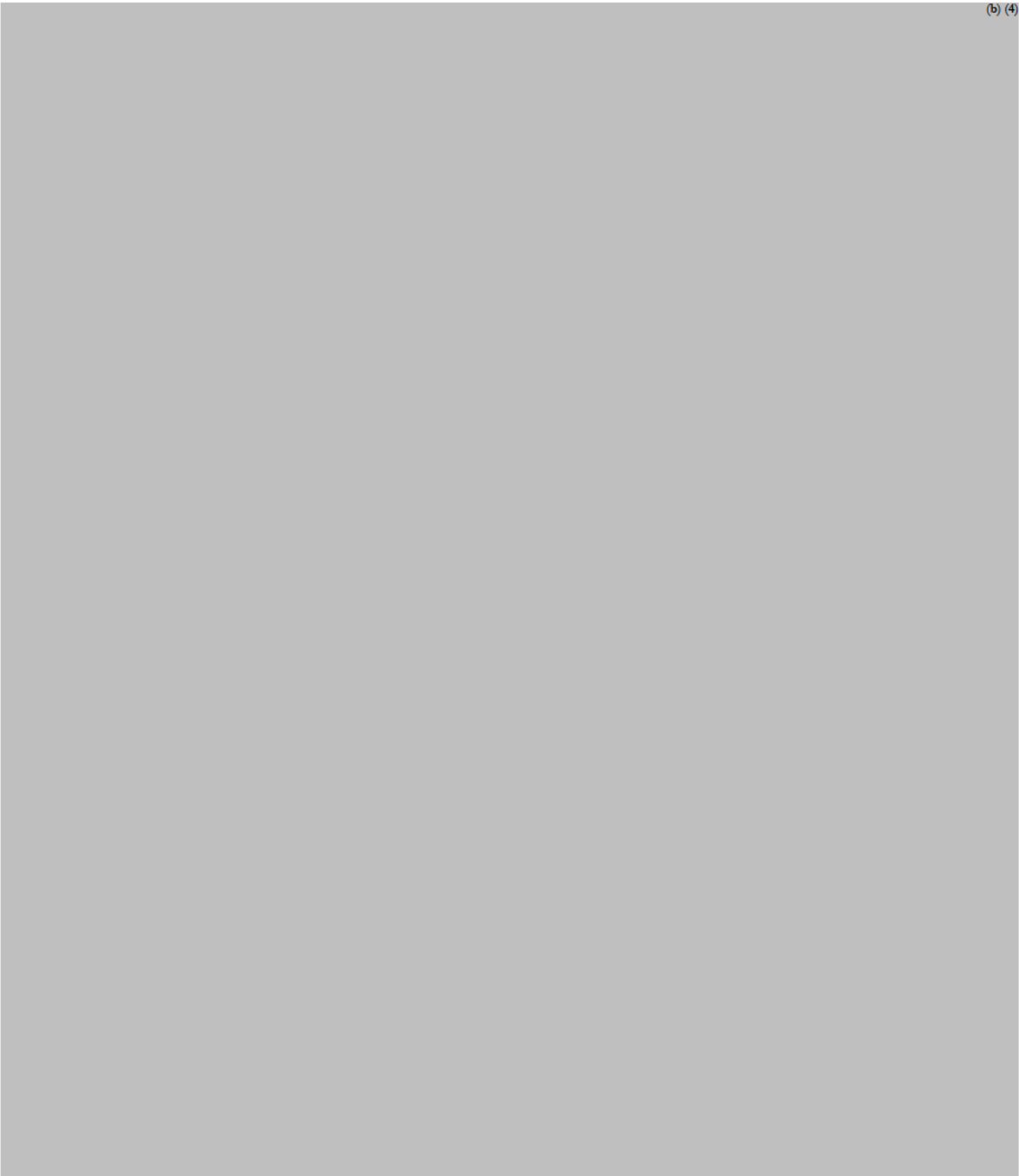


(b) (4)

Appendix E: Approved Simponi Prefilled Syringe and Autoinjector Carton Labeling

Approved 50 mg/0.5 mL Prefilled Syringe-Trade

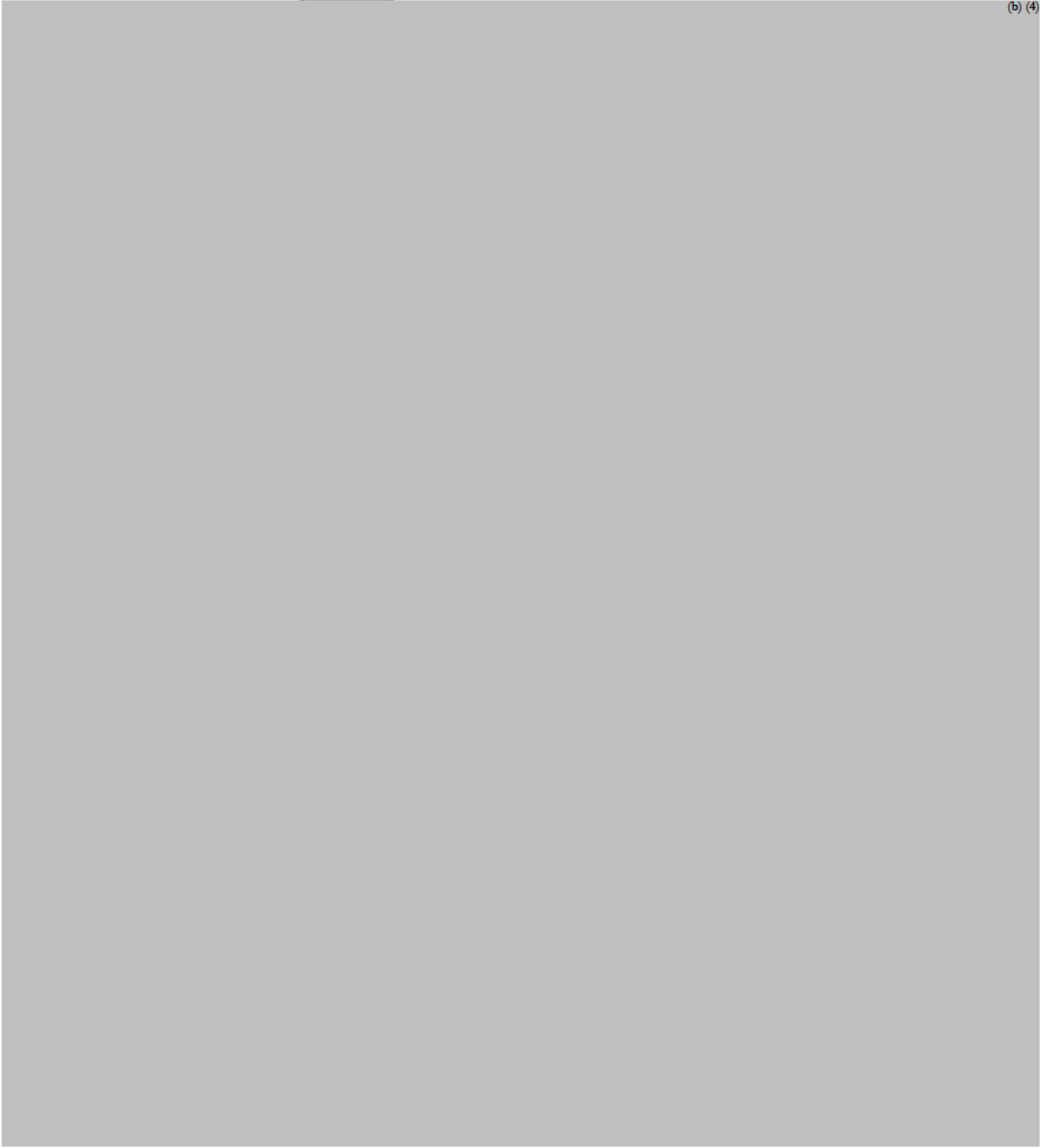
(b) (4)





Approved 50 mg/0.5 mL Autoinjector-Trade

(b) (4)



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/s/

TERESA S MCMILLAN
06/14/2013

LUBNA A MERCHANT
06/14/2013

SCOTT M DALLAS
06/14/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 5, 2013

TO: Christine Chung, Regulatory Project Manager
Susan Limb, M.D., Medical Team Leader
Rosemarie Neuner, M.D., M.P.H., Medical Officer
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125433

APPLICANT: Janssen Biotech, Inc.

DRUG: golimumab IV
NME: No

THERAPEUTIC CLASSIFICATION/REVIEW: Standard review

INDICATION: Treatment of patients with active rheumatoid arthritis

CONSULTATION REQUEST DATE: December 6, 2012 (signed)
INSPECTION SUMMARY GOAL DATE: May 31, 2013 (original)
DIVISION ACTION GOAL DATE: July 18, 2013
PDUFA DATE: July 18, 2013

I. BACKGROUND:

Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human tumor necrosis factor (TNF) alpha. This interaction prevents the binding of TNF alpha to its receptors, thereby inhibiting the biological activity of TNF alpha (a cytokine protein). The approved golimumab subcutaneous (SC) formulation is indicated for the following uses: (a) in combination with methotrexate (MTX), for the treatment of adult patients with moderately to severely active rheumatoid arthritis, (b) alone or in combination with MTX, for the treatment of adult patients with active psoriatic arthritis, and (c) the treatment of patients with active ankylosing spondylitis.

For the clinical site audit for this new IV formulation of golimumab, CDER DPARP selected a single domestic site and a single foreign site enrolling subjects in Study Protocol CNTO148ART3001. The application for Simponi™, a subcutaneous (SC) formulation of golimumab, was originally approved in April 2009.

Study Protocol CNTO148ART3001

CNTO148ART3001 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter, two-arm study of the safety and efficacy of IV golimumab. The primary objective of the study was to assess the clinical efficacy of IV administration of golimumab 2 mg/kg + MTX compared with MTX alone in subjects with active RA despite MTX therapy. The secondary objectives of this study were to evaluate the pharmacokinetics and pharmacodynamics, safety parameters, physical function and disability, and the effects on structural damage of the IV formulation of golimumab. The primary efficacy endpoint was the percentage of randomized patients with an American College of Rheumatology (ACR) 20 response at Week 14. An ACR 20 response was defined as percentage of study participants achieving at least a 20% improvement from baseline examination, based on the following sub-item component measures analyzed statistically: (1) swollen joint count (66 joints) and tender joint count (68 joints), and (2) at least 20% improvement in three of the following five assessments: (a) patient's assessment of pain, (b) patient's global assessment of disease activity (c) physician's global assessment of disease activity, (d) patient's assessment of physical function as measured by the Health Assessment Questionnaire, and (e) C-reactive protein (CRP).

II. RESULTS:

Name of CI City, State	Protocol/Study Site/ n, number of subjects	Insp. Date	Final Classification*
Melvin A. Churchill, MD Lincoln, NE	CNT0148ART3001 Site #113 n=15 subjects enrolled	December 17-19, 2012	NAI
Jacek Pazdur, M.D. Warsaw, Poland	CNT0148ART3001 Site #4810 52 subjects enrolled	February 11-15, 2013	Preliminary: NAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

1. Melvin Churchill, M.D./Protocol CNT0148ART3001 Site #113 Lincoln, NE

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from [REDACTED] (b) (4). At this site, 15 subjects were screened and enrolled, and nine subjects were randomized in the study. All nine randomized subjects completed the Week 14 primary efficacy endpoint assessment; however, only four subjects completed the entire study (Note: No specific information was provided in the clinical site audit report why there was a drop from 15 enrolled to nine randomized subjects).

An audit of nine subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Jacek Pazdur, M.D./Protocol CNTO148ART3001 Site #4810

Warsaw, Poland

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from [REDACTED]^{(b) (4)}. A total of 52 subjects were screened and enrolled, 20 subjects were randomized, and 16 subjects completed the study (Note: No specific information was provided in the clinical site preliminary inspection report why there was a drop from 52 enrolled to 20 randomized subjects. Further, Subjects 228 and 135 discontinued prior to Week 52, Subject 135 withdrew consent, and Subject 118 discontinued due to an adverse event of rash).

