Janssen Research & Development *

Synoptic Clinical Study Report

A Golimumab Phase 3b, Multicenter, Assessment of Intravenous Efficacy in Rheumatoid Arthritis Subjects Who Have Diminished Disease Control Despite Treatment with Infliximab (REMICADE®)

REGAIN

Protocol CNTO148ART3003; Phase 3b

SIMPONI® golimumab

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EudraCT Number: 2013-001809-91

COORDINATING INVESTIGATOR: N/A

SPONSOR'S RESPONSIBLE MEDICAL OFFICER: [redacted] MD

DATE STUDY INITIATED: 18 October 2013

DATE STUDY COMPLETED: 30 December 2014

Status: Approved
Date: 4 May 2015
Prepared by: Janssen Research & Development, LLC
EDMS no & version: EDMS-ERI-100960351, 1.0

GCP Compliance: This study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.

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APPENDICES

Appendix 1: Protocol and Protocol Amendment(s)

All other documents or data not included in this report are available upon request.

Protocol No.: CNTO148ART3003

Title of Study: A Golimumab Phase 3b, Multicenter, Assessment of Intravenous Efficacy in Rheumatoid Arthritis Subjects Who Have Diminished Disease Control Despite Treatment with Infliximab (REMICADE®)

Study Name: REGAIN

EudraCT Number: 2013-001809-91

NCT No.: NCT01962974

Clinical Registry No.: CR102117

Coordinating Investigator: N/A

Study Centers: Canada and United States

Publication (Reference): None

Study Period: 18 October 2013 to 30 December 2014; Database lock: 30 January 2015

Phase of Development: 3b

OBJECTIVES:

Primary Objective:

The primary objective of this study was to determine the efficacy of golimumab 2 mg/kg intravenous (IV) plus methotrexate (MTX) in subjects with rheumatoid arthritis (RA) who initially responded to infliximab plus MTX but then had a diminished response to this therapy. The primary efficacy objective was to have been determined by the proportion of subjects that achieved an American College of Rheumatology (ACR20) response at 24 weeks.

Major Secondary Objectives:

The major secondary objectives of the study were to assess the following:

- The efficacy of golimumab 2 mg/kg IV plus MTX in subjects who had a confirmed presence of antibodies to infliximab (ie, the level of antibodies to infliximab detected in the sample was not equivocal per the lower limit of quantification [LLOQ]).
- The efficacy of golimumab 2 mg/kg IV plus MTX in subjects with trough infliximab levels below the LLOQ.
- The safety of golimumab plus MTX in subjects with RA who switched from infliximab plus MTX to golimumab plus MTX.

Exploratory Objectives:

Other objectives of the study included additional measures of response, health-related outcomes, patient preference, inflammatory markers, ribonucleic acid analysis, trough serum concentrations, and the development of antibodies to both infliximab and golimumab. Pharmacogenomics was also to be evaluated in consenting subjects.

METHODS:

This was a Phase 3b, single-arm, multicenter study of the efficacy of golimumab 2 mg/kg IV in subjects with active RA who were receiving MTX and had inadequate disease control (defined as an erythrocyte sedimentation rate [ESR]-based Disease Activity Score in 28 joints [DAS28] ≥3.2 and ≥4 swollen and ≥4 tender joints) despite current anti-TNFα therapy with infliximab every 4 weeks (q4w), 2 to 5 mg/kg q5w, 3 to 6 mg/kg q6w, 3 to 7 mg/kg q7w, or 4 to 8 mg/kg q8w, inclusive for each dose range, with at least 1 dose escalation or reduction in dose interval.

The study employed an open-label "active switch" design wherein subjects were moved from infliximab to golimumab 2 mg/kg IV. The Screening Visit occurred between Week -12 and Week -10. Consenting subjects who met screening criteria were enrolled and received their final dose of infliximab at Week -8 as part of actual clinical practice. Golimumab IV treatment, which was supplied by the sponsor, was received at Weeks 0, 4, 12, 20, and 28. The primary endpoint was planned at Week 24, the final efficacy assessment at Week 32, and a follow-up safety assessment by telephone at Week 44.

