SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	CNO 1959 (guselkumab)

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Status: Approved

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Prepared by: Janssen Research & Development, LLC

Protocol No.: CNTO1959PSO1003

Title of Study: A Phase I, Open-label, Drug Interaction Study to Evaluate the Effect of Guselkumab (CNTO 1959) on Cytochrome P450 Enzyme Activities Following a Single Subcutaneous Administration in Subjects with Moderate to Severe Plaque-type Psoriasis

NCT No.: NCT02397382

Clinical Registry No.: CR106796

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Study Center(s): United States of America (7 sites)

Publication (Reference): None

Study Period: 16 June 2015 – 31 August 2016

Phase of Development: 1

Objectives:

Primary Objective

The primary objective of this study was to evaluate the potential effects of a single subcutaneous (SC) dose of 200 mg guselkumab on the pharmacokinetics (PK) of a cocktail of representative probe substrates of CYP isozymes (CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2) in subjects with moderate to severe psoriasis.

Secondary Objective

The secondary objective of the study was to assess the safety and tolerability of a single SC dose of 200 mg guselkumab and a cocktail of representative probe drug substrates for CYP isozymes when administered alone or in combination.

Methodology:

This was an open-label, multicenter, Phase 1 drug interaction study designed to evaluate the effect of a single SC dose of 200 mg guselkumab on the PK of a cocktail of representative probe substrates of CYP isozymes (midazolam [CYP3A4], warfarin [CYP2C9], omeprazole [CYP2C19], dextromethorphan [CYP2D6], and caffeine [CYP1A2]) in men and women 18 to 65 years of age, inclusive, who had a diagnosis of moderate to severe plaque-type psoriasis (with or without psoriatic arthritis [PsA]) with a screening Psoriasis Area and Severity Index (PASI) ≥12 and Investigator's Global Assessment (IGA) ≥3.

Approximately 18 subjects were to be enrolled in this study, with the expectation of having 12 subjects that completed the Day 40 assessments for the PK of probe substrates.

There was 1 treatment group in this study. Randomization was not to be used in this study. All subjects were to receive a single SC dose of 200 mg guselkumab on Day 8. All subjects were to receive a probe cocktail administration on Days 1, 15, and 36.

The probe cocktail consisted of oral doses of 0.03 mg/kg of midazolam, 10 mg of warfarin (+10 mg of vitamin K), 20 mg of omeprazole, 30 mg of dextromethorphan, and 100 mg of caffeine.

Dose Regimens For Cytochrome P450 Probe Substrates

CYP Isozyme	Probe	Route	Dose
CYP3A4	midazolam	oral	0.03 mg/kg
CYP2C9	warfarin[a]	oral	10 mg
CYP2C19	omeprazole	oral	20 mg
CYP2D6	dextromethorphan	oral	30 mg
CYP1A2	caffeine	oral	100 mg

a : Vitamin K was co-administered with warfarin.

Number of Subjects (planned and analyzed):

A total of 17 subjects with psoriasis, genotyped to exclude poor metabolizers of CYP2C9, CYP2D6, and CYP2C19, were enrolled into the study, of which 16 subjects received at least 1 probe cocktail administration, 14 subjects received treatment with guselkumab, and 12 subjects completed the study. All subjects received study agents were analyzed for pharmacokinetics (subjects with unverified midazolam dose were excluded from the PK evaluation for midazolam) and safety.

Diagnosis and Main Criteria for Inclusion:

Men or women at least 18 years of age, with a diagnosis of moderate to severe plaque-type psoriasis (with or without PsA) for at least 6 months before Day 1; with a PASI ≥12, IGA ≥3, and involved body surface area ≥10% at screening; and who were candidates for phototherapy or systemic treatment for psoriasis (either naïve or history of previous treatment), were eligible for enrollment into the study. Subjects with a pulse oximetry value <94% at screening (a single retest of pulse oximetry is permitted if necessary), or genetically determined poor metabolizers of CYP2C9, CYP2C19, and CYP2D6 substrates (ie, subjects who did not have at least 1 functional allele for CYP2C9, CYP2C19, and CYP2D6), or had an organ transplant, or were pregnant, nursing, or planning a pregnancy (both men and women) during the study, and for at least 12 weeks after receiving the last administration of guselkumab, were to be excluded from the study.

