SYNOPSIS

Study Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Guselkumab in Subjects with Active Lupus Nephritis

Study Number: CNTO1959LUN2001

Study Phase: Phase 2

Name of Study Intervention: CNTO1959 (guselkumab)

Name of Sponsor/Company: Janssen Research & Development*

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Status: Approved

Date: 20 September 2023

Prepared by: Janssen Research & Development, LLC

Study Name: ORCHID-LN

Regulatory Agency Identifier Number:

EudraCT	2018-003155-38
IND	140547
CT.gov	NCT04376827

Number of Study Center(s) and Countries/Territories:

This study was conducted at 20 centers in Argentina, Mexico, Poland, Russia, Spain, Thailand, Taiwan, Ukraine, and United States of America.

Publications (if any):

None

Study Period:

18 November 2020 to 01 February 2023

Rationale:

Lupus nephritis (LN) is a manifestation of SLE affecting up to 60% of SLE patients at some point in their disease course. Clinicopathologic Class III (focal proliferative) and Class IV (diffuse proliferative) LN per the current classification system of International Society of Nephrology/Renal Pathology Society

(ISN/RPS) are considered more severe and have a poorer prognosis than Class I (minimal disease) or Class II (mesangial proliferative). Both Class III and IV LN may have active (proliferative), inactive (sclerosing), or combined active and inactive lesions. Approved therapies for active LN are lacking, and patients with Class III or IV disease have a 50 to 75% risk of end-stage renal disease requiring dialysis within 10 years. There is a high unmet need for new treatment options in LN that are safe and effective, especially new therapies that can provide improved long-term efficacy (ie, sustained remission) over currently available therapies.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of guselkumab in participants with active lupus nephritis (LN)	**Primary endpoint**: Proportion of participants achieving at least 50% decrease in proteinuria from baseline at Week 24 **Major secondary endpoints** to include: • Proportion of participants achieving complete renal response (CRR) at Week 24 • Proportion of participants achieving a sustained reduction in steroid dose ≤10 mg/day of prednisone or equivalent from Week 16 to Week 24 • Proportion of participants achieving at least 50% decrease in proteinuria from baseline at Week 52 • Proportion of participants achieving CRR at Week 52 • Proportion of participants with Urine Protein to Creatinine Ratio (UPCR) <0.5 mg/mg at Week 24 • Proportion of participants with UPCR <0.75 mg/mg at Week 24 • Time to achievement of CRR • Time to treatment failure (TF).
Secondary	
To evaluate the safety and tolerability of guselkumab in participants with active LN	• Frequency and type of adverse events (AEs), serious adverse events (SAEs), reasonably related AEs, AEs leading to discontinuation of study intervention, infections, serious infections, and infections requiring oral or parenteral antimicrobial treatment, AEs temporally associated with an infusion, and injection-site reactions. • Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry). • Summary of maximum Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade for postbaseline laboratory values (hematology and chemistry)

	• Systolic and diastolic blood pressures over time.
To evaluate the pharmacokinetics (PK) and immunogenicity in participants with active LN	• Serum guselkumab levels over time • Serum anti-guselkumab antibodies through Week 24, through Week 60, end of long-term extension (LTE), and in participants discontinuing study intervention early.

Hypothesis

The primary hypothesis of this study is that guselkumab plus standard-of-care is superior to placebo plus standard-of-care in participants with active LN as measured by the proportion of guselkumab-treated participants achieving at least a 50% reduction of proteinuria with protocol specified steroid tapering regimen at Week 24.

Methodology (Study Design):

This was a Phase 2, randomized, double-blind, placebo-controlled, parallel, multicenter, interventional study conducted in 20 centers across 9 countries to assess the efficacy, safety, PK, immunogenicity, and PD of guselkumab in adult patients with active LN on a standard-of-care regimen of MMF/MPA and glucocorticoids.