Subjects were to receive golimumab treatment of 2 mg/kg IV at Weeks 0 and 4 as an induction regimen, followed by a maintenance regimen of 2 mg/kg IV q8w. All subjects were to continue taking their current MTX treatment regimen. There was a maximum of 36 weeks between the last infliximab infusion at Week -8 and the last infusion of golimumab at Week 28. The duration of study participation was expected to be approximately 56 weeks.

The schedule for the various study procedures and evaluations are described in detail in the Time and Events Schedule located in the protocol (Appendix 1).

Number of Subjects (planned and analyzed):

Approximately 200 subjects were planned to be enrolled at approximately 85 global sites. The REGAIN study was terminated early due to low recruitment; only 7 subjects were enrolled at 5 investigational sites. All 7 subjects were included in the analyses.

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were men or women who were receiving infliximab plus MTX in actual clinical practice, who were ≥18 to ≤76 years of age with active RA, and had previously demonstrated initial and/or temporary improvement in disease signs and symptoms, but then exhibited a diminished response and inadequate disease control despite continued treatment. Subjects must have received infliximab in combination with MTX for a minimum of 9 months prior to Week -8.

Test Product, Dose and Mode of Administration, Batch No.:

The 50 mg Golimumab Final Vialed Product IV for IV administration was supplied as a single-use, sterile solution containing CNTO 148 Immunoglobulin G in a 4 mL, Type I glass vial. Each vial contained a 4 mL solution of 12.5 mg/mL golimumab in an aqueous medium of histidine, sorbitol, and polysorbate 80 at pH 5.5. No preservatives were present (Lot number DDS25_1 with expiration date 03 April 2015).

Reference Therapy, Dose and Mode of Administration, Batch No.:

Not Applicable.

Duration of Treatment:

Subjects were to receive golimumab treatment of 2 mg/kg IV at Weeks 0 and 4 as an induction regimen, followed by a maintenance regimen of 2 mg/kg IV q8w for a maximum of 36 weeks.

The total study duration for each subject was to be approximately 56 weeks (including the screening and enrollment period, 32 weeks of golimumab treatment and assessment, and a 12-week safety follow-up).

Criteria for Evaluation:

Efficacy Evaluations/Endpoints

Primary Endpoint: The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at Week 24.

If the proportion was less than 33.2%, the lower limit of the expected 95% confidence interval (CI), the study was considered negative.

Secondary Endpoints:

- For subjects who had a confirmed presence of antibodies to infliximab (ie, the level of antibodies to infliximab detected in the sample was not equivocal per the LLOQ), the proportion who achieved an ACR20 response at Week 24.
- For subjects with trough infliximab levels below the LLOQ at Week 0, the proportion who were to achieve an ACR20 response at Week 24.

Pharmacokinetic and Immunogenicity Evaluations

Prior to any IV administration of golimumab at baseline (Week 0), blood samples for measuring trough serum infliximab concentration and antibodies to infliximab were collected from all subjects. Analyses for serum infliximab concentration and antibodies to infliximab were to be performed using validated methods. Blood samples for measuring trough serum golimumab concentrations were collected prior to an infusion from all subjects at Weeks 0, 12, 24, and 28, or at the time of early termination. Analyses for serum golimumab concentration and antibodies to golimumab were to be performed using a validated method.