An audit of 19 enrolled subjects' records was conducted for informed consent documentation, DNA sample consent, and primary efficacy endpoints. Four enrolled subjects' (Subjects 178, 215, 304, and 357) records were audited for inclusion and exclusion criteria, concomitant medications, adverse events, liver function and CRP values, and foot and hand radiographic documentation. Additionally, the inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this BLA, a single domestic site and a single foreign clinical investigator site were inspected in support of this application.

No regulatory deficiencies were observed for Melvin Churchill, M.D. and Jacek Pazdur, M.D. The final classification for the inspection of Dr. Melvin Churchill was NAI (No Action Indicated). The preliminary classification for the inspection of Dr. Pazdur was also NAI. Based on review of inspectional findings for these clinical investigator sites, the study data collected appear generally reliable in support of the requested indication.

Note: Observations noted above for Dr. Jacek Pazdur are based on preliminary communications from the field investigator; an inspection summary addendum will be generated if conclusions change significantly upon receipt and final review of the EIR.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
04/05/2013

JANICE K POHLMAN
04/05/2013

SUSAN D THOMPSON
04/05/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: BLA 125433
Application Type: New BLA
Name of Drug: Golimumab for Infusion
Applicant: Janssen Biotech, Inc.
Submission Date: September 18, 2012
Receipt Date: September 18, 2012

1.0 Regulatory History and Applicant's Main Proposals

Janssen submitted an original BLA for approval of IV golimumab 50 mg/ 4 mL vials for the treatment of adult patients with moderately to severely active rheumatoid arthritis. BLA 125289 Simponi (golimumab) 50 mg/0.5 mL prefilled autoinjector and syringe are current approved for the same indication but for subcutaneous administration.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by December 14, 2012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Selected Requirements of Prescribing Information (SRPI)

Comment:

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- YES** 12. All text must be **bolded**.
Comment:
- NO** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
Comment:
- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.
Comment:
- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)
Comment:
- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”
Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES

42. All text is **bolded**.

Comment:

NO

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

YES

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES

45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

Proposed “See FDA-approved patient labeling (Medication Guide and Patient Instructions for Use)” Drop “Patient” before IFU; this comment was conveyed in 74-day letter, however, the following may have been more appropriate: “See FDA-approved patient labeling (Medication Guide)”

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/s/

CHRISTINE H CHUNG
02/27/2013

SANDRA L BARNES
03/01/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMO

TO: BLA 125,433 (SIMPONI ARIA[®] [Golimumab for Infusion; Anti-TNF- α Monoclonal Antibody] for treatment of Rheumatoid Arthritis)

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Pharmacology/Toxicology Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: June 17, 2013

I concur with Dr. Mamata De's review dated May 29, 2013 that recommends approval of the BLA. This was an original BLA proposing the use of golimumab administered by the intravenous (IV) route for the treatment of rheumatoid arthritis (RA). The recommended dosing for the RA indication for golimumab is 2 mg/kg given as a 30 minute IV infusion at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter. Golimumab, administered by the subcutaneous route, is approved for the treatment of the treatment of RA (BLA 125289). The approved dose is 50 mg administered by subcutaneous injection once a month.

No new nonclinical pharmacology and toxicology studies were provided in this application. To support the clinical use of golimumab, nonclinical pharmacology, safety pharmacology, ADME, general toxicology, and reproductive toxicology studies were conducted by the sponsor and reviewed under BLA 125289 that was approved on April 24, 2009.

With the proposed IV dosing regimen, there is an approximate 2-fold increase in AUC and 26-fold increase in C_{max} as compared to the approved subcutaneous dosing regimen.

Dr. De's review consulted the 6-month IV chronic toxicology, embryo-fetal development (EFD), and pre- and post-natal development studies in Cynomolgus monkeys for evaluating the safety of the proposed IV dosing regimen with golimumab. In addition, intravenous reproductive toxicity studies in mice with a surrogate anti-TNF- α antibody were also consulted for the assessment of reproductive and developmental toxicity. These nonclinical studies provide adequate safety margins for the proposed IV dosing regimen. See Dr. De's review dated May 29, 2013 and the nonclinical review of BLA 125289 dated February 26, 2009 for additional details.

Labeling changes were recommended for Section 8.1 to adjust exposure ratios given the higher clinical exposure achieved with IV dosing. In addition, labeling changes were recommended for Section 13.1 to clarify the dose and route for the fertility study in mice with a surrogate anti-TNF- α antibody. See Dr. De's review for additional details.

There are no outstanding PharmTox issues at this time.

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/s/

TIMOTHY W ROBISON
06/17/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY **BLA REVIEW AND EVALUATION**

Application number: 125,433

Supporting document/s: 125,433/0/0 (original)

Sponsor's letter date: 09-18-2012

CDER stamp date: 09-18-2012

Product: SIMPONI ARIA[®] (Golimumab for Infusion; Anti-TNF- α Monoclonal Antibody)

Indication: Treatment of Rheumatoid arthritis

Sponsor: Janssen Pharmaceuticals Company

Review Division: Pulmonary, Allergy, and Rheumatology Products

Reviewer: Mamata De, Ph.D.

Supervisor/Team Leader: Timothy W. Robison, Ph.D., D.A.B.T.

Division Director: Badrul Chowdhury, M.D., Ph.D.

Project Manager: Christine Chung, Pharm D.

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Golimumab is a fully human IgG1 κ -type monoclonal antibody (mAb) which targets the tumor necrosis factor- α (TNF α) protein in both soluble as well as membrane bound forms and prevents interaction with cognate receptors TNFR1 (p55) and TNFR2 (p75). Golimumab 50 mg administered by subcutaneous injection once a month is currently marketed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), active psoriatic arthritis (PSA), and ankylosing spondylitis (AS). With BLA 125,433, the Sponsor presented clinical and biopharmaceutical data to support use of intravenous (IV) golimumab administratio (b) (4)

in adult patients with moderately to severely active RA. The recommended dosing for the RA indication for golimumab is 2 mg/kg given as a 30 minute IV infusion at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter.

To support the clinical use of golimumab, nonclinical pharmacology, safety pharmacology, ADME, general toxicology (6-month IV and SC), reproductive toxicology (embryo-fetal developmental toxicology, pre and post natal reproductive toxicology) studies in Cynomolgus monkeys were conducted. All of these study reports were submitted with the original BLA 125,289. Dr. Gary Bond completed the primary pharmacology and toxicology review of BLA 125,289 on February 26, 2009. Dr. Adam Wasserman completed a supervisory pharmacology memorandum. Dr. Paul Brown completed a tertiary pharmacology review on March 26, 2009. In these reviews, the nonclinical pharmacology and toxicology program for golimumab was judged to be complete and approval was recommended for golimumab, 50 mg administered by subcutaneous injection once a month for the treatment of adult patients with moderately to severely active RA, PSA, and AS. With BLA125, 433, the Applicant did not submit any new nonclinical pharmacology or toxicology studies with golimumab.

In this review, the 6-month IV chronic toxicity, embryo-fetal developmental (EFD) toxicity, and pre and post-natal toxicity studies in Cynomolgus monkeys were consulted for evaluating the safety of golimumab IV administration in the RA patient population. In addition, intravenous reproductive toxicity studies in mice with a surrogate anti-TNF- α antibody were also consulted for the assessment of reproductive and developmental toxicity. Given the higher clinical dose for the RA indication with IV administration of golimumab compared to that of the subcutaneous administration, the mean exposure of golimumab from the NOAELs of the EFD and pre and post natal toxicity studies in Cynomolgus monkeys were compared to the mean exposure in RA patients receiving IV golimumab to determine the exposure margins. Labeling changes were recommended based on the revised exposure margins.

1.2 Nonclinical Findings

Golimumab binds to human and chimpanzee TNF- α with similar affinities (IC_{50} values $\approx$ 3 ng/mL). The binding to human TNF- α is approximately 10-72-fold higher than baboon, rhesus monkey, Cynomolgus monkey, macaque, and dog TNF- α . No neutralization of rat or mouse TNF α by golimumab was observed. Further, experiments with recombinant Cynomolgus monkey TNF α demonstrated high affinity binding by golimumab and efficient neutralization though this represented a 34-fold lower affinity and 72-fold lower potency compared with human TNF- α . Therefore, Cynomolgus monkeys were used in toxicity studies as it appeared to be the most relevant species.

In addition, since golimumab did not neutralize mouse TNF α , an analogous anti-mouse TNF α mAb (murine IgG2a isotype, the functional equivalent of the human IgG1 isotype), designated as cV1q, was characterized and tested in reproductive and developmental toxicology studies in mice to support BLA 125,289.

The following paragraphs summarize toxicity findings from the pivotal toxicity studies to support IV administration of golimumab.

In a 25-Week IV toxicity study, Cynomolgus monkeys were administered 0, 25, or 50 mg/kg per week of the test article with an interim sacrifice at Week 13 (13th dose on Day 85, sacrificed on Day 91), a terminal sacrifice at week 25 (25th dose on Day 169, sacrificed on Day 175), and a sacrifice after the 12-week recovery period. There were no treatment-related effects on mortality, clinical observations, physical examination, ophthalmic examination, body weights, feed consumption, ECG, blood pressure or heart rate, lymphocyte subsets, hematology parameters, coagulation, clinical chemistry parameters, urinalysis parameters, organ weights, and macroscopic and microscopic pathology. There was a dose-related increase in test article exposure (C_{max} and AUC). No sex-related differences in drug exposures were noted. ADA was detected in one (female) out of 32 animals dosed with the test article. A NOAEL of 50 mg/kg was identified from this study. C_{max} and AUC 0-7d (from Day 168-175 day) values at this NOAEL dose (steady state Day 113, Dose 17) were 2,627 mcg/mL and 11,635 mcg $\cdot$ day/mL, respectively. A terminal half-life of 18 days was reported at this NOAEL dose. The intravenous test article administration was associated with dose-responsive decreases of IgG and IgM antibody responses to a KLH challenge. IgG antibody production was more affected than IgM antibody production. Similar changes were not noted in monkeys that received identical doses of the test article by subcutaneous administration in a 6-month SC toxicity study. However, lower exposures were achieved in the SC toxicity study; at the NOAEL dose of 50 mg/kg/week in the SC toxicity study, C_{max} and AUC values were 2,459 mcg/mL and 5657 mcg $\cdot$ day/mL, respectively. These results suggested that golimumab might be more immunosuppressive after IV administration as compared to SC administration due to the higher systemic exposures achieved following IV administration.

For the evaluation of potential toxic effects on embryo-fetal development, pregnant female Cynomolgus monkeys (12/group, age = 3-10 years; body weight =2.5 to 4.48 kg on Day 0 of gestation) were dosed by the subcutaneous route from Days 20 to 51 of gestation at doses of 0, 25, or 50 mg/kg twice weekly. Body weight gain for high dose group dams was 8% lower than controls, while body weight gain for low dose dams was comparable to controls. There were no test article-related toxic effects on embryo-fetal development observed in this study. Golimumab had no effects on the B and T lymphocyte subsets based upon immunohistological examinations of umbilical cord blood, fetal spleen, thymus, and mesenteric lymph nodes. Golimumab crossed the placenta and fetuses were exposed to drug. The fetal: maternal drug ratios ranged from 0.25-0.56 (mean of 0.38) at 25 mg/kg and from 0.51-3.61 (mean of 1.32) at 50 mg/kg. The NOAEL was 50 mg/kg/day with respect to maternal and embryo-fetal developmental toxicity. AUC was calculated from Day 51 to Day 86. At the NOAEL, AUC Day 51-Day 86 was 27,051 mcg•day/mL and Cmax was 1,613 mcg/mL.