The planned total sample size was approximately 60 participants who were to be randomly assigned to 1 of 2 treatment groups.

- Guselkumab: Participants were to receive guselkumab 400 mg IV at Weeks 0, 4 and 8 (ie, 3 IV doses) and guselkumab 200 mg SC q4w from Week 12 through Week 48.
- Placebo: Participants were to receive placebo IV at Weeks 0, 4 and 8 (ie, 3 IV doses) and placebo SC q4w from Week 12 through Week 48.

Randomization was stratified by geographic region (North America, Latin America, Asia Pacific, and Europe) and UPCR level (<3 mg/mg and ≥3 mg/mg).

The study also included a 2-yr LTE phase which was to begin after assessments were completed at Week 52.

Participants in the study were to maintain their standard-of-care treatment of mycophenolate mofetil (MMF)/mycophenolic acid (MPA) and background glucocorticoid following the protocol-specified glucocorticoid taper schedule.

Efficacy, safety, PK, immunogenicity, and biomarkers (where local regulations permit) were to be assessed according to the SoA. An optional pharmacogenomic blood sample was to be collected from participants who consented to the collection of these samples (where local regulations permitted). Participants who experienced an LN flare during the study were to be discontinued from study intervention and were required to complete the final efficacy/safety follow-up visits.

An external independent DMC was commissioned for the study.

This study was originally planned to enroll a target of approximately 60 participants with a total duration of up to approximately 68 weeks for the double-blind period. Due to enrollment challenges, the Sponsor decided to stop screening of new participants and terminate the study early. As a result, 33 participants of the planned 60 were enrolled in the study. Following the decision to terminate the study early, only 1 DBL was planned.

Number of Participants (planned and analyzed):

An original target of approximately 60 participants were to be randomly assigned in this study with a 1:1 ratio.

Of the 105 participants screened, a total of 33 participants with active LN were enrolled and randomized to receive guselkumab (17 participants) or placebo (16 participants).

Diagnosis and Main Criteria for Inclusion:

The target population consisted of adult participants with active LN on a standard-of-care regimen of MMF/MPA and glucocorticoid. The target population were men and women aged 18 to 75 (inclusive) who met SLE classification by 2019 EULAR/ACR criteria; had documented active ISN/RPS proliferative LN (Class III/IV LN with or without Class V membranous nephritis) based on kidney biopsy within the last 6 months prior to screening or during screening. Participants were required to have had UPCR values of ≥1.0 mg/mg assessed on 2 first morning urine void specimens during screening; this requirement was to be met after at least 8 weeks of MMF/MPA treatment, and after stable glucocorticoid dosing was achieved at the dose intended at the time of randomization. At screening and randomization, participants were required to be receiving oral glucocorticoids at a minimum prednisone equivalent dose of 10 mg/day and maximum 1 mg/kg/day or ≤60 mg/day, whichever was lower, for ≥6 weeks with stable dosing for ≥2 weeks prior to randomization. The dose of MMF was required to be ≤3 g/day or MPA was required to be at dose of ≤2 g/day.

Study Interventions, Dose, and Mode of Administration:

Participants were randomized to 1 of 2 treatment groups as described below:

- Guselkumab 400 mg IV at Weeks 0, 4 and 8 (ie, 3 IV doses) and guselkumab 200 mg SC q4w from Week 12 through Week 48.
- Placebo IV at Weeks 0, 4 and 8 (ie, 3 IV doses) and placebo SC q4w from Week 12 through Week 48.

During the LTE, participants were to receive the study intervention SC every 4 weeks (q4w) that was assigned at randomization. Study blinding procedure was to be maintained through the LTE phase.

In addition, participants in the study maintained their standard-of-care treatment of MMF/MPA and background glucocorticoid. The glucocorticoid dose was required to be tapered starting from Week 2 with an aim to achieve dose of 5 mg QD prednisone equivalent by Week 12 based on protocol-specified schedule.