Biomarker Evaluations

Serum-based markers of inflammation that have been linked to RA disease activity were to be measured in all subjects. The markers of inflammation, including but not limited to interleukin-6 (IL-6), metalloproteinase-1 (MMP-1), and MMP-3, vascular cell adhesion molecule 1 (VCAM-1), and S-100 proteins, were to be evaluated. Serum-based biomarkers of bone and cartilage destruction and absorption, including but not limited to osteoprotegrin (OPG) and receptor activator of nuclear factor kappa-B ligand (RANK-L) were to be evaluated. RNA from whole blood was to be used for differential gene expression analyses to better understand the pathological mechanisms involved in RA, the effects of golimumab on whole blood gene expression, and to potentially identify a gene expression signature reflective of response to golimumab. Additional biomarkers such as but not limited to microRNAs could be measured in whole blood or serum.

Pharmacogenomic (DNA) Evaluations

Only deoxyribonucleic acid (DNA) research related to golimumab or infliximab or to the diseases for which these drugs were developed was to be performed. Genome wide pharmacogenomic and/or epigenetics testing were to be undertaken in this study in consenting subjects. Subjects participating in this portion of the study had to sign a separate informed consent form. Further, a subject could withdraw such consent at any time without affecting their participation in other aspects of the study, or their future participation in the study.

Safety Evaluations

Safety evaluations included adverse events (AEs), vital signs including weight, screening chest radiograph/chest computed tomography scan, tuberculosis testing and monitoring, hepatitis testing, concomitant medication review, pregnancy testing, urinalysis, and routine laboratory tests.

Statistical Methods:

Sample Size Determination

The objectives of this study were to be evaluated by the achievement of an ACR20 response. The projected sample size was based on the length of the CI for the proportion of subjects who achieve an ACR20 response at Week 24. If the proportion was 40%, then with 200 subjects, the 95% CI would be 33.2% to 47.1%.

Efficacy Analyses

For binary efficacy endpoints such as the primary endpoint, ACR20 at Week 24, the proportion of subjects with a response were to be determined and a 95% 2-sided CI calculated by the exact method. For continuous efficacy endpoints, summary statistics, such as mean, standard deviation (SD), and median, were to be determined and a 2-sided 95% CI calculated. All subjects who received at least 1 dose of 2 mg/kg IV golimumab were to be included in the analysis (modified intent-to-treat population). Missing data for efficacy variables was to be imputed by the last observation carried forward. For composite efficacy parameters, the data was to be imputed for the components first. If there was no baseline value, it was to be imputed with the median of all observed baseline values from subjects in the analysis population.

Treatment Failure Criteria:

If a subject met any of the following treatment failure criteria, the subject was to be considered as a nonresponder from that time onward for the binary endpoints. For continuous endpoints, the observed value was to be replaced with the 95th percentile based on data from subjects who were not treatment failures from that time onward.

1. Initiated treatment with disease-modifying antirheumatic drugs (other than MTX), systemic immunosuppressives, long acting opioids, and/or biologics for RA.
2. Increased the dose of MTX, sulfasalazine, or hydroxychloroquine above the baseline dose.
3. Initiated treatment with IV, intramascular, or epidural corticosteroids for RA.
4. Increased the dose of oral corticosteroids for RA above the baseline dose; initiated treatment with oral corticosteroids for RA for subjects not taking such medication at baseline; or use of oral corticosteroids for any therapeutic use including treatment for a diagnosis other than RA from Week 20 up to and including Week 24.
5. Discontinued study agent infusions due to an unsatisfactory therapeutic effect.

Pharmacokinetics

Descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum, were to be used to summarize serum concentrations of infliximab and golimumab at each sampling timepoint. The proportions of subjects with serum infliximab or golimumab concentration below the LLOQ at each timepoint were to be provided.

Immunogenicity Analyses

The incidence of antibodies to infliximab at baseline (Week 0) was to be summarized for all subjects who had serum samples for the detection of antibodies to infliximab. The incidence of antibodies to golimumab was to be summarized for all subjects who received a dose of golimumab and had serum samples for detection of antibodies to golimumab. Samples were to be obtained at Weeks 0, 12, 24, and 28.