For the evaluation of potential test article-related toxic effects on pre- and post-natal reproductive development, pregnant female Cynomolgus monkeys (12/group, age = 3-10 years; body weight =2.5 to 4.48 kg on Day 0 of gestation) were dosed by the subcutaneous route from Gestation Day 50 through Lactation Day 33 at the doses of 0, 25, or 50 mg/kg 2x weekly. There were no test article related changes in the pre and post-natal reproductive and developmental toxicity parameters. Immune function in the neonates as determined by humoral immune response to tetanus toxoid (TTX) and KLH and Delayed Type Hypersensitivity (DTH) responses to TTX was unaffected by exposure to golimumab (both in utero and postnatal). A NOAEL of 50 mg/kg/day was identified with respect to maternal toxicity and neonatal development, which was associated with maternal Cmax values of 1,482 mcg/mL and highest neonatal blood level of 537 mcg/mL. Drug levels in maternal milk were 3.6 mcg/mL at 50 mg/kg. Drug levels in neonatal blood were approximately 36% of maternal blood levels.

In addition to the EFD and ePPND studies in Cynomolgus monkeys, reproductive toxicity studies were conducted in CD1 mice using an anti-mouse TNF antibody (cV1qmuG2a), which is a surrogate antibody. cV1q was administered by the intravenous route to mice. For male and female fertility assessments, male mice were given cV1q (10 or 40 mg/kg, IV) or control vehicle once weekly beginning 56 days (8 weeks) before cohabitation and continuing through cohabitation (2 weeks) and the week before sacrifice. The female mice were given cV1q (10 or 40 mg/kg, IV) or control vehicle once weekly beginning 2 weeks before cohabitation (maximum of 14 days) and on Day 0 and Day 7 of gestation. cV1q at weekly dosages of 10 and 40 mg/kg IV in male and female CD-1 mice did not produce any toxic effects on fertility or reproductive performance parameters in male and female mice. For assessment of potential toxic effects on embryo-fetal development, cV1q (anti-mouse TNF mAb) was administered at intravenous

doses of 10 and 40 mg/kg once on Day 6 of gestation and once on Day 12 of gestation. cV1q anti-mouse TNF alpha mAb did not produced any maternal or developmental toxicity in this study. For the assessment of pre- and post-natal development and reproductive toxicity, cV1q was administered at intravenous doses of 10 and 40 mg/kg once on Days 6, 12, and 18 of gestation and on Days 3, 9, and 15 of lactation. A reduction in the pregnancy rate of F1 mice was noted (76%), which was slightly below the historical rate (83 to 100%). cV1q administration in mice revealed no maternal or developmental toxicity up to the 40 mg/kg dosage. No treatment-related effects were observed in the F2 generation. A decrease in the humoral immune response was noted at the 40 mg/kg, which was considered as an anticipated pharmacological action of cV1q in dams. Exposures of male and female F1 mice to CV1q in utero and during lactation did not result in statistically significant alterations in the IgM antibody-forming cell response to sheep red blood cells (SRBCs) with a dose of 40 mg/kg and evaluation of mice at either 11 or 22 weeks of age. Intravenous administration of cV1q at dosages up to 40 mg/kg/day in CD-1 mice did not show any developmental toxicity. Mice appeared to develop anti-cV1q-antibodies; however, high serum concentrations of cV1q were noted throughout the treatment periods. A few of the cV1q treated mice died during treatment. The deaths appeared to be related to post-dose reactions due to the repetitive injections of the cV1q protein.

No carcinogenicity study was conducted with golimumab. Potential tumorigenic concerns were identified for marketed anti-TNF- α monoclonal antibodies based on the mechanism of action and post-marketing observations. The current labeling for golimumab already has warnings regarding potential immunosuppressant effects and risks of malignancies (See Section 5.2 of the labeling). A carcinogenicity study in rodents was not considered necessary.

Safety Assessment

An IR was sent to Sponsor dated 05-01-2013 to provide the mean steady state human exposure (AUC 0-8 weeks) value at an interval of 0-8 weeks for the proposed dosing regimen of 2 mg/kg IV at 0 and 4 weeks and every 8-week thereafter. The Sponsor submitted a response to this IR on 05-07-2013. The mean $\pm$ SD steady-state AUC over an 8-week interval for the dosing regimen of 2 mg/kg + MTX at Weeks 0, 4, and every 8 weeks was 245 ± 112 mcg·day/mL based on simulation of 500 replicates of the study population in CNTO148ART3001 using the final 2-compartment IV population PK model.

Safety margins (SM) for reproductive toxicity assessments were calculated from the monkey toxicity studies based on exposures (e.g., AUC and C_{max}). The proposed human dose is 2 mg/kg given IV with an associated AUC of 245 mcg·day/mL (for 8 weeks i.e. 56 days). A C_{max} of 45 mcg/mL was obtained from this study.

The mean maternal exposure ($AUC_{\text{Day 51-Day 86}}$) in Cynomolgus monkeys from the EFD study at the NOAEL of 50 mg/kg twice weekly was 27,051 mcg/day/mL mcg*hr/mL for 35 days. The human exposure over a 35 day interval was estimated to be (245 mcg.day/mLx35 days/56 days) 153 mcg/day/mL. The exposure ($AUC_{56-81\text{days}}$) in monkeys at 50 mg/kg/twice a week provided an exposure margin of 179-fold relative to the human exposure at the proposed intravenous clinical dose (Monkey AUC/Human AUC =27,051/153= 179-fold).

Exposure Comparison

Safety Margins between Nonclinical Cynomolgus Monkey Study Doses and Proposed Human Dose for Golimumab							
Study	Duration	Route	NOAEL mg/kg	Blood levels		Safety Margins	
				AUC (mcg*day/mL)	Cmax (mcg/mL)	AUC	Blood level- based
EFD	Gestation	S	5	27,051	1,613	179	36
PPN D	2-generation	S	5	NR	1482 (parent)	NA	33
		C	0	NR	537 (neonate)	NA	12

Human AUC = 153 mcg*day/mL (human study # CNT0148ART3001) for 8 weeks and Cmax of 45 mcg/mL (human study # C0524T14) following 2 mg/kg (30 mins infusion) at Week 0, 4 and then every 8 weeks thereafter) IV dosing at in patients with RA

NR – not reported
NA- not applicable

The exposure margins from the reproductive toxicity assessments were incorporated into Section 8.1 of the label.

1.3 Recommendations

From the nonclinical pharmacology and toxicology perspective, the application is recommended for approval.

Sections 5.1, 5.4, 6.1, 8.1, 12.1, and 13.1 of the proposed product label were reviewed.

Section 8.1 was revised to conform to CFR 21 Section 201.57. Golimumab is proposed for IV administration to patients with RA. Animal to human dose ratios were adjusted in the recommended labeling based upon the increased clinical

dose for this indication. In addition, the route and doses were added to the fertility study with mice listed under Section 13.1.

Recommended labeling for Sections 8.1 and 13.1 is shown below.

1.3.3 Recommended Product labeling

8.1 Pregnancy

Sponsor's version



Reviewer's version**Pregnancy Category B**

Pregnancy Category B – There are no adequate and well-controlled studies of SIMPONI ARIA[®] pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, it is not known whether SIMPONI ARIA[®] can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI ARIA[®] should be used during pregnancy only if clearly needed.

An embryofetal developmental toxicology study was performed in which pregnant cynomolgus monkeys were treated subcutaneously with golimumab during the first trimester with doses up to 50 mg/kg twice weekly (179 times greater than the maximum recommended human dose-MHRD) and has revealed no evidence of harm to maternal animals or fetuses. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. In this study, *in utero* exposure to golimumab produced no developmental defects to the fetus.

A pre- and post-natal developmental study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the second and third trimesters, and during lactation at doses up to 50 mg/kg twice weekly (33 times and 12 times greater than the maximal steady state human blood levels for maternal animals and neonates, respectively) and has revealed no evidence of harm to maternal animals or neonates. Golimumab was present in the neonatal serum from the time of birth and for up to six months postpartum. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants.

IgG antibodies are known to cross the placenta during pregnancy and have been detected in the serum of infants born to patients treated with these antibodies. Since TRADENAME is an IgG antibody, infants born to women treated with TRADENAME during their pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to TRADENAME *in utero* is not recommended for 6 months following the mother's last TRADENAME infusion during pregnancy [see *Warnings and Precautions (5.10)*].

13 NONCLINICAL TOXICOLOGY**13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility****Sponsor's Version**

Reviewer's version

Long-term animal studies of golimumab have not been conducted to evaluate its carcinogenic potential. Mutagenicity studies have not been conducted with golimumab. A fertility study in mice using an analogous anti-mouse TNF α administered by the intravenous route at doses up to 40 mg/kg once per week showed no impairment of fertility.

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/s/

MAMATA DE
05/29/2013

TIMOTHY W ROBISON
05/29/2013
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA or Supplement

BLA Number: 125,433

**Applicant: Janssen
Pharmaceutical Company**

Stamp Date: 09-18-2012

STN125433/0/0

**Product: Intravenous
Golimumab: Human Anti-
Tumor Necrosis Factor
alpha Monoclonal Antibody
(rTNV148B)**

BLA Type: Supplement

Indication: RA

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?		x	No PharmTox studies were provided in this submission. The review will reference earlier reviews of PharmTox studies submitted to this BLA.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?		x	See comment for #1
3	Is the pharmacology/toxicology section legible so that substantive review can begin?		x	See comment for #1.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	x		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	x		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
BLA or Supplement**

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special toxicity studies/data requested by the Division during pre-submission discussions?	x		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed?	x		
11	Has the applicant addressed any abuse potential issues in the submission?		x	Not required
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		x	Not required

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

There are no potential filing issues for the BLA STN 125,433/0/0

Mamata De 11-16- 2012

 Reviewing Pharmacologist Date

 Team Leader/Supervisor Date

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/s/

MAMATA DE
11/16/2012

TIMOTHY W ROBISON
11/16/2012
I concur

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

STATISTICAL REVIEW(S)



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 #: STN 125433/0/0

Drug Name: Simponi (golimumab) 2 mg/kg IV

Indication(s): Treatment of moderately to severely active Rheumatoid Arthritis (RA) in adults in combination with methotrexate

Applicant: Janssen

Date(s): Letter Date: September 18, 2012

Review Priority: Standard

Biometrics Division: Division of Biometrics 2

Statistical Reviewer: Ruthanna Davi

Concurring Reviewers: Joan Buenconsejo, Statistics Team Leader

Medical Division: Division of Pulmonary Allergy Rheumatology Products

Clinical Team: Rosemarie Neuner, Medical Reviewer
Susan Limb, Medical Team Leader

Project Manager: Christine Chung

Keywords: phase 3, adaptive randomization

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1 EXECUTIVE SUMMARY

Study 3001 demonstrates statistically significant effects on the primary efficacy endpoint, ACR20 at week 14, and all four major secondary efficacy endpoints, DAS28 at week 14, HAQ-DI at week 14, ACR50 at week 24, and the vdH-S score at week 24, for Simponi relative to placebo. These conclusions are not sensitive to the methods applied for missing data. Statistical methods that appropriately account for the adaptive randomization were also supportive of these conclusions and in fact yielded nearly identical results to traditional statistical tests. And although the inequitable management of placebo and Simponi patients with respect to escape was unfortunate, the impact of this study design flaw is likely relative small in that the rate of Simponi patients who met the escape criteria was relatively low.

No statistically significant differences in the treatment effect in terms of the primary efficacy endpoint across gender, race, age, geographic region, or screening CRP level (<1.5 mg/dL versus ≥1.5 mg/dL) categories were identified.

2 INTRODUCTION

Simponi 50 mg administered by subcutaneous injection once a month, in combination with methotrexate, is currently FDA approved for the treatment of rheumatoid arthritis and psoriatic arthritis in adult patients. Simponi is also indicated for the treatment of adult patients with ankylosing spondylitis.