Duration of Study Intervention:

The planned total duration of the main study was up to 68 weeks (≤8-Week screening period, a 48-week double-blind treatment period, and a 12-week safety follow-up period after the last dose). Participants starting MMF/MPA at/or within 2 weeks of screening could extend screening for up to 4 additional weeks.

Statistical Analyses:

Due to enrollment challenges, the Sponsor decided to stop screening of new participants and terminate the study early; hence, some of the planned analyses were not performed. The main estimand for the primary efficacy endpoint and major secondary efficacy endpoints were analyzed and presented in this abbreviated CSR. Selected PK (serum concentration) and immunogenicity analyses were performed. All safety results were summarized.

Simple descriptive statistics, such as n, mean, standard deviation (SD), median, interquartile (IQ) range, minimum and maximum for continuous variables and counts and percentages for discrete variables were used to summarize most data.

For the secondary time to event endpoints, survival curves using KM estimates were provided. In addition, the hazard ratio using a Cox proportional hazards model adjusted for geographic region and baseline UPCR level (<3 mg/kg and ≥3 mg/kg) and its 80% CI were also provided.

Treatment-emergent adverse events (TEAEs) were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA), Version 25.1, using the lower-level term (LLT) as the description most closely related to the investigator's terminology, a preferred term describing a group of closely related LLTs, and the system organ class (SOC), which is the broad category including related preferred terms.

Sample Size Determination

Total sample size of 60 were planned to provide 90% power to detect a significant difference with a 1-sided alpha of 10%, assuming the proportion of placebo participants with ≥50% decrease in proteinuria is 49%, and the difference between intervention group is 30%. Due to the Sponsor's decision to terminate the study early, 33 participants were enrolled in the study.

SUMMARY OF RESULTS AND CONCLUSIONS:

Treatment and Participant Disposition:

Of the 105 participants screened, a total of 33 participants with active LN and receiving ongoing standard-of-care were enrolled and randomized to receive guselkumab (17 participants) or placebo (16 participants). Majority of the participants were from Europe (15 [45.5%]; Russia and Ukraine) and Latin America (13 [39.4%]; Argentina and Mexico) followed by Asia Pacific (4 [12.1%]; Thailand and Taiwan) and North America (1 [3.0%]).

Study treatment:

Of 33 participants, 32 participants (16 in the guselkumab group and 16 in the placebo group) completed treatment through Week 24 (defined as received treatment through Week 20). One participant in the guselkumab group discontinued study treatment prior to Week 24 due to a TEAE.

A total of 16 (48.5%) participants completed study intervention (received treatment through Week 48) while 17 (51.5%) participants (10 [58.8%] in the guselkumab group and 7 [43.8%] in the placebo group) discontinued study treatment prior to the end of the main study.

Additionally, 5 participants (1 in the guselkumab group and 4 in the placebo group) received treatment in the LTE phase of the study. None of the participants completed the treatment in the LTE phase.

Study participation:

All participants completed study participation through Week 24 (timepoint at which data from the primary efficacy and some secondary endpoints were analyzed).

A total of 16 (48.5%) participants (9 [52.9%] participants in the guselkumab group and 7 [43.8%] participants in the placebo group) discontinued study participation prior to the end of the main study. The most common reason for discontinuation of study participation was study terminated by the Sponsor, which was reported by 14 (42.4%) participants (8 [47.1%] in the guselkumab group and 6 [37.5%] in the placebo group).

Of the 5 (15.2%) participants who entered the LTE, 1 (5.9%) was in the guselkumab group and 4 (25.0%) were in the placebo group. None of the participants completed the LTE.

Demographic and Baseline Characteristics

Of the 33 participants, a higher proportion were female versus male participants (29 [87.9%] versus 4 [12.1%]) and the majority were White (26 [78.8%] participants). The mean (SD) age of all the study population was 37.0 (10.86) years (range: 20 to 71 years). Two (6.1%) participants were ≥55 years of age. The mean (SD) BMI was 26.01 (4.880) kg/m^2 with 6 (18.2%) participants who were obese (BMI ≥30 kg/m^2). The age, gender, and BMIs were balanced across both treatment groups.