Biomarker Analyses

Changes in the concentration of individual pharmacodynamic markers from baseline to the selected post treatment timepoints were to be summarized at Weeks 4, 12, and 28. The pharmacodynamics analysis was to characterize the response of subjects to golimumab and to determine if response to golimumab could be predicted. Results were to be presented in a separate biomarker technical report.

Pharmacogenomic Analyses

Results were to be presented in a separate pharmacogenomic technical report.

Medical Resource Utilization and Health Economics Analyses

Medical resource utilization and health economics were to be summarized using descriptive statistics as appropriate.

Safety Analyses

Adverse events were coded using the current version (17.0) of Medical Dictionary for Regulatory Activities. All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that had worsened since baseline) were to be included in the analysis. For each AE, the percentage of subjects who experienced at least 1 occurrence of the given event was to be summarized.

Summaries, listings, datasets, or subject narratives were to be provided, as appropriate, for those subjects who died, who discontinued treatment due to an AE, or who experienced a severe or a serious AE. Vital signs, and clinical laboratory test results, and changes from baseline, were tabulated at each scheduled timepoint, using descriptive statistics. Frequency tabulations of the abnormalities were to be made.

Data Quality Assurance:

The study was monitored according to the sponsor's current Standard Operating Procedure for the Monitoring of Clinical Trials. Steps taken to ensure the accuracy and reliability of the clinical study data included the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated study-site personnel prior to study start, and periodic monitoring visits by the sponsor or their delegate. The study-specific monitoring guidelines are stored in the trial master file (TMF).

During the course of this study, several activities were implemented to ensure proper operational study oversight (reference to TMF). These activities were focused on identification and resolution of operational and quality issues to ensure data integrity, protocol compliance, and safety of the study participants.

Written instructions were provided for the collection of source documentation. Source documentation was reviewed for accuracy and completeness by the sponsor during on-site monitoring visits, except for source data directly transmitted from the selected laboratory into the sponsor's database, and internal data reviews by various functions throughout the study and at the time of database lock. Discrepancies were resolved with the investigator or designees, as appropriate.

RESULTS:

STUDY POPULATION:

The REGAIN study actively recruited subjects; however, enrollment did not meet Study Team expectations. To address enrollment, the REGAIN Study Team solicited input from internal and external stakeholders. After consideration of multiple options, the decision was made to terminate the REGAIN study due to poor enrollment of subjects. Arrangements were made to ensure that post-termination of the study, each enrolled patient was given access to commercial product so they could receive the expected 6 doses outlined in the study.

From a safety perspective, golimumab was generally well tolerated, with a safety profile consistent with the golimumab prescribing information. No new safety issues were identified. This synoptic CSR describes the available data from the seven subjects who were enrolled in the REGAIN study. The seven subjects were enrolled at 5 study sites (4 in the US and 1 in Canada).

All seven subjects enrolled in the REGAIN Study were women, with a median age of 63.0 years, and an age range from 43 to 76 years (4 subjects <65 years; 3 subjects ≥65 years). Four (57.1%) subjects were white, 1 subject was black or African American, 1 subject was Asian and 1 subject did not identify her race. The median weight was 73.0 kg, and ranged from 59.0 kg to 92 kg. (Table 1)

The mean (SD) duration of infliximab treatment prior to the study as reported at Week -8 was 324.7 (222.0) weeks. The median infusion dose of infliximab at the enrolment visit was 5.0 mg/kg and ranged from 3 to 7 mg/kg. Each of the seven subjects enrolled received at least 1 dose of golimumab 2 mg/kg IV; 2 subjects received 4 doses, 1 subject received 3 doses, and 4 subjects received 2 doses of golimumab. The median duration of golimumab exposure was 33.0 days and ranged from 31.0 to 141.0 days (Attachment TSIEXP07). The median cumulative dose of golimumab was 373.75 mg and ranged from 243.8 mg to 715.0 mg (Attachment TSIEXP10).