The current submission provides data relevant to the use of Simponi, administered intravenously (IV) in combination with methotrexate, [REDACTED] (b) (4) [REDACTED] for adult patients with moderately to severely active rheumatoid arthritis (RA).

2.1 Overview

In the current submission, the sponsor has provided the results of a phase 3 study titled, “A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, an Anti-TNF α Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy” (and numbered CNTO148ART3001 hereafter referred to as study 3001) intended to support the demonstration of efficacy of Simponi IV for treatment of RA in adult patients with active rheumatoid arthritis despite MTX therapy.

Communication with the sponsor regarding this protocol occurred between 2006 and 2012. A Pre-IND (pre-phase 3) meeting, an End of Phase 2 meeting, and a pre-BLA meeting were held May 10, 2006, June 17, 2009, and October 3, 2011, respectively. Additional teleconferences and written communication were also exchanged regarding this program during this time period. The key statistical agreements and recommendations made between the sponsor and FDA that are relevant to the review of this submission are summarized below. The following agreements/statements were generated at the pre-BLA meeting.

- The FDA requested that a sensitivity analysis for the primary efficacy endpoint and any other dichotomous endpoint, incorporating all patients who discontinue treatment for any reason prior to the endpoint assessment as treatment failures (non-responder imputation) be provided.
- The FDA requested that sensitivity analyses for any continuous endpoint that is proposed for labeling, utilizing a “retrieved dropout” approach be provided.
- The FDA indicated that all patients who discontinue randomized treatment, increase MTX or steroid doses or initiate DMARDS for any reason prior to endpoint assessment should be considered treatment failures for purposes of the ACR response endpoints.
- The sponsor was informed that because of the adaptive randomization, re-randomization tests would be necessary to evaluate the statistical significance of endpoints that are proposed for inclusion in product labeling. In addition, the sponsor was asked to provide complete details regarding the proposed adaptive randomization method.
- The sponsor was informed that although some endpoints such as ACR response, ACR response over time, improvement in ACR components, and HAQ results have been included in labeling of other FDA-approved products for RA, in study 3001, many of these endpoints did not have an appropriate multiplicity adjustment and that may limit inclusion of these endpoints in labeling.
- In response to the sponsor’s proposal to apply multiplicity adjustments retrospectively, the FDA stated that these retrospective adjustments would be viewed as post-hoc.
- FDA agreed to the use of linear extrapolation to impute radiographic endpoints for patients with missing data.

2.2 Data Sources

The week 24 study report, week 52 study report, protocol, and statistical analysis plan for study CNTO148ART3001 were utilized in the review of this submission. The following data sets were submitted electronically and utilized in the review of this submission.

[\\cber-fs3\m\ectd_submissions\stn125433\0000\m5\datasets\cnto148art3001\analysis\legacy\datasets\24wk\addo.xpt](\\cber-fs3\m\ectd_submissions\stn125433\0000\m5\datasets\cnto148art3001\analysis\legacy\datasets\24wk\addo.xpt)
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[\\cber-fs3\m\ectd_submissions\stn125433\0000\m5\datasets\cnto148art3001\analysis\legacy\datasets\52wk\adxv.xpt](\\cber-fs3\m\ectd_submissions\stn125433\0000\m5\datasets\cnto148art3001\analysis\legacy\datasets\52wk\adxv.xpt)

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality and integrity of the submitted data (i.e. study reports, protocol, statistical analysis plan, and electronic data sets) were adequate for review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 3001 was a multicenter, randomized, double-blind, parallel-group, and placebo controlled study in subjects with active rheumatoid arthritis (RA) despite methotrexate therapy. The primary objective of this study was to assess the efficacy of IV administration of Simponi compared to placebo in subjects receiving background methotrexate (MTX).

Eligible subjects were patients with a diagnosis of moderate to severely active RA (according to the revised 1987 criteria of the American Rheumatism Association) for at least three months prior to screening. Subjects had to have been treated with and tolerated MTX at a stable dose between 15 mg and 25 mg/week for at least three months prior to screening. At week 0 subjects were randomly assigned using an adaptive randomization scheme (described below) in a 2:1 ratio to one of the two following treatment groups. Randomization was stratified by CRP level at screening (<1.5 mg/dL or ≥ 1.5 mg/dL) and investigational site.

- Simponi IV (2 mg/kg of golimumab intravenously at weeks 0, 4, and q8w)
- Placebo

Treatment randomization was performed by using a centralized interactive voice response system (IVRS). In order to assure relatively even treatment balance within the stratification factors, CRP levels at screening (< 1.5 mg/dL or ≥ 1.5 mg/dL), and investigational site, subject allocation to a treatment group was performed using minimization with biased-coin assignment. The desired balance between treatment groups was 2:1 for Simponi:placebo. The treatment-balancing algorithm was to utilize two levels (<1.5 mg/dL or ≥ 1.5 mg/dL) for screening CRP levels, and approximately 100 levels for site. The measure used to calculate lack of balance in the minimization algorithm was the variance. Subjects were to be assigned to the treatment group with the lowest total imbalance measure with an acceptance probability of 0.87. Weights for the balancing factors were screening CRP levels (1), Site (3), Overall Study (1). (Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31(1):103-115.)

The primary efficacy variable was ACR20 response at week 14. A subject was classified as having achieved an ACR20 response if the following were achieved:

- (1.) An improvement of $\geq 20\%$ from baseline in both the swollen joint count (66 joints) and tender joint count (68 joints) and
- (2.) An improvement of $\geq 20\%$ from baseline in at least three of the following five assessments:
 - (a.) Patient's assessment of pain visual analog scale (VAS)
 - (b.) Patient's global assessment of disease activity (VAS)
 - (c.) Physician's global assessment of disease activity (VAS)
 - (d.) Patient's assessment of physical function as measured by HAQ-DI
 - (e.) CRP

The major secondary efficacy endpoints were

- The proportion of subjects with moderate or good DAS28 response (using CRP) at week 14
- Change from baseline in HAQ-DI at week 14
- The proportion of subjects with ACR50 response at week 24
- Change from baseline in vdH-S score at week 24

Subjects initially randomized to placebo had an opportunity to enter early escape at week 16 if he or she demonstrated a <10% improvement in both tender and swollen joint count. Subjects originally randomized to Simponi were not given this opportunity to enter early escape at week 16. Escape was managed thru the interactive voice recognition system so that neither patients or investigators were un-blinded to treatment assignment as a result of this study design feature. The discrepancy between treatment groups in allowing escape will not have affected those analyses conducted at week 14 but is potentially problematic for the by-treatment group comparison of those endpoints analyzed after week 16 that is ACR50 response at week 24 and the change from baseline in vdH-S score at week 24. As specified in the protocol, ACR50 response at week 24 was replaced with ACR50 response at week 16 for those placebo patients who escaped. It is unclear whether this imputation would systematically benefit the placebo or the Simponi group. (Refer to section 3.2.3 for further comment on this issue in the context of description of the observed data.) Presuming that placebo subjects who escaped at week 16 were provided an effective treatment, this discrepancy in the management of the subject in each treatment group would bias the by-treatment group comparison of vdH-S score in favor of the placebo group therefore, the vdH-S score analysis at week 24 remains valid in the presence of demonstration of a positive treatment effect for Simponi.

3.2.2 Statistical Methodologies

The protocol specified that the efficacy analyses were to be performed using the intent-to-treat (ITT) population defined as all randomized subjects. The primary efficacy endpoint, the proportion of ACR20 responders, was to be compared between the Simponi and placebo groups using the protocol-specified two-sided $\alpha=0.05$ level Cochran Mantel-Haensel test stratified by CRP level at screening. To account for the use of an adaptive randomization scheme, a sensitivity analysis on the primary endpoint was also to be performed using a re-randomization test. Subjects who met the treatment failure criteria (i.e., increase in subject's MTX dose above baseline for RA, initiate treatment with DMARDs (including commercial MTX), systemic immunosuppressives, and/or biologics for RA, initiate treatment with oral corticosteroids for RA, increase the dose of oral corticosteroids for RA above the baseline dose, or receive IV or IM administration of corticosteroids for RA, or discontinue study agent infusions due to an unsatisfactory therapeutic effect) were considered ACR20 non-responders for purposes of efficacy analyses. Missing ACR values at week 14 were replaced by that subject's last non-missing observation (including baseline). A sensitivity analysis incorporating subjects with missing ACR20 status at week 14 as failures was also pre-specified.

The proportion of subjects with moderate or good DAS28 response at week 14 was to be analyzed using methods similar to that of the primary efficacy analysis (i.e., a two-sided $\alpha=0.05$ level Cochran Mantel-Haensel test stratified by CRP level at screening) and the same missing data imputation. Re-randomization tests for this endpoint were also provided.

The change from baseline to week 14 in HAQ-DI score was to be compared between treatment groups using a two-sided $\alpha=0.05$ analysis of variance on the van der Waerden normal scores with treatment group and CRP level at screening as covariates in the model and the same missing data

imputation as described for the primary efficacy endpoint. Re-randomization test for this endpoint were also provided.

The proportion of subjects with ACR50 response at week 24 was to be compared between treatment groups with equivalent methods to those of the primary efficacy endpoint with the additional requirement that the week 24 ACR for subjects who escaped at Week 16 was to be replaced with that subject's ACR at week 16.

The change from baseline in vdH-S score at week 24 was to be compared between treatment groups using a two-sided $\alpha=0.05$ level ANOVA on the van der Waerden normal scores with treatment group and CRP level at screening as covariates. Missing week 24 vdH-S scores were to be linearly extrapolated using the baseline and week 16 vdH-S scores.

To maintain type I error among the primary and major secondary efficacy endpoints, the endpoints were to be tested sequentially. The primary endpoint was to be analyzed. If that was statistically significant, then the major secondary endpoints were to be tested in the order described above if the previous major secondary endpoint was statistically significant. If the previous major secondary endpoint was not statistically significant, no further comparisons were to be made. All statistical tests were to be two-sided and performed at $\alpha=0.05$.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

As described in Table 1, of the 592 subjects randomly assigned in a 2:1 ratio stratified by CRP level and site at week 0, 197 were assigned to receive placebo and 395 were assigned to receive Simponi. At week 16, 68 (35%) of placebo subjects met early escape criteria and began receiving Simponi. Seventeen (4%) of Simponi subjects met early escape criteria at week 16 but as per-protocol did not discontinue randomized study treatment with Simponi.

This discrepancy in the management of subject escape for each treatment group was previously described in section 3.2.1 and has the potential to bias efficacy comparisons made after week 16. In considering the primary and major secondary efficacy endpoints, this is likely potentially problematic for the ACR50 response only. In this case though, the proportion of Simponi subjects who met early escape criteria was relatively low (4%) and smaller than the observed treatment effect for this endpoint (see section 3.2.4) so in reality this study design flaw is not expected to have overly influenced the outcome of the by-treatment group comparison of ACR50 at week 24.

Table 1: Subject Randomization and Early Escape (ITT)

	Placebo	Simponi
Subjects Randomized	197	395
Subjects Met Early Escape Criteria	68 (35%)	17 (4%)
Subjects with Early Escape	68 (35%)	0 (0%)

Source: Adapted from Wk 24 Clinical Study Report, Table 5

As shown in Table 2, premature study treatment discontinuation and premature study discontinuation were infrequent and balanced across treatment groups and therefore neither is expected to have substantially impacted the primary or major secondary efficacy analyses.