The ethnicity reported for randomized participants consisted of 11 (33.3%) Hispanic or Latino origin. There were slightly more Hispanic or Latino participants in the guselkumab group (7 [41.2%]) than in the placebo group (4 [25%]).

There were some differences in baseline disease characteristics observed between the treatment groups with respect to duration of LN disease, proteinuria level, eGFR, and antibody titers.

Prior and Concomitant Therapy

All randomized participants received standard-of-care treatment with MMF/MPA and oral glucocorticoids, with a comparable mean daily dose between the treatment groups. There were more participants with ongoing ACE inhibitors or angiotensin receptor blockers in the placebo group (81.3%) than in the guselkumab group (41.2%). Additionally, a slightly higher proportion of participants in the placebo group (68.8%) were taking ongoing antimalarials compared to the guselkumab group (52.9%).

Protocol Deviations

Overall, 12 participants (9 in the guselkumab group and 3 in the placebo group) had major protocol deviations during the study. The most common deviation was that the assessment of suicidal ideation or behavior using the eC-SSRS was not done at the scheduled visit participants. Majority of the deviations were reported in the European region.

One participant from the guselkumab group did not meet an inclusion criterion and 1 participant from the placebo group met an exclusion criterion. These deviations did not have any impact on the study or its results.

Exposure:

The median total duration of treatment exposure was 44.14 weeks in guselkumab group and 48.36 weeks in the placebo group. Overall, 16 (94.1%) participants in the guselkumab group and 16 (100.0%) participants in the placebo group were treated for >12 weeks. The median total dose (IV and SC) was 2800.0 mg in the guselkumab group. All randomized participants received the assigned study intervention.

Efficacy Results:

Primary Efficacy Endpoint

Proportion of Participants Who Achieved 50% Decrease in Proteinuria

There was no statistically significant difference between treatment groups in participants achieving at least 50% decrease in proteinuria from baseline at Week 24. A numerically greater proportion of participants in the placebo group achieved at least 50% decrease in proteinuria from baseline at Week 24 than those in the guselkumab group (1-sided p-value = 0.891).

Major Secondary Endpoints

Proportion of participants achieving CRR at Week 24

At Week 24, no notable difference was observed in the proportion of participants achieving CRR between the guselkumab and placebo treatment groups. The 1-sided p-value was 0.572.

Proportion of participants achieving a sustained reduction in steroid dose ≤10 mg/day of prednisone or equivalent from Week 16 to Week 24

The proportion of participants who achieved a sustained reduction in steroid dose of ≤10 mg/day of prednisone or equivalent from Week 16 to Week 24 was higher in the guselkumab group compared to the placebo group. The 1-sided p-value was 0.247.

Proportion of participants achieving at least 50% decrease in proteinuria from baseline at Week 52

Based on the FAS, the proportion of participants achieving at least 50% decrease in proteinuria from baseline at Week 52 was similar between both treatment groups. The treatment difference based on the main composite estimand was -12.7% with an 80% CI of -44.7% to 19.4%. The 1-sided p-value was 0.694. Results using the FASC52 were consistent with the results of the FAS (p-value = 0.648).

Proportion of participants achieving CRR at Week 52

Based on the FAS, the proportion of participants achieving CRR at Week 52 was lower in the guselkumab group compared to the placebo group. The 1-sided p-value was 0.962. Results using the FASC52 were consistent with the results of the FAS.

Proportion of participants with UPCR <0.5 mg/mg at Week 24

A higher proportion of participants in the guselkumab group compared to those in the placebo group had a UPCR of <0.5 mg/mg at Week 24. The 1-sided p-value was 0.400.