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

The term "study agent" referred to guselkumab, the term "probe cocktail" referred to the combination of midazolam, warfarin (+vitamin K), omeprazole, dextromethorphan, and caffeine, and the term "probe substrate" referred to the individual compounds midazolam, warfarin, omeprazole, dextromethorphan, and caffeine.

All subjects were to receive a single SC dose of 200 mg guselkumab (administered as 2 injections, 100 mg each) on Day 8. All subjects were to receive a probe cocktail on Days 1, 15, and 36. The probe

cocktail consisted of oral doses of 0.03 mg/kg of midazolam, 10 mg of warfarin (+10 mg of vitamin K), 20 mg of omeprazole, 30 mg dextromethorphan, and 100 mg of caffeine.

The lot number information of the guselkumab supply used in the study is as follows: 4370588, 4371818, and 437818. The probe substrates which made up the probe cocktail were to be stored according to their commercial labeling.

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

No reference therapy was used in this study.

Duration of Treatment:

The total duration of study participation was to be approximately 17 weeks, including a screening visit up to 4 weeks prior to first probe cocktail administration. Subjects were to have 4 in-patient periods, 3 periods consisting of 3 days and 2 nights each, and 1 period consisting of 2 days and 1 night. There were to be study visits at Days 64 and 92 for safety assessments and for collection of guselkumab PK and immunogenicity samples.

There were to be approximately 12 weeks of safety follow-up after guselkumab administration. Completion of the Day 92 visit constituted a subject's completion of the study.

Criteria for Evaluation:

Pharmacokinetics:

Blood samples were collected for the measurement of plasma concentration of CYP probe substrates including midazolam, omeprazole, S-warfarin, dextromethorphan and caffeine. PK parameters for midazolam, omeprazole, S-warfarin, dextromethorphan and caffeine were calculated from plasma concentration-time data using non-compartmental analyses. PK parameters included, but were not limited to, maximum observed plasma concentration (C_{max}), time to reach the maximum observed plasma concentration (T_{max}), area under the concentration versus time curve from time 0 to infinity with extrapolation of the terminal phase (AUC_{inf}), area under the concentration versus time curve from time zero to the time corresponding to the last quantifiable concentration (AUC_{last}), area under the concentration time curve between 0 and 24 hours (AUC_{0-24h}, for midazolam, omeprazole, dextromethorphan, and caffeine), area under the concentration time curve between 0 and 96 hours (AUC_{0-96h}, S-warfarin only), terminal half-life ($T_{1/2}$), apparent total systemic clearance after oral administration (CL/F), apparent volume of distribution based on terminal phase after oral administration (V_z/F).

Blood samples were also collected for the evaluation of serum guselkumab concentrations.

Immunogenicity:

To assess the immunogenicity of guselkumab, serum samples were collected for the detection of antibodies to guselkumab.

Serum-based Biomarkers:

Serum samples collected for concentration of guselkumab and antibodies to guselkumab could also be used for analysis of pro-inflammatory cytokines. If a positive drug interaction was observed with guselkumab and any of the probe substrates, these samples were to be analyzed to explore changes in pro-inflammatory cytokines known to be downstream of interleukin (IL)-23 (eg, IL-17A and IL-17F), and known to impact the expression of CYP450 isozymes (eg, interferon-γ, IL-1β, IL-6, and tumor necrosis factor-α) following administration of guselkumab.

Pharmacogenomics:

After obtaining written informed consent, a CYP genotyping blood sample was to be obtained at screening to determine eligibility for the study. Deoxyribonucleic acid samples from subjects who met the remaining inclusion/exclusion criteria were to be genotyped for the common polymorphisms in the CYP2C9, CYP2C19, and CYP2D6 genes to identify poor metabolizers to CYP2C9, CYP2C19, and CYP2D6.