Table 2: Subject Disposition (ITT)

	Placebo	Simponi
Subjects Randomized	197	395
Early Study Treatment Discontinuation	4 (2%)	12 (3%)
Early Study Discontinuation	2 (1%)	4 (1%)
Reason for Early Trt/Study Discontinuation		
Death	1 (0.5%)	0 (0%)
Lost to follow-up	0 (0%)	1 (0.3%)
Withdrawal of consent	2 (1%)	4 (1%)
Adverse event	2 (1%)	9 (2%)
Lack of efficacy	1 (0.5%)	1 (0.3%)
Protocol violation	0 (0%)	1 (0.3%)

Source: Adapted from Wk 24 Clinical Study Report, Tables 6 and 7

Demographic and baseline characteristics for the two randomized treatment groups are described in Table 3. As would be expected because of the random treatment assignment, these factors were generally well-balanced across treatment groups.

Table 3: Subject Demographics and Baseline Characteristics (ITT)

		Placebo	Simponi
Sample Size*		197	395
Age (years)	Mean ± SD	51.4 ± 11.3	51.9 ± 12.6
	Range	19 to 78	18 to 83
Gender [n (%)]	Male	40 (20%)	69 (18%)
	Female	157 (80%)	326 (83%)
Race [n (%)]	American Indian / Alaskan Native	4 (2%)	7 (2%)
	Asian	12 (6%)	31 (8%)
	Black or African American	0 (0%)	1 (0.3%)
	White	160 (81%)	315 (80%)
	Other	21 (11%)	40 (10%)
Weight (kg)	Mean ± SD	71.9 ± 17.2	71.5 ± 16.1
	Range	42 to 122	39 to 125
BMI (kg/m²)	Mean ± SD	27.0 ± 5.7	26.8 ± 5.5
	Range	17 to 45	17 to 47
Number of swollen joints	Mean ± SD	14.8 ± 8.5	15.0 ± 8.2
	Range	5 to 47	4 to 56
Number of tender joints	Mean ± SD	25.9 ± 14.1	26.4 ± 13.9
	Range	14 to 36	15 to 35
CRP (mg/dL)	Mean ± SD	2.2 ± 1.9	2.8 ± 2.9
	Range	0.02 to 10.6	0.07 to 21.1
Physician's global assessment of disease (VAS: 0 to 10 cm)	Mean ± SD	6.3 ± 1.6	6.2 ± 1.7
	Range	0.2 to 9.5	1.5 to 10.0
Patient's global assessment of disease (VAS: 0 to 10 cm)	Mean ± SD	6.5 ± 1.9	6.5 ± 1.8
	Range	0.7 to 10.0	1.4 to 10.0
Patient's assessment of pain (VAS: 0 to 10 cm)	Mean ± SD	6.5 ± 2.0	6.5 ± 1.9
	Range	0.3 to 10.0	1.3 to 10.0
HAQ disability index (0-3)	Mean ± SD	1.5 ± 0.6	1.6 ± 0.7
	Range	0 to 3.0	0 to 3.0
Subjects taking oral corticosteroids	Yes	134 (68%)	251 (64%)
Subject taking NSAIDs	Yes	156 (79%)	323 (82%)

*Small amount (<1%) of missing data for certain endpoints ignored in calculations.

Source: Adapted from Wk 24 Clinical Study Report, Tables 8 thru 11

3.2.4 Results and Conclusions

The pre-specified primary efficacy analysis, as provided by the sponsor is shown in Table 4. Subjects who met the treatment failure criteria (i.e., increase in subject’s MTX dose above baseline for RA, initiate treatment with DMARDs (including commercial MTX), systemic immunosuppressives, and/or biologics for RA, initiate treatment with oral corticosteroids for RA, increase the dose of oral corticosteroids for RA above the baseline dose, or receive IV or IM administration of corticosteroids for RA, or discontinue study agent infusions due to an unsatisfactory therapeutic effect) were considered ACR20 non-responders for purposes of this analysis. The proportion of subjects who met treatment failure criteria thru week 14 was 2.5% in the placebo group and 1.8% in the Simponi group. Missing ACR values at week 14 were replaced by that subject’s last non-missing observation (including baseline). A sensitivity analysis incorporating subjects with missing ACR20 status at week 14 as failures was also pre-specified and is shown in the later portion of Table 4. Conclusions regarding the treatment effect on the ACR20 response are consistent regardless of the handling of the approach to missing ACR values at week 14. The proportion of subjects achieving an ACR20 response at week 14 was statistically significant higher in the Simponi group than the placebo group.

Table 4: Primary Efficacy Analysis: Proportion of Subjects Who Achieved ACR20 Response at Week 14 (ITT)

	Primary Analysis		Sensitivity Analysis with Missing as Non-Responders	
	Placebo	Simponi	Placebo	Simponi
Sample Size	197	395	197	395
ACR20 Response	49 (25%)	231 (58%)	48 (24%)	226 (57%)
Difference between treatment groups (p-value)	34% (p<0.001)		33% (p<0.001)	

Source: Adapted from Wk 24 Clinical Study Report, Table 18 and Attachment 3.6

To account for the use of an adaptive randomization scheme, a sensitivity analysis on the primary endpoint was also performed using a re-randomization test. Results of this analysis were nearly identical to the pre-specified analysis displayed in Table 4. The statistical significance associated with the difference between treatment groups of 34% remained unchanged from the pre-specified analysis at p<0.001.

Since the by-treatment group comparison for the primary efficacy endpoint was statistically significant and according to the pre-specified multiplicity plan, inferential statistical analysis may proceed to the first major secondary efficacy endpoint, the proportion of subjects with moderate or good DAS28 response at week 14. The pre-specified statistical analysis of the DAS28 response is shown in Table 5. The proportion of subjects achieving a DAS28 response at week 14 was statistically significantly higher in the Simponi group (81%) than the placebo group (40%). For this analysis, as pre-protocol, missing DAS28 values at week 14 were replaced by that subject’s last non-missing observation (including baseline). A sensitivity analysis incorporating subjects with missing DAS28 response at week 14 as failures is shown in the later portion of Table 5. Conclusions regarding the treatment effect on the DAS28 response are

consistent regardless of the handling of the approach to missing DAS28 response at week 14. Re-randomization tests for this endpoint confirmed the statistically significant difference between treatment groups with $p < 0.001$.

Table 5: Major Secondary Efficacy Analysis: DAS28 Response at Week 14 (ITT)

	Primary Analysis		Sensitivity Analysis with Missing as Non-Responders	
	Placebo	Simponi	Placebo	Simponi
Sample Size	197	395	197	395
DAS28 Response at Week 14	79 (40%)	321 (81%)	79 (40%)	315 (80%)
Difference between treatment groups (p-value)	41% ($p < 0.001$)		40% ($p < 0.001$)	

Source: Adapted from Wk 24 Clinical Study Report, Table 19 and Summary of Clinical Efficacy Appendix Table 8

Since the by-treatment group comparisons for the primary efficacy endpoint and the first major secondary efficacy endpoint were statistically significant and according to the pre-specified multiplicity plan, inferential statistical analysis may continue to the second major secondary efficacy endpoint, the change from baseline to week 14 in HAQ-DI score. The pre-specified statistical analysis of the HAQ-DI is show in Table 6. HAQ-DI values for subjects who met the treatment failure criteria (i.e., increase in subject’s MTX dose above baseline for RA, initiate treatment with DMARDs (including commercial MTX), systemic immunosuppressives, and/or biologics for RA, initiate treatment with oral corticosteroids for RA, increase the dose of oral corticosteroids for RA above the baseline dose, or receive IV or IM administration of corticosteroids for RA, or discontinue study agent infusions due to an unsatisfactory therapeutic effect) or who had missing HAQ-DI values at week 14 were replaced by that subject’s last non-missing observation (including baseline). A sensitivity analysis utilizing the observed data regardless of whether or not a subject met the treatment failure criteria (i.e., “retrieved dropout”) is shown in the later portion of Table 6. Conclusions regarding the treatment effect on the HAQ-DI are consistent regardless of the handling of the approach to subjects meeting the treatment failure criteria. Re-randomization tests for this endpoint confirmed the statistically significant difference between treatment groups with $p < 0.001$.

Table 6: Major Secondary Efficacy Analyses: HAQ-DI at Week 14 (ITT)

	Primary Analysis		Sensitivity Analysis with Retrieved Dropout	
	Placebo	Simponi	Placebo	Simponi
Sample Size	197	395	197	395
Mean HAQ-DI at Week 14 (st dev)	0.2 (0.6)	0.5 (0.6)	0.2 (0.6)	0.5 (0.6)
Difference between treatment groups (p-value)	0.3 ($p < 0.001$)		0.3 ($p < 0.001$)	

Source: Adapted from Wk 24 Clinical Study Report, Table 20 and Summary of Clinical Efficacy Appendix Table 11

Since the by-treatment group comparisons for the primary efficacy endpoint and the first two major secondary efficacy endpoints were statistically significant and according to the pre-specified multiplicity plan, inferential statistical analysis may continue to the third major secondary efficacy endpoint, the proportion of subjects with ACR50 response at week 24. The pre-specified statistical analysis of the ACR50 response at week 24 is shown in Table 7. The proportion of subjects achieving a ACR50 response at week 24 was statistically significant higher in the Simponi group (81%) than the placebo group (40%). For this analysis, as per-protocol, missing ACR50 values at week 24 were replaced by that subject's last non-missing observation (including baseline) and week 24 ACR for subjects who escaped at week 16 was replaced with that subject's ACR at week 16. A sensitivity analysis incorporating subjects with missing ACR50 response at week 24 and subjects who escaped at week 16 as failures is shown in the later portion of Table 7. Conclusions regarding the treatment effect on the ACR50 response are consistent regardless of the handling of the approach to missing ACR50 response at week 24. Re-randomization tests for this endpoint confirmed the statistically significant difference between treatment groups with $p < 0.001$.

Table 7: Major Secondary Efficacy Analysis: ACR50 Response at Week 24 (ITT)

	Primary Analysis		Sensitivity Analysis with Missing as Non-Responders	
	Placebo	Simponi	Placebo	Simponi
Sample Size	197	395	197	395
ACR50 Response at Week 24	26 (13%)	138 (35%)	26 (13%)	138 (35%)
Difference between treatment groups (p-value)	22% ($p < 0.001$)		22% ($p < 0.001$)	

Source: Adapted from Wk 24 Clinical Study Report, Table 21 and Summary of Clinical Efficacy Appendix Table 5

Since the by-treatment group comparisons for the primary efficacy endpoint and the first three major secondary efficacy endpoints were statistically significant and according to the pre-specified multiplicity plan, inferential statistical analysis may continue to the fourth major secondary efficacy endpoint, the change from baseline in vdH-S score at week 24. The pre-specified statistical analysis of the change from baseline in vdH-S score at week 24 is shown in Table 8. The mean change from baseline to week 24 in vdH-S score was statistically significantly lower in the Simponi groups than the placebo group ($p < 0.001$). For this analysis, scores for subjects who underwent early escape at week 16 or who had missing week 24 vdH-S scores at week 24 and had at least two non-missing vdH-S scores prior to week 24 were linearly extrapolated using the baseline and week 16 vdH-S scores (68 (35%) placebo subjects and 21 (5%) Simponi subjects). Missing baseline vdH-S scores were imputed by median change in the same CRP stratum (4 (2%) placebo subjects and 4 (1%) Simponi subjects). For subjects without at least two non-missing vdH-S scores prior to week 24, the median change in the same CRP stratum was imputed for the week 24 score (9 (5%) placebo subjects and 21 (5%) Simponi subjects). To address the sensitivity of the pre-specified analysis for this endpoint to the linear extrapolation, an additional analysis utilizing observed data regardless of the early escape was conducted and is shown in the middle of Table 8. To address the sensitivity of the pre-specified analysis for this endpoint to the imputation of missing baseline scores, an additional analysis

exclude those subjects with missing baseline images was conducted and is shown in the later portion of Table 8. Conclusions regarding the treatment effect on the vdH-S score at week 24 are consistent regardless of the handling of the approach to escaped subjects and subjects with missing baseline scores. Re-randomization tests for this endpoint also confirmed the statistically significant difference between treatment groups with $p < 0.001$.