Proportion of participants with UPCR <0.75 mg/mg at Week 24

A UPCR of <0.75 mg/mg at Week 24 was almost similar between the treatment groups. The 1-sided p-value was 0.567.

Time to achievement of CRR

Through Week 24 hazard ratio between the treatment groups was 0.62 (0.27, 1.41) with a 1-sided log-rank p-value of 0.7807.

Time to treatment failure (TF)

There was no notable difference between treatment groups in the time to TF. Approximately 20% of participants in both treatment groups had TFs by Week 52 (1-sided long-rank p-value of 0.4654).

Safety Results:

The frequencies of all TEAEs reported during the study was comparable between the treatment groups.

Adverse Events

Overall, the distribution of TEAEs was similar across treatment groups. At least 1 TEAE was reported by 12 (70.6%) participants in the guselkumab group and 12 (75.0%) participants in the placebo group throughout the study.

Majority of the TEAEs were assessed as mild or moderate in severity except for LN and anaemia reported in the guselkumab group and basal ganglia stroke reported in the placebo group.

The MedDRA SOCs with the most frequently reported TEAEs (>20% frequency in the guselkumab versus placebo group) were Infections and infestations, Renal and urinary disorders, Blood and lymphatic system disorders, Metabolism and nutrition disorders, and Gastrointestinal disorders.

The most frequently reported infections (>10% frequency in the guselkumab versus placebo group) were urinary tract infection, COVID-19, influenza, and herpes zoster.

No treatment emergent deaths were reported during the study.

Serious Adverse Events

One participant each in the guselkumab and placebo treatment groups experienced an SAE: LN (guselkumab group) and basal ganglia stroke (placebo group).

Discontinuations Due to Adverse Events

Two participants in the guselkumab group and 1 participant in the placebo group discontinued study intervention due to a TEAE. All 3 reports of discontinuations were related to the underlying condition (systemic lupus erythematosus and LN).

Adverse Events of Clinical Interest

No opportunistic infections, active TB, serious infections, malignancies, anaphylactic or serum sickness reactions, hypersensitivity reactions, events of suicidal behavior or suicidal self-injurious behavior, or venous thromboembolic events were reported during the study.

Other Significant Adverse Events

One participant from the placebo group reported a MACE of basal ganglia stroke during the study.

One participant from the placebo group reported TEAEs temporally associated with an infusion of the study intervention (tension headache and hypertension). Another participant, also from the placebo group, had an injection site reaction (injection site erythema).

Evaluation of Clinical Laboratory Tests and Vital Signs

There were no consistent, potentially clinically meaningful changes observed for either treatment group during the study. No clinically significant findings were noted in the clinical laboratory values or vital signs data.

Pharmacokinetic Results:

Following IV administration of 400 mg guselkumab at Weeks 0, 4 and 8, median serum guselkumab concentrations 1 hour post IV infusion at Week 0 was 141.86 µg/mL. One participant from the guselkumab group had all tested concentrations below LLOQ and was excluded from all other PK-related analysis.

At Week 24, the time of the primary efficacy endpoint, median trough serum guselkumab concentration was 5.39 µg/mL following SC maintenance dose of 200 mg q4w starting from Week 12.

Immunogenicity Results:

The incidence of antibodies to guselkumab through Week 60 was observed in 1 (5.9%) of 17 participants. None of the ADA-positive participants had positive NAbs to guselkumab.

Conclusions:

Due to enrollment challenges, the Sponsor decided to stop screening of new participants and terminate the study early. As a result of the small sample size, this study lacks sufficient power to differentiate between the treatment groups.

Overall, participants enrolled in the study exhibited relatively mild disease. Based on limited data, there is not enough evidence to reach a clear conclusion for efficacy of guselkumab used in the treatment of participants with LN who also received background standard-of-care.

Guselkumab was well tolerated in participants with active LN. Safety data in the study were consistent with the known safety profile of guselkumab and there were no new safety signals.

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