Of the enrolled subjects, the median cumulative dose of MTX received from Week -8 to Week 0 was 126.4 mg, and the mean (SD) duration of MTX treatment from Week -8 to Week 0 was 8.3 (0.40) weeks (Attachment TSIPM02). Of the enrolled subjects the median dose of MTX at baseline was 15.0 mg and ranged from 10 mg to 20 mg (Attachment TSIPM03). The median cumulative dose of MTX received by enrolled subjects from Week 0 to end of study was 242.9 mg and the mean duration of treatment was 16.8 weeks (Attachment TSICM02).

The infusion duration for all 7 subjects, who received a total of 19 infusions, was between 25 to 35 min; the median infusion duration was 30 min (range: 28 to 35 min) (Attachment TSIEXP03).

Table 1: Summary of Demographics at Baseline

mITT Analysis Set (Study CNTO148ART3003)

	Golimumab 2 mg/kg IV
Subjects in mITT population	**7**
Age (years)	
N	7
Mean (SD)	60.0 (11.06)
Median	63.0
IQ range	(51.0; 67.0)
Range	(43; 76)
Category	
< 65 Years old	4 (57.1%)
≥ 65 Years old	3 (42.9%)
Sex	
N	7
Male	0
Female	7 (100.0%)
Race	
N	7
White	4 (57.1%)
Black or African American	1 (14.3%)
Asian	1 (14.3%)
American Indian or Alaskan native	0
Native Hawaiian or other Pacific islander	0
Other	1 (14.3%)
Unknown	0
Ethnicity (Hispanic/Latino?)	
N	7
Yes	1 (14.3%)
No	6 (85.7%)
Unknown	0
Weight (kg)	
N	7
Mean (SD)	76.30 (11.873)
Median	73.00
IQ range	(68.90; 88.90)
Range	(59.0; 92.0)
Category	
<= 75 kg body weight	4 (57.1%)
> 75 kg body weight	3 (42.9%)

Key: IQ=interquartile range; IV=intravenous; mITT=modified intent-to-treat; SD=standard deviation
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Summary of concomitant medications by Anatomical Therapeutic Chemical (ATC) class and drug are summarized in Attachment TSICM01. Summary of prior medications by ATC Class and drug are summarized in Attachment TSIPM01. The most common types of prior and concomitant medications used by ATC class were angiotensin-converting-enzyme inhibitors (plain), folic acid derivatives, and HMG COA reductase inhibitors (each 42.9% [3/7] for both prior as well as concomitant medications).

The other RA medications used at baseline were prednisone, folic acid, hydroxychloroquine phosphate, MTX, celecoxib, ibuprofen hydrocodone, and paracetamol (Attachment LSICM03).

EFFICACY RESULTS

The efficacy data for the 7 subjects is provided in Table 2.

DAS28 (ESR):

- Compared to the Week 0 visit, 5 subjects were reported to have improvement in their DAS28 scores at early termination; the DAS28 score was missing for the remaining 2 subjects at early termination.

Tender Joint Count (TJC):

- Compared to the Week 0 visit, 6 subjects were reported to have a decrease in TJC at early termination, and 1 subject reported an increase in TJC at early termination.

Swollen Joint Count (SJC):

- Compared to the Week 0 visit, all 7 subjects were reported to have a decrease in SJC and 2 subjects reported no swollen joints at early termination.

Patient Global Assessment (PGA):

- Compared to Week 0 PGA scores, six subjects showed a decrease (improvement) in PGA scores at early termination.

ESR:

- Compared to the respective week 0 ESR value, 4 subjects were reported to have a decrease in ESR values at early termination; the ESR value was missing for 3 subjects at early termination.

Since only 7 subjects were enrolled in the REGAIN trial and provided data at the time of termination, conclusive statements regarding efficacy cannot be made.