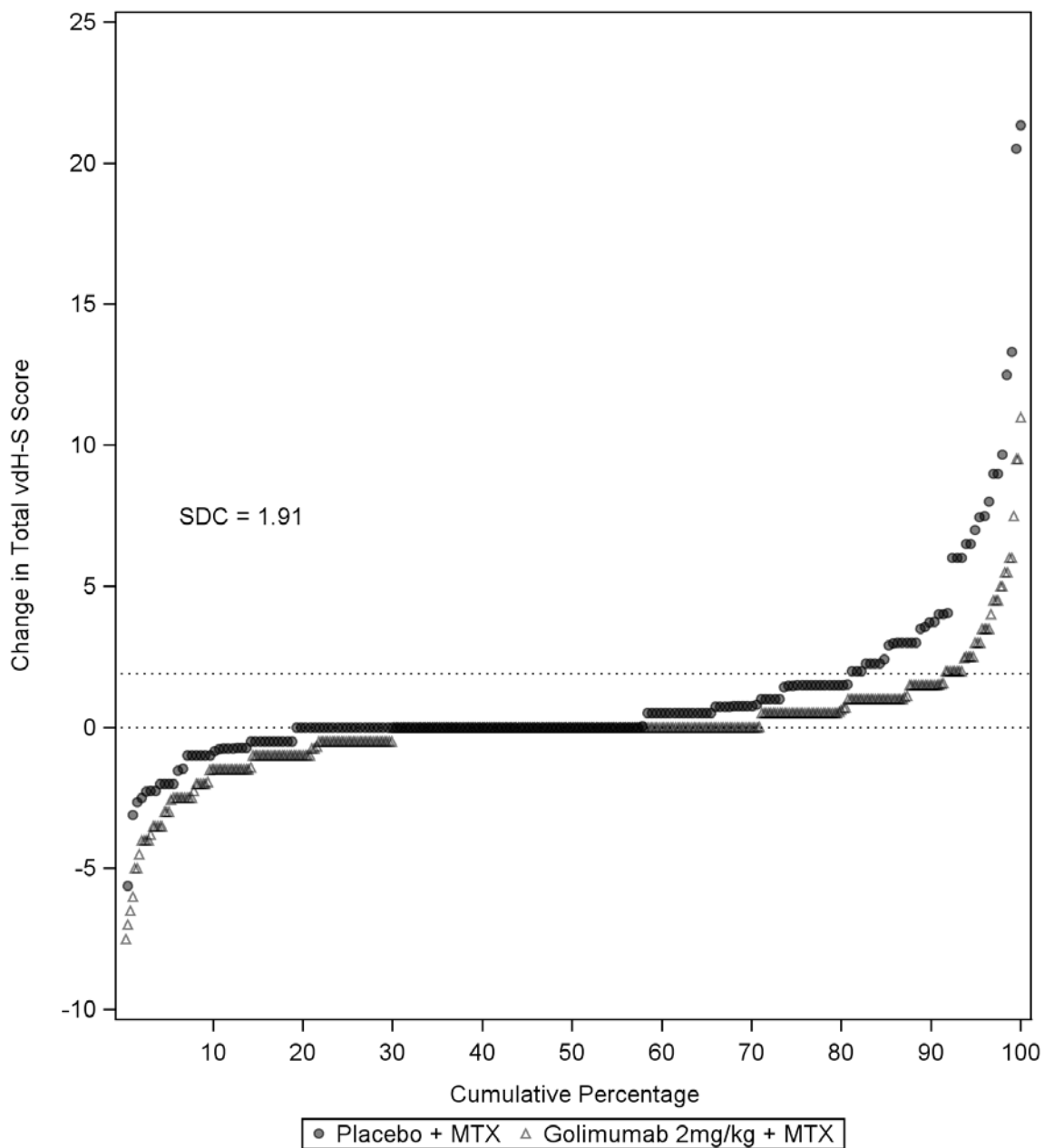
Table 8: Major Secondary Efficacy Analysis: Change from Baseline in vdH-S at Week 24 (ITT)

	Primary Analysis		Sensitivity Analysis Utilizing Observed Data for Escaped Subjects		Sensitivity Analysis Excluding Subjects with Missing Baseline	
	Placebo	Simponi	Placebo	Simponi	Placebo	Simponi
Sample Size	197	395	197	395	193	391
Mean vdH-S score at Week 24 (st dev)	1.1 (3.2)	0.03 (1.9)	1.1 (3.0)	0.04 (1.9)	1.2 (3.3)	0.04 (2.0)
Difference between treatment groups (p-value)	1.06 ($p < 0.001$)		1.06 ($p < 0.001$)		1.16 ($p < 0.001$)	

Source: Adapted from Wk 52 Clinical Study Report, Table 4 and Attachments 3.3 and 3.4

The cumulative probability plot for the change from baseline in total vdH-S score at week 24 is shown in Figure 1. The data used here employ the imputation methods previously described as the main pre-specified analysis of this endpoint. A difference between treatment groups is evident as the proportions of Simponi subjects with at least each threshold of change are smaller than those of placebo subjects. This figure also highlights two apparent outliers, subjects with a change from baseline to week 24 in the total vdH-S of more than 20. These values each originate with a placebo subject. One is an imputed value by linear extrapolation. The other is an observed value. Exclusion of these two subjects from the analysis of the change from baseline to week 24 in the vdH-S score has very little impact on the by-treatment group comparison (mean placebo response = 0.9, mean Simponi response = 0.03, $p < 0.001$)

Figure 1: Cumulative Probability Plot for Change from Baseline in Total van der Heijde modified Sharp Score at Week 24



3.3 Evaluation of Safety

During the course of this review, no safety endpoints were identified as requiring more rigorous statistical evaluation. The reader is referred to the medical review of this application for an evaluation of the safety of Simponi.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

No statistically significant differences in the treatment effect in terms of the primary efficacy endpoint across gender, race, or age categories were identified ($p=0.2$, $p=0.054$, and $p=0.4$, respectively for the subgroup-by-treatment interaction). Nevertheless analysis of the primary efficacy endpoint, ACR20 at week 14, is presented stratified by gender, race, age, and geographic region in Table 9. The results indicate that the treatment effect of Simponi over placebo is present and relatively consistent across these strata.

Table 9: Primary Efficacy Analysis: Prop of Subj With ACR20 Response at Week 14 (ITT)

	Male		Female	
	Placebo	Simponi	Placebo	Simponi
Sample Size	40	69	157	326
ACR20 Response	15%	58%	27%	59%
Diff btwn trt grps p-value	p<0.001		p<0.001	
	Caucasian		Black	
	Placebo	Simponi	Placebo	Simponi
Sample Size	160	315	0	1
ACR20 Response	20%	57%		
Diff btwn trt grps p-value	p<0.001		NA	
	Asian		Other	
	Placebo	Simponi	Placebo	Simponi
Sample Size	12	31	25	48
ACR20 Response	17%	65%	60%	69%
Diff btwn trt grps p-value	p=0.01		p=0.456	
	Age<45 years		Age 45 to <65 years	
	Placebo	Simponi	Placebo	Simponi
Sample Size	45	92	134	244
ACR20 Response	38%	69%	22%	54%
Diff btwn trt grps p-value	p<0.001		p<0.001	
	Age at least 65			
	Placebo	Simponi		
Sample Size	18	59		
ACR20 Response	11%	61%		
Diff btwn trt grps p-value	p=0.002			
	North America		Europe	
	Placebo	Simponi	Placebo	Simponi
Sample Size	6	17	121	234
ACR20 Response	17%	59%	16%	50%
Diff btwn trt grps p-value	p=0.102		p<0.001	
	Latin America		Asia Pacific	
	Placebo	Simponi	Placebo	Simponi
Sample Size	53	104	17	40
ACR20 Response	51%	75%	12%	63%
Diff btwn trt grps p-value	p=0.003		p=0.002	

Source: Adapted from Wk 24 Clinical Study Report, Attachment 3.44

4.2 Other Special/Subgroup Populations

Analysis of the primary efficacy endpoint, ACR20 at week 14, is presented stratified by screening CRP level in Table 10. The results indicate that the treatment effect of Simponi over placebo is present and relatively consistent across both CRP strata (<1.5 mg/dL versus $\geq$ 1.5 mg/dL).

Table 10: Primary Efficacy Analysis: Proportion of Subjects Who Achieved ACR20 Response at Week 14 by screening CRP strata (ITT)

	Subjects with screening CRP<1.5 mg/dL		Subjects with screening CRP $\geq$ 1.5 mg/dL	
	Placebo	Simponi	Placebo	Simponi
Sample Size	34	69	163	326
ACR20 Response	8 (24%)	42 (61%)	41 (25%)	189 (58%)
Difference between treatment groups (p-value)	37% (p<0.001)		33% (p<0.001)	

Source: Adapted from Wk 24 Clinical Study Report, Attachment 3.2

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During the course of this review, the following statistical issues were identified and resolved. Each issue is further described in the context of the referenced sections.

- Inequitable management of escape for placebo and Simponi subjects (sections 3.2.1 and 3.2.3)
- Pre-specified missing data imputation for the primary and major secondary efficacy endpoints were not ideal (sections 3.2.2 and 3.2.4)
- Adaptive randomization requires use of re-randomization tests (sections 3.2.1 and 3.2.4)

5.2 Collective Evidence

Since a single phase 3 study was reviewed in support of this application, no assessment of collective evidence across its studies is provided in this review and the reader is referred to section 5.3 for the conclusions and recommendations resulting from the review of study 3001.

5.3 Conclusions and Recommendations

Study 3001 demonstrates statistically significant effects on the primary efficacy endpoint, ACR20 at week 14, and all four major secondary efficacy endpoints, DAS28 at week 14, HAQ-DI at week 14, ACR50 at week 24, and the vdH-S score at week 24, for Simponi relative to placebo. These conclusions are not sensitive to the methods applied for missing data. Statistical methods that appropriately account for the adaptive randomization were also supportive of these

conclusions and in fact yielded nearly identical results to traditional statistical tests. And although the inequitable management of placebo and Simponi patients with respect to escape was unfortunate, the impact of this study design flaw is likely relatively small in that the rate of Simponi patients who met the escape criteria was relatively low.

No statistically significant differences in the treatment effect in terms of the primary efficacy endpoint across gender, race, age, geographic region, or screening CRP level (<1.5 mg/dL versus ≥1.5 mg/dL) categories were identified.

5.4 Labeling Recommendations (as applicable)

The sponsor has proposed text to be inserted in section 14 of the product label (b) (4)

(b) (4)
Therefore, from a statistical perspective, these (b) (4)
should not be (b) (4) in labeling unless (b) (4) necessary from a
clinical perspective to understand the full context of the treatment effect.

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

/s/

RUTHANNA C DAVI
06/13/2013

JOAN K BUENCONSEJO
06/13/2013
I concur.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

BLA FILING REVIEW

BLA: STN 125433/0/0

Drug Name: Golimumab IV (human anti-tumor necrosis factor alpha monoclonal antibody (r TNV148B))

Indication(s): Treatment of moderately to severely active rheumatoid arthritis

Applicant: Janssen

Stamp Date: September 18, 2012

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Ruthanna Davi, Ph.D.

Concurring Reviewer: Joan Buenconsejo, Ph.D.

Medical Division: Division of Pulmonary, Allergy, and Rheumatology Products

Medical Team: Rosemarie Neuner, M.D., Medical Reviewer
Susan Limb, M.D., Medical Team Leader

Project Manager: Christine Chung

Keywords: NDA filing review

Introduction

The sponsor has submitted the results of one key study (study number CNTO148ART3001, hereafter referred to as study 3001) in support of the efficacy of intravenous (IV) golimumab for treatment of patients with moderately to severely active rheumatoid arthritis (RA) despite treatment with methotrexate (MTX). Study 3001 was a randomized (2:1 using an adaptive stratified randomization design to achieve balance within CRP level at screening (<1.5 mg/dL or ≥ 1.5 mg/dL) and investigational site), double-blind, parallel group (with eligibility for early escape at 16 weeks based on protocol-defined criteria, $<10\%$ improvement in both tender and swollen joint count from week 0 to week 16), multi-center study evaluating the efficacy and safety of golimumab as an addition to MTX therapy.