Safety:

Assessment of safety included laboratory measurements (hematology, serum chemistry, coagulation, serology, drug screen, alcohol screen, testing for tuberculosis [TB], pregnancy testing), physical examination findings, electrocardiogram (ECG), height, body weight, body mass index (BMI), pulse oximetry, vital sign measurements, and monitoring of adverse events (AEs) and injection-site reactions. Urine drug screen and alcohol breath test were to be performed.

Statistical Methods:

Study population information was to be summarized on all subjects who had signed an informed consent form and received at least 1 dose of study agent (guselkumab or probe cocktail). Demographic data were to be summarized using descriptive statistics.

Sample Size Determination:

There was no formal hypothesis to be tested in this study. Therefore, no formal sample size power calculation was undertaken. Approximately 18 subjects were to be enrolled in this study, with the expectation of having 12 subjects that completed the Day 40 PK assessments for probe substrates.

Pharmacokinetics:

PK analyses were to be based on all subjects who received at least 1 dose of CYP probe cocktail before or after guselkumab treatment and had at least one postdose sample collected. PK evaluable subjects were all subjects who provided a C_{max} or AUC for at least one CYP probe substrate before and after guselkumab treatment. Descriptive statistics, including arithmetic mean, standard deviation (SD), coefficient of variation (CV), median, minimum, maximum, and geometric mean (when applicable) were to be used to summarize plasma concentration data of each probe substrate at each planned sampling time point and for all PK parameters of probe substrates.

Serum guselkumab concentrations were also to be summarized using descriptive statistics.

Immunogenicity:

The incidence of antibodies to guselkumab was to be summarized for all subjects who received guselkumab treatment and had at least 1 serum sample obtained for the detection of antibodies to guselkumab after guselkumab treatment.

Serum Based Biomarkers Analyses:

Exploratory serum based biomarker measurements (pro-inflammatory cytokines) would be reported in an independent technical report if the samples were analyzed.

Assessments of Disease Severity of Psoriasis

Investigator's Global Assessment (IGA) to assess grade lesions for induration, erythema, and scaling; and Psoriasis Area and Severity Index (PASI) to assess and grade the severity of psoriatic lesions and their response to therapy were evaluated prior to and after guselkumab treatment.

Safety:

For safety, the incidence of adverse events was to be summarized by body system and preferred term. Laboratory data were to be summarized by type of laboratory test and the incidence of abnormal laboratory parameters (hematology and chemistry). Descriptive statistics were to be calculated for laboratory analytes at screening and at each scheduled time point. Descriptive statistics of heart rate and blood pressure (systolic and diastolic) values and changes from baseline were to be summarized at each scheduled time point. Abnormal Grade 2 or higher abnormal laboratory test results, abnormal physical examination findings, and clinically significant abnormal ECG findings were to be listed.

RESULTS:

STUDY POPULATION:

A total of 17 subjects with psoriasis were enrolled into the study, of which 16 subjects received at least 1 probe cocktail administration and 14 subjects received treatment with guselkumab. Of the 16 subjects who received study agents (either probe cocktail or guselkumab), 12 subjects completed the study and 4 subjects were discontinued from the study due to an AE, lost to follow-up, physician decision (difficult blood draws), and pregnancy (each 1 subject). One subject withdrew consent before receiving any treatment with study agents (either probe cocktail or guselkumab) due to scheduling conflicts.

Seven men and 9 women received treatment with study agents during the study. The mean (SD) age was 43.1 (14.39) years and the mean (SD) BMI was 35.02 (8.30) kg/m^2. A majority of the subjects were white (15 subjects [93.8%]).

Major protocol deviations were reported in 3 subjects during the study; however, none of these deviations had an impact on the integrity of the study.

According to protocol specifications, all 16 subjects received the probe cocktail on Day 1, 14 subjects received guselkumab on Day 8, 13 subjects received the probe cocktail on Day 15, and 12 subjects received the probe cocktail on Day 36.