Table 2: List of Efficacy Data for Each Subject; mITT Population

Subject ID	Week	DAS 28 (ESR[a])[b]	TJC[c]	SJC[d]	PGA[e]	ESR
[redacted]	-8	5.240	5	4	29	75
	0	6.244	16	4	35	68
	Early term	.	22	1	77	.
	-8	6.251	12	10	73	31
	0	7.043	18	9	73	55
	Early term	5.715	10	2	69	.
	-8	.	10	9	78	.
	0	5.708	9	9	23	60
	12	3.330	3	0	14	22
	24	3.439	2	0	19	30
	Early term	2.713	1	0	4	20
	-8	.	21	21	50	.
	0	7.699	21	16	91	50
	12	4.725	5	3	78	15
	24	5.565	20	1	32	28
	Early term	.	0	0	14	.
	-8	7.079	20	16	69	35
	0	7.368	24	18	61	40
	Early term	6.218	17	17	47	20
	-8	5.405	9	5	53	29
	0	6.200	13	9	43	50
	12	4.819	5	4	37	35
	Early term	4.603	5	2	41	30
	-8	6.153	17	12	32	32
	0	6.952	25	12	54	32
	Early term	3.469	3	2	3	19

[a] Erythrocyte sedimentation rate (mm/h).
[b] Disease Activity Index Score based on ESR and 28 joints.
[c] Tender joint count (28 joints).
[d] Swollen joint count (28 joints).
[e] Patient Global Assessment.

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PHARMACOKINETIC RESULTS

There were no pharmacokinetic results obtained in this study due to the low number of subjects enrolled.

IMMUNOGENICITY ANALYSES RESULTS

There were no immunogenicity results obtained in this study due to the low number of subjects enrolled.

BIOMARKER ANALYSES RESULTS

There were no biomarker analyses results obtained in this study due to the low number of subjects enrolled.

PHARMACOGENOMIC RESULTS

There were no pharmacogenomic analyses obtained in this study due to the low number of subjects enrolled.

MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS RESULTS

There were no medical resource utilization or health economics analyses obtained in this study due to the low number of subjects enrolled.

SAFETY RESULTS:

- None of the subjects reported AEs, serious AEs, or AEs leading to discontinuation of the study agent.
- None of the subjects reported a delayed hypersensitivity reaction.
- No subjects died after start of the study.
- No subject became pregnant during the study.
- No subject had more than 1 postbaseline markedly abnormal hematology or serum chemistry values.
- No subject had a postbaseline alanine transaminase or aspartate aminotransferase value >3 x upper limit of normal.
- No subject had more than 1 postbaseline markedly abnormal value in vital signs.
- No subject had a positive tuberculosis test postbaseline.

Study Limitations:

The primary limitation for the REGAIN Study was the very low enrolment, ie, 7 subjects which led to the early termination of the study. These 7 subjects received a total of 19 infusions and the median cumulative dose of golimumab was 373.75 mg.

CONCLUSIONS:

- Due to the very small sample size, it is not possible to make any definitive conclusions regarding efficacy of the study drug.
- No adverse events were noted; however due to the small sample size and limited number of infusions, no definitive safety conclusion can be made.

REFERENCES

None.

LOCAL SPONSORS

Legal Entity Considered as the Sponsor	for Investigational Sites Located In:
Janssen Scientific Affairs – US	US
Janssen Biotech - Canada	Canada

SIGNATURE OF SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE:	A Golimumab Phase 3b, Multicenter, Assessment of Intravenous Efficacy in Rheumatoid Arthritis Subjects Who Have Diminished Disease Control Despite Treatment with infliximab (REMICADE®)
REPORT CONTRIBUTORS:	[redacted] PhD; [redacted] PhD; [redacted] MD; [redacted] PhD; [redacted] PhD; [redacted] PhD; [redacted] BA

SPONSOR'S RESPONSIBLE MEDICAL OFFICER

NAME:	[redacted] MD
TITLE:	[redacted]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE:	[redacted]
DATE:	04 MAY 2015

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