Study 3001

Efficacy

According to the sponsor, the primary objective of study 3001 was to assess the clinical efficacy of IV administration of golimumab 2 mg/kg and MTX compared with MTX alone in subjects with active RA despite MTX therapy.

The protocol-specified primary efficacy endpoint was the proportion of subjects with an ACR20 response at week 14. The study report provides comparison of the proportions of subjects in the golimumab 2 mg/kg and MTX group and the placebo and MTX group using the protocol-specified approach, a two-sided ($\alpha=0.05$) Cochran Mantel Haenszel test, stratified by CRP level at screening (<1.5 mg/dL or ≥ 1.5 mg/dl). As was defined in the protocol, subjects with no ACR data at week 14 were considered treatment failures for the primary efficacy analysis. It appears that all randomized subjects were included in the primary analysis.

The protocol-specified major secondary endpoints and analysis methods for these endpoints were the following. The study reports provide these analyses and appear to incorporate all randomized subjects.

- (1.) Proportion of subjects with moderate or good DAS 28 scores (using CRP) at week 14
By-treatment group comparison utilized the protocol-specified approach of a two-sided ($\alpha=0.05$) Cochran Mantel Haenszel test, stratified by CRP level at screening (<1.5 mg/dL or ≥ 1.5 mg/dl)
- (2.) Change from baseline in HAQ at week 14 (i.e., week 14 minus baseline)
By-treatment group comparison utilized the protocol-specified approach of a two-sided ($\alpha=0.05$) ANOVA on the van der Waerden normal scores with treatment group and CRP level at screening (<1.5 mg/dL or ≥ 1.5 mg/dL) as covariates in the model
- (3.) Proportion of subjects with ACR50 improvement at week 24
By-treatment group comparison utilized the protocol-specified approach of a two-sided ($\alpha=0.05$) Cochran Mantel Haenszel test, stratified by CRP level at screening (<1.5 mg/dL or ≥ 1.5 mg/dl)
- (4.) Change from baseline in vdH-S score at week 24
By-treatment group comparison utilized the protocol-specified approach of a two-sided ($\alpha=0.05$) ANOVA on the van der Waerden normal scores with treatment group and CRP level at screening (<1.5 mg/dL or ≥ 1.5 mg/dL) as covariates in the model. Linear extrapolation will be used to impute week 24 data for subjects who escaped at week 16.
Cumulative probability plots are also provided by the sponsor.

The protocol states that these secondary analyses are to be performed only if the primary efficacy comparison is statistically significant and in sequential order (as listed above) to account for multiplicity in endpoints and control the type I error.

These primary and secondary efficacy endpoints, as well as the ACR20, 50, and 70 across time and the components of the ACR score at week 14, form the basis for efficacy claims made in the Clinical Studies section of the sponsor's proposed label.

On their face, the methods used in the analysis of the primary and major secondary efficacy endpoints are not objectionable except that these methods do not appropriately account for the adaptive random treatment assignment that was utilized for this study. Nearly all of the analyses of the primary and major secondary

efficacy endpoints that are provided in the study report are *traditional* in that they utilized comparison of the test statistic to established theoretical statistical distributions which assume independence between observations. In the case of study 3001, this assumption may be violated due to the adaptive randomization used to generate treatment assignment. As such, in pre-submission correspondence and meetings, the Division informed the sponsor that re-randomization test would be necessary for the primary and major secondary efficacy variables as traditional test may not be valid. The sponsor's study reports provide re-randomization tests, as sensitivity analyses, for the primary efficacy variable, ACR20 at week 14, and one of the major secondary efficacy endpoints, change from baseline in vdH-S score at week 24 but the study reports also contain many other analyses of these endpoints that are not modified to account for the adaptive randomization. Analyses of the remaining major secondary efficacy endpoints, proportion of subjects with moderate or good DAS 28 scores (using CRP) at week 14, change from baseline in HAQ at week 14, and proportion of subjects with ACR50 improvement at week 24, do not account for the adaptive randomization. In addition, sensitivity analyses utilizing a re-randomization test for these endpoints could not be located in the submission. At a minimum, re-randomization tests for the following major secondary efficacy endpoints; proportion of subjects with moderate or good DAS 28 scores (using CRP) at week 14, change from baseline in HAQ at week 14, and proportion of subjects with ACR50 improvement at week 24; should be requested from the sponsor. The adequacy of the use of the *traditional* statistical methods and therefore the reliability of many of the results in the study report will be further assessed as part of the statistical review of this application and interactions among the statistical and clinical team will be advised regarding whether or not to rely on the results of the *traditional* analyses.

Subgroup analyses of the primary endpoint by gender, age, and race were provided in attachment 3.45 to the study report; however, it is not clear if the methods employed were the protocol-specified primary analysis methods. Analyses of the major secondary efficacy endpoints by gender, age, and race do not appear to be provided in the submission. Subgroup analyses of the primary and major secondary efficacy endpoints using the protocol specified primary analysis methods should be requested from the sponsor. Tests of the interaction of treatment with each of age, gender, and race for each of the primary and major secondary efficacy endpoints should also be requested from the sponsor.

Safety

Analysis of the safety data beyond week 16 for study 3001 is complicated by the fact that subjects may have escaped from the placebo+MTX group to treatment with golimumab+MTX at week 16. Tabulations of adverse events are provided in the sponsor's study report for four categories: the traditional, as-randomized, groupings (i.e., patients randomized to placebo+MTX and patients randomized to golimumab+MTX) as well as according whether escape occurred (i.e., patients randomized to placebo+MTX with early escape to golimumab+MTX and patients who received at least one dose of golimumab, that is, combining data for patients who started taking golimumab at week 16 with those who took golimumab from week 0). Data provided for these groupings are descriptive only (i.e., proportions). Now inferential comparisons are made. On its face, this is not objectionable and is acceptable for filing.

Electronic Data

The electronic analysis data sets including the efficacy data for study 3001 that are provided in the submission appear adequate for review of the study.

Reviewer's Conclusion

From a statistical perspective the application is sufficient for filing and there are no issues to convey in the 74-day letter. The following are not required for filing but should be requested from the sponsor.

- (1.) Provide re-randomization tests for the following major secondary efficacy endpoints; proportion of subjects with moderate or good DAS 28 scores (using CRP) at week 14, change from baseline in HAQ at week 14, and proportion of subjects with ACR50 improvement at week 24. If these are already included in the submission, provide their location.
- (2.) Provide subgroup analyses by age, gender, and race of the primary and major secondary efficacy endpoints using the protocol specified primary analysis methods. Also provide tests for the interaction of

treatment with each of age, gender, and race in the overall patient group. If these are already included in the submission, provide their location.

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

/s/

RUTHANNA C DAVI
11/17/2012

JOAN K BUENCONSEJO
11/17/2012
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125433Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D., Associate Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Division Director Summary Review
NDA/BLA #	BLA 125433
Supplement #	original
Applicant Name	Janssen Biotech, Inc.
Date of Submission	September 18, 2012
PDUFA Goal Date	July 19, 2013
Proprietary Name / Established (USAN) Name	Simponi Aria / golimumab
Dosage Forms / Strength	2 mg/kg intravenous infusion
Proposed Indication(s)	1. Rheumatoid Arthritis in adults
Action:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
CDTL Review	Susan Limb, M.D.
Medical Officer Review	Rosemarie Neuner, M.D., M.P.H.
Statistical Review	Ruthanna Davi, Ph.D.; Joan Buenconsejo Ph.D.
Pharmacology Toxicology Review	Mamata De, Ph.D.; Timothy Robison Ph.D., D.A.B.T.
CMC Review/OBP Review	Erik Read, Ph.D.; Kurt Brorson, Ph.D.
BMAB/Office of Compliance	Reyes Candau-Chacon, Ph.D.; Patricia Hughes, Ph.D.
Clinical Pharmacology/ Pharmacometrics Review	Liang Zhao, Ph.D.; Suresh Doddapaneni, Ph.D.; Atul Bhattaram, Ph.D.
OPDP	LCDR Roberta Szydlo, RPh, M.B.A.
DMPP (patient labeling)	CAPT Twanda Scales RN, MSN
OSE/DMEPA	Teresa McMillan, Pharm.D.; Lubna Merchant, Pharm.D., M.S.
DSI	Anthony Orenca, M.D.

OND=Office of New Drugs
 CDTL=Cross-Discipline Team Leader
 CMC=Chemistry, Manufacturing, and Controls
 OBP=Office of Biotechnology Products
 BMAB=Biotechnology Manufacturing Assessment Branch
 OPDP=Office of Prescription Drug Promotion
 DMPP=Division of Medical Policy Programs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations

1. Introduction

This biologic license application (BLA) pertains to a new route of administration (intravenous), new dose (2 mg/kg) and dosing regimen (infusions at Weeks 0 and 4, then every 8 weeks thereafter) for the previously approved molecular entity, golimumab, for the indication of moderately to severely rheumatoid arthritis (RA). Golimumab is a human IgG1 monoclonal antibody targeting tumor necrosis factor (TNF)- α , and was the fifth TNF inhibitor approved in the U.S. at the time of its approval. The subcutaneous (SC) formulation of golimumab (tradename, Simponi®) was first approved on April 24, 2009 at a dose of 50 mg SC once a month for the indications of moderately to severely active RA, active ankylosing spondylitis (AS), and active psoriatic arthritis (PsA). SC golimumab was subsequently also approved for ulcerative colitis (UC) at a dose of 200 mg initially, followed by 100 mg at Week 2, then every 4 weeks thereafter.

The intravenous (IV) golimumab application is based primarily on a single randomized, controlled clinical trial in RA patients (Study CNTO148ART3001) and a supportive Phase 2 dose ranging trial using a different regimen (every 12 weeks). The applicant did not perform a direct comparison of the efficacy, safety, or pharmacokinetics of the proposed IV golimumab regimen and the approved SC golimumab dose/regimen, thus the ability to rely on the efficacy and safety of SC golimumab is limited.

2. Background

As shown in Table 1 below, excluding non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, there have been 18 drugs/biologics approved for RA in the U.S. Five of these products are TNF inhibitors, including SC golimumab. One of these TNF inhibitors, infliximab (Remicade®), is approved for IV infusion.

TNF inhibitors are thus a well-established class of disease-modifying anti-rheumatic drugs (DMARDs) and most have been documented to reduce progression of structural damage due to RA. However, convincing evidence of a structural benefit has not been demonstrated in the SC golimumab development program.

In any case, the applicant chose not to rely on the SC golimumab program and did not provide a bridging PK or efficacy study that would allow for a direct comparison of SC and IV golimumab regimens. At the pre-BLA meeting in September 2011, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) noted that in light of the PK differences and the absence of a direct comparison to the SC formulation, the IV golimumab program would be viewed as a standalone program with a requirement for independent substantiation of efficacy. However, DPARP also noted that robust efficacy results for the radiographic outcome might be able to serve as independent substantiation of the efficacy observed for the clinical outcomes in the study.