PHARMACOKINETIC, IMMUNOGENICITY, PHARMACODYNAMIC AND PHARMACOGENOMIC RESULTS:

Pharmacokinetics

Cytochrome P450 Probe Substrates

Midazolam

- The geometric mean ratios for C_{max} of midazolam for Day 15/Day 1 and Day 36/Day 1 were 1.112 (90% confidence interval [CI]: 0.752 to 1.645) and 1.137 (90% CI: 0.765 to 1.690), respectively, which indicate that midazolam C_{max} was not affected by guselkumab treatment.
- The geometric mean ratios for AUC_{inf} of midazolam for Day 15/Day 1 and Day 36/Day 1 were 1.005 (90% CI: 0.697 to 1.449) and 1.039 (90% CI: 0.749 to 1.442), respectively, which indicate that midazolam AUC_{inf} was not affected by guselkumab treatment.

S-Warfarin

- The geometric mean ratios for C_{max} of S-warfarin for Day 15/Day 1 and Day 36/Day 1 were 1.067 (90% CI: 0.900 to 1.265) and 0.904 (90% CI: 0.736 to 1.110), which indicate that S-warfarin C_{max} was not affected by guselkumab treatment.

- The geometric mean ratios for AUC_{inf} of S-warfarin for Day 15/Day 1 and Day 36/Day 1 were 1.124 (90% CI: 0.903 to 1.398) and 1.054 (90% CI: 0.817 to 1.361), respectively, which indicate that S-warfarin AUC_{inf} was not affected by guselkumab treatment.

Omeprazole

- The geometric mean ratios for C_{max} of omeprazole for Day 15/Day 1 and Day 36/Day 1 were 0.958 (90% CI: 0.717 to 1.281) and 0.955 (90% CI: 0.671 to 1.359), respectively, which indicate that omeprazole C_{max} was not affected by guselkumab treatment.
- The geometric mean ratios for AUC_{inf} of omeprazole for Day 15/Day 1 and Day 36/Day 1 were 0.964 (90% CI: 0.613 to 1.517) and 1.193 (90% CI: 0.749 to 1.900), respectively, which indicate that omeprazole AUC_{inf} was not affected by guselkumab treatment.

Dextromethorphan

- The geometric mean ratios for C_{max} of dextromethorphan for Day 15/Day 1 and Day 36/Day 1 were 1.055 (90% confidence interval [CI]: 0.457 to 2.434) and 1.326 (90% CI: 0.553 to 3.181), respectively; and the geometric mean ratios for AUC_{inf} of dextromethorphan for Day 15/Day 1 and Day 36/Day 1 were 1.127 (90% CI: 0.558 to 2.275) and 1.240 (90% CI: 0.464 to 3.314), respectively.
- The numerically higher C_{max} and AUC_{inf} values of dextromethorphan on Day 36 versus Day 1 are likely to be attributed to large inter-subject variability in PK of dextromethorphan (coefficient of variation, relative SD [CV%] >100%). Given the inconsistent trend of dextromethorphan C_{max} and AUC_{inf} values for each individual subject before and after guselkumab treatment, the PK of dextromethorphan were not considered to be affected by treatment with guselkumab. These results are in line with the in vitro finding that IL-23 did not modulate the expression or activity of CYP2D6.

Caffeine

- The geometric mean ratios for C_{max} of caffeine for Day 15/Day 1 and Day 36/Day 1 were 1.073 (90% CI: 0.940 to 1.224) and 1.058 (90% CI: 0.888 to 1.262), respectively, which indicate that caffeine C_{max} was not affected by guselkumab treatment.
- The geometric mean ratios for AUC_{inf} of caffeine for Day 15/Day 1 and Day 36/Day 1 were 1.004 (90% CI: 0.770 to 1.311) and 1.018 (90% CI: 0.765 to 1.354), respectively, which indicate that caffeine AUC_{inf} was not affected by guselkumab treatment.

Guselkumab

- The mean serum guselkumab concentrations were 15.31 and 5.69 µg/mL, respectively, on Days 15 and 36 when subjects received CYP probe cocktail administrations.

Pharmacodynamics

No pharmacodynamic analyses were performed during the study.

Immunogenicity

None of the 14 subjects who received guselkumab treatment and had appropriate samples collected for immunogenicity evaluation tested positive for antibodies to guselkumab during the study period.

Pharmacogenomics

No pharmacogenomic analyses were performed during the study.

ASSESSMENT OF DISEASE SEVERITY OF PSORIASIS

The PASI and IGA data from this study indicate that the majority of subjects experienced a substantial improvement in their disease after a single SC administration of guselkumab. Therefore, in this study the metabolic activities of CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2 were not affected by the decreased inflammation associated with the improvement of disease activity in subjects with moderate to severe plaque psoriasis.

SAFETY RESULTS:

In the 16 subjects who received probe cocktail prior to receiving guselkumab, the probe cocktail was generally well tolerated. Four subjects (25.0%) who received probe cocktail only, 1 subject (7.1%) who received guselkumab only, and 5 subjects (38.5%) who received probe cocktail in the presence of guselkumab exposure reported at least 1 treatment-emergent adverse event (TEAE). The majority of the TEAEs were mild or moderate in intensity. Three subjects (23.1%) who received probe cocktail in the presence of guselkumab exposure had 1 or more TEAEs of cellulitis, viral gastroenteritis, urinary tract infection, and heart rate increased that were considered to be reasonably related to the study agents.

No death was reported during the study. One subject who received probe cocktail only (prior to receiving guselkumab) had SAEs of carotid artery stenosis, cervical radiculopathy, and lacunar infarction; but this was likely related to his prior medical conditions, not to the probe cocktail drugs. One subject had SAEs of impaired gastric emptying and viral gastroenteritis following receiving both guselkumab and probe cocktail during the study. This latter subject was terminated early from the study due to these SAEs. Another subject was terminated early from the study due to pregnancy (reported as a nonserious AE) and was subsequently lost to follow-up.

In subjects who received guselkumab only (prior to receiving the 2^{nd} and 3^{rd} doses of probe cocktail), 1 subject each had a single TEAE of musculoskeletal chest pain, pregnancy, and dyspnea. For the combined treatment period (probe cocktail administration in the presence of guselkumab exposure), the highest number of subjects who experienced TEAEs was observed in the Infections and Infestations system organ class (SOC) (30.5%); TEAEs of cellulitis, viral gastroenteritis, upper respiratory tract infection, urinary tract infection, and viral upper respiratory tract infection were observed in 1 subject each. Frequency of TEAEs reported during period of treatment with probe cocktail in combination with guselkumab (38.5%) was slightly higher than treatment with cocktail alone (25.0%); overall there was not a pattern suggestive of a meaningful difference in TEAEs between treatment with cocktail alone and in combination with guselkumab.

No subjects experienced injection-site TEAEs during the study. No clinically significant mean changes from baseline were observed for vital signs, ECGs, physical examinations, and/or laboratory parameters.

STUDY LIMITATIONS: No study limitations were identified by the Sponsor.

CONCLUSIONS:

- Results from this study indicate that systemic exposures (C_{max} and AUC_{inf}) of midazolam, S-warfarin, omeprazole, dextromethophan, and caffeine (probe substrates of CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2, respectively) were not affected by treatment with guselkumab.
- Results from this study confirm the findings from in vitro study that IL-23 did not modulate the expression or activity of multiple CYP450 enzymes, suggesting therapeutic protein-drug interactions between guselkumab and CYP substrates (CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2) are unlikely in subjects with psoriasis.

- Results from this study suggest that the metabolic activities of CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2 were not affected by the decreased inflammation associated with the improvement of disease activity in subjects with psoriasis.
- The probe cocktail was generally well tolerated when administered alone and in combination with guselkumab.

- Two subjects discontinued study due to TEAEs. An SAE of viral gastroenteritis was considered to be related to guselkumab.
- Guselkumab was well tolerated as a single SC 200 mg administration in subjects with moderate to severe plaque-type psoriasis. No significant or new safety findings were observed.

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