Table 1: FDA-Approved Drugs/Biologics for RA (excluding NSAIDs and steroids)

FDA-approved drugs/biologics for RA (excluding NSAIDs and steroids)			
Drug Name	Presentation and Route of Administration	Target/Mechanism of Action	Approved for RA*
sulfasalazine	500 mg tablets, 250 mg/5ml suspension; oral	anti-inflammatory/ immunomodulatory	date unknown (first approved 6/20/1950)
methotrexate	2.5 mg tablets; oral	anti-metabolite (inhibits dihydrofolate reductase)	10/31/1988 (first approved 12/7/1953)
hydroxychloroquine	200 mg tablets; oral	interference with T-cell activation/ antigen processing?	date unknown (first approved 4/18/1955)
azathioprine	50 mg tablets; oral	immunosuppressive anti-metabolite; cytotoxic	date unknown (first approved 3/20/1968)
penicillamine	250 mg capsules; oral	Unknown	date unknown (first approved 12/4/1970)
cyclosporine	25, 100 mg capsules; 100 mg/mL solution; oral	T-cell inhibitor	5/22/1997 (first approved 11/14/1983)
auranofin	3 mg capsules; oral	Unknown	date unknown (first approved 5/24/1985)
leflunomide	10, 20, 100 mg tablets; oral	anti-metabolite (pyrimidine synthesis inhibitor)	9/10/1998
etanercept	25 mg vial; 25 or 50 mg PFS; 50 mg AI; SC injection	TNF inhibitor; fusion protein of TNFR and IgG1 Fc	11/2/1998
infliximab	100 mg vial; IV infusion	TNF inhibitor; chimeric IgG1 mAb against TNF α	11/10/1999 (first approved 8/24/1998)
anakinra	100 mg/0.67 mL PFS; SC injection	IL1 inhibitor; recombinant IL1 receptor antagonist	11/14/2001
adalimumab	20 or 40 mg PFS; 40 mg AI; SC injection	TNF inhibitor; human IgG1 mAb against TNF α	12/31/2002
abatacept	250 mg lyophilized in vial for IV infusion; 125 mg PFS for SC injection	T-cell activation inhibitor; recombinant CTLA-4 fused to IgG1 Fc	12/23/2005
rituximab	100 mg and 500 mg vials; IV infusion	B-cell depletion; chimeric IgG1 mAb against CD20	2/28/2006 (first approved 11/26/1997)
golimumab	50 or 100 mg PFS; 50 or 100 mg AI; for SC injection	TNF inhibitor; human IgG1 mAb against TNF α	4/24/2009
certolizumab	200 mg lyophilized in vial; 200 mg PFS; for SC injection	TNF inhibitor; recombinant humanized Fab against TNF α	5/13/2009 (first approved 4/22/2008)
tocilizumab	80 mg, 200 mg, 400 mg vials; IV infusion	IL6 inhibitor; humanized IgG1 mAb against IL6	1/8/2010
tofacitinib	5 mg tablets; oral	JAK inhibitor	11/6/2012

* Approval dates can only be verified from 1984 to the present

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name
PFS = prefilled syringe; AI = autoinjector; SC = subcutaneous; IV = intravenous

3. CMC/Device

I concur with the conclusions reached by the product quality team regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports the requested commercial expiry period of 24 months when stored at 2-8°C and protected from light. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology team that there are no outstanding pharm/tox issues that preclude approval. No new nonclinical pharmacology/toxicology studies were requested or provided in this application.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics team that there are no outstanding clinical pharmacology issues that preclude approval.

Pharmacokinetics of golimumab

Following the proposed IV dose regimen (2 mg/kg at Weeks 0, 4, and every 8 weeks thereafter), serum concentrations reached steady-state by Week 12. With concomitant methotrexate (MTX), steady-state serum trough concentrations were 0.35 ± 0.38 µg/mL at Week 12, 0.31 ± 0.44 µg/mL at Week 20, and 0.42 ± 0.54 µg/mL at Week 52. Pharmacokinetics were dose-proportional from 0.1 to 10.0 mg/kg following a single IV dose. Patients developing anti-golimumab antibodies tended to have lower serum trough values with a 33% increase in golimumab clearance. Because the IV golimumab development program did not include a direct comparison to SC dosing, the review team performed cross-study comparisons. These indicate the proposed IV golimumab dose regimen results in a higher mean C_{max} and an AUC that is 2- to 3- fold higher than the approved SC golimumab dose regimen for RA.

Dose selection

Study C0524T12 evaluated 2 mg/kg IV every 12 weeks vs. 4 mg/kg IV every 12 weeks vs. placebo in 643 RA patients with or without concomitant MTX for a total duration of 48 weeks. Neither dose was significantly different than placebo for the primary endpoint of proportion of ACR50 responders at Week 14. The applicant concluded that the failure of the trial was attributable to low systemic drug concentrations observed during the latter part of the 12-week dosing interval, leading to the selection of the 8 week dosing interval studied in the pivotal study CNTO148ART3001 (hereafter abbreviated as Study 3001).

6. Clinical Microbiology

I concur with the conclusions reached by the Biotechnology Manufacturing Assessment Branch (BMAB) reviewer that there are no outstanding microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The primary evidence of the efficacy of the proposed IV golimumab dose regimen is based on Study 3001, a 112-week randomized, double-blind, placebo controlled trial in 592 RA patients on background MTX. Patients were randomized 2:1 to receive either IV golimumab 2 mg/kg or placebo at Weeks 0, 4, and every 8 weeks thereafter. Patients in the placebo group were eligible to enter early escape to active IV golimumab treatment at Week 16 if less than 10%

improvement in tender and swollen joint count was noted. At Week 24, all remaining placebo group patients were switched to IV golimumab.

The primary efficacy endpoint was the proportion of patients meeting the American College of Rheumatology 20% improvement response criteria (ACR20) at Week 14. An ACR20 response was defined as an at least 20% improvement from baseline in both the swollen joint count (66 joints) and tender joint count (68 joints), $\geq 20\%$ improvement from baseline in at least 3 of the following 5 core variables:

- Patient pain on a visual analog scale (VAS)
- Patient global assessment of disease activity (VAS)
- Physician's global assessment of disease activity (VAS)
- Physical function, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI), and
- C-reactive protein (CRP).

At Week 14, 58% of patients in the golimumab treatment arm met criteria for an ACR20 response compared to 25% of placebo-treated patients ($p < 0.001$). Results of the sensitivity analyses and secondary clinical endpoints (e.g., ACR 50, ACR70, moderate or good DAS28 response, DAS28 < 2.6 , change from baseline in HAQ-DI) were consistent with a conclusion of a treatment benefit associated with IV golimumab.

For the radiographic outcome of change from baseline to Week 24 in van der Heide-Sharp (vdH-S) score, golimumab treatment was associated with a mean change of 0.03, compared to a mean change of 1.1 in the placebo treatment group ($p < 0.001$). A higher proportion of patients in the IV golimumab treatment group experienced no progression in vdH-S score at week 24 (71%) compared to the placebo group (57%). The statistical review team performed several sensitivity analyses including exclusion of outliers and different imputation strategies for missing data. These analyses supported the pre-specified analysis and the conclusion of a robust structural benefit associated with IV golimumab treatment.

Based on the results of Study 3001, the clinical and statistical review teams are in agreement that substantial evidence of the efficacy of IV golimumab has been demonstrated, and I concur.

8. Safety

The safety of IV golimumab is based on results from Study 3001, which is the only study available of the dose and dosing frequency proposed for marketing. Data from Study C0524T12 and the SC golimumab development program are considered supportive due to the different (lower) systemic exposures. Data from Study 3001 included up to 584 patients exposed to golimumab for any period of time, with an average duration of 44 weeks of exposure and 6 doses received.

Overall, the safety profile of IV golimumab appears to be generally consistent with the safety profile of other TNF inhibitors, including SC golimumab. The primary risk of TNF inhibitors

is infection, and an imbalance in serious infections was observed in Study 3001. Through the 24-week controlled period, 4 serious infections (0.9%) were reported in the golimumab arm versus no cases in the placebo arm. The exposure-adjusted incidence of serious infections with IV golimumab was approximately 4 events per 100 patient-years. This is consistent with the exposure-adjusted incidence of serious infections in the SC golimumab program, which ranged from 3.4 cases per 100 patient-years with golimumab 50 mg monthly to 5.0 cases per 100 patient-years with golimumab 100 mg monthly.

There were 6 deaths reported in Study 3001 as of the 120-day safety update—1 placebo patient who died of a stroke, 2 patients who had crossed from placebo to golimumab at Week 24 (1 who died while swimming, and 1 who died of *C. difficile* colitis), 3 patients in the golimumab group who died of myocardial infarction, acute abdominal syndrome in the setting of tuberculosis, and septic shock secondary to pyogenic lung abscess (in a patient with a history of latent TB). The frequency and causes of mortality in the IV golimumab program are consistent with other RA development programs.

One case of breast cancer was reported (on Study Day 164) in a patient in the IV golimumab treatment group versus no cases of malignancy in the placebo arm through Week 24. Three additional cases of malignancy were reported in the follow-up period (basal cell carcinoma, cervix carcinoma, and chronic lymphocytic leukemia). The frequency and types of malignancy also appear to be consistent with those observed with other TNF inhibitors.

Approximately 4% of patients who received at least one dose of IV golimumab developed anti-golimumab antibodies. Based on a limited number of patients, anti-drug antibodies (ADA) did not appear to be associated with adverse events or decreased efficacy, although ADA did appear to be associated with decreased exposure.

Infusion reactions, defined as any adverse event occurring during or within 1 hour of infusion, were reported in 4% of patients receiving IV golimumab during the 24-week controlled period, compared to 0.5% of placebo patients. Infusion reactions did not appear to be associated with positive ADA.

The clinical review team has concluded that, overall, the safety profile of IV golimumab is consistent with the safety profile observed with other TNF inhibitors and no new safety signals were identified. I concur with these conclusions.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as golimumab is not a new molecular entity, and no issues were identified that warranted advisory committee input.

10. Pediatrics

This application triggers a requirement under the Pediatric Research Equity Act (PREA) for a study in patients with juvenile idiopathic arthritis (JIA), and was discussed at the May 1, 2013 meeting of the Pediatric Review Committee (PeRC). A waiver was granted for patients under 2 years of age, as there are so few patients in this age range that studies would be impossible or highly impractical. The applicant received a deferral for a study in PJIA patients 2 to 17 years of age. The applicant proposes to conduct a 52-week randomized withdrawal trial in patients with active JIA despite MTX. The proposed dose for study is 80 mg/m² at weeks 0, 4, and every 8 weeks thereafter. Because of the unavailability of a clear exposure-response rationale to justify the IV dose selection for JIA patients, the review team considered the proposed randomized withdrawal trial justified in order to confirm efficacy and acceptable safety for the proposed pediatric dosing regimen.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- **Proprietary name**

“Simponi Aria” has been found acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP).

- **Physician labeling**

Simponi Aria will have a label separate from the currently approved SC formulation, Simponi. The Warnings and Precautions section will be consistent with the other TNF-inhibitor labels. Section 6, Adverse Reactions, and Section 14, Clinical Studies will not include data from the SC golimumab program.

- **Carton and immediate container labels**—No issues
- **Medication guide** will be consistent with medication guide of other TNF-inhibitors.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

The applicant has submitted adequate data to support approval of IV golimumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis, in combination with methotrexate. The action on this application will be Approval.

- **Risk Benefit Assessment**

The overall risk-benefit assessment supports approval of IV golimumab for the treatment of moderately to severely active rheumatoid arthritis. The efficacy findings were robust, and

included efficacy for structural/radiographic outcomes as well as clinical responses. The safety profile of IV golimumab appeared to be consistent with the safety profile of other TNF inhibitors and no new safety signals were identified. Thus the overall risk-benefit profile in patients with RA is acceptable.

- **Postmarketing Risk Evaluation and Mitigation Strategies**

Risk Evaluation and Mitigation Strategies (REMS) are not warranted, as the safety profile of IV golimumab is consistent with the safety profile of other TNF inhibitors approved for RA.

- **Postmarketing Requirements and Commitments**

Under PREA, the applicant is required to conduct a trial to evaluate the safety, efficacy, PK/PD, and immunogenicity of IV golimumab in pediatric patients between the ages of 2 to 17 years and 11 months with active Juvenile Idiopathic Arthritis (JIA) despite standard therapy with methotrexate.

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/s/

SARAH K YIM
07/18/2013