SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	To be determined
Name of Active Ingredient(s)	CNTO 1959 (Guselkumab)

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 28 August 2014

Prepared by: Janssen Research & Development, LLC

Protocol No.: CNTO1959NAP1001

Title of Study: Phase 1, Open-label, Randomized, Parallel Study to Assess the Pharmacokinetic Comparability of 2 Formulations and to Evaluate Pharmacokinetic Comparability of Guselkumab (CNTO 1959) Delivered by 2 Different Devices in Healthy Subjects

NCT No.: NCT01866007

Clinical Registry No.: CR100969

Principal Investigator: Mark J. Allison, MD, Celerion, [redacted], USA.

Study Centers: [redacted], USA; [redacted], USA; [redacted], USA

Publication (Reference): None

Study Period: 15 May 2013 to 09 October 2013; Data Base Lock: 24 October 2013

Phase of Development: 1

Objectives: The primary objectives were:

- To evaluate the Pharmacokinetic (PK) comparability of lyophilized and liquid formulations following a single subcutaneous (SC) administration of 100 mg guselkumab in healthy subjects.
- To evaluate the PK comparability of a single SC administration of 100 mg guselkumab delivered by a prefilled syringe with an UltraSafe Passive™ Delivery System (PFS-U) or prefilled syringe with a facilitated injection device (PFS-FID) in healthy subjects.

The secondary objectives were:

- To assess the absolute bioavailability of guselkumab following SC administration in healthy subjects.
- To evaluate the safety, tolerability, and immunogenicity of single SC or intravenous (IV) administrations of 100 mg guselkumab in healthy subjects.

Methodology: This was an open-label, randomized, parallel-group, single dose study of guselkumab in healthy male and female subjects. One hundred and forty subjects aged 18 to 55 years (inclusive), who

met all inclusion and none of the exclusion criteria were to be enrolled into the study. Eligible subjects were randomly assigned in the ratio of 2:2:2:1 to the following 4 treatment groups, respectively.

- Group 1: A single SC injection of 100 mg guselkumab prepared from lyophilized formulation (N=40).
- Group 2: A single SC injection of 100 mg guselkumab, liquid formulation with PFS-U (N=40).
- Group 3: A single SC injection of 100 mg guselkumab, liquid formulation with PFS-FID (N=40).
- Group 4: A single IV infusion of 100 mg guselkumab prepared from liquid formulation (N=20).

Subjects were to be screened within 4 weeks before administration of the study agent and were to be admitted to the study center on Day -1. Subjects were to receive a single dose of study agent according to their randomized treatment group on Day 1. After the administration of study drug on Day 1, subjects were to stay in the clinical study unit until Day 7 and were to be followed for safety, PK and immune response up to Day 85.

Number of Subjects (planned and analyzed): A total of 140 subjects were planned to be enrolled, while 141 were randomized and treated in the study. All 141 subjects were analyzed for pharmacokinetics and safety.

Main Criteria for Inclusion: Healthy men and women aged between 18 and 55 years (inclusive), with a body mass index (BMI) between 18.5 and 29.0 kg/m² (inclusive) were to be included in the study. Male subjects had to have a body weight in the range of 60.0 to 90.0 kg, inclusive, and female subjects had to have a body weight in the range of 50.0 to 80.0 kg, inclusive, to be included in the study.

Test Product, Dose and Mode of Administration, Batch No.: Guselkumab final lyophilized product was to be supplied as white solid cake in a 2 mL Type 1 glass vial to be reconstituted with sterile water for injection (without bacteriostat), to yield a 100 mg/mL solution. It was designed for single use only and was to be administered through SC injection. Batch number: 100381.

Guselkumab was also to be supplied as Becton-Dickinson (BD) Hypak® for Biotech glass syringe. The formulation was to be composed of 100 mg/mL (100 mg/mL in 1 mL volume) guselkumab, containing histidine, sucrose, polysorbate 80 at pH 5.8. Batch numbers: DBS68 and DBS6A.

Duration of Treatment: Each subject received a single SC injection or IV infusion of 100 mg guselkumab prepared from either lyophilized or liquid formulations. The total duration of the study was to be approximately 17 weeks including a screening period of up to 4 weeks and in-patient period of 1 week and follow-up period of up to 12 weeks.

Criteria for Evaluation:

Pharmacokinetics: Blood samples were to be collected for the measurement of serum guselkumab concentration and detection of antibodies to guselkumab. PK parameters following a single SC administration of guselkumab were to include, but were not limited to maximum observed serum concentration (C_{max}), time to reach maximum observed serum concentration (T_{max}), area under the serum concentration versus time curve from time zero to 70 days (AUC_{0-70d}), area under the serum concentration versus time curve from time zero to infinity with extrapolation of the terminal phase (AUC_{inf}), area under the serum concentration versus time curve from time zero to the time corresponding to the last quantifiable concentration (AUC_{last}), terminal half-life ($T_{1/2}$), apparent total systemic clearance after extravascular administration (CL/F), apparent volume of distribution based on terminal phase after extravascular administration (V_z/F), and absolute bioavailability (F). PK parameters following a single IV administration of guselkumab were to include, but were not limited to C_{max}, AUC_{inf}, AUC_{last}, $T_{1/2}$, total systemic clearance after IV administration (CL), and volume of distribution based on terminal phase after IV administration (V_z).

Safety: Safety assessments were to include monitoring of AEs and SAEs including injection-site reactions and infusion reactions, clinical laboratory tests (urine drug screen, serology, urinalysis, hematology, and serum chemistry), ECGs, vital signs, physical examination, and pregnancy testing. HIV, hepatitis B virus (HBV), hepatitis C (HCV), and QuantiFERON TB Gold testing (or tuberculin skin testing) were to be required at time of screening.

Statistical Methods: There was no formal statistical sample size and power calculation in this study. Sample size was chosen based on the empirical convention for assessing F% and PK comparability following a single-dose administration in healthy subjects. No imputation was to be done for missing data.

No formal hypothesis testing was to be conducted.

PK parameters of guselkumab were to be calculated from serum concentration over time data using noncompartmental analyses. All calculations were to be based on actual sampling times. PK parameters and concentrations were to be summarized by treatment group among PK evaluable subjects.

C_{max} and $AUC_{0\text{-}70d}$ were to be compared descriptively using ratio of geometric means and 90% confidence interval between subjects receiving 100 mg SC injection of lyophilized guselkumab and liquid formulated guselkumab for the evaluation of PK comparability between 2 formulations. In addition, C_{max} and $AUC_{0\text{-}70d}$ were to be compared descriptively using ratio of geometric means and 90% confidence interval between subjects receiving guselkumab 100 mg SC injected with PFS-FID and PFS-U for the evaluation of PK comparability between PFS-U and PFS-FID.

The incidence of antibodies to guselkumab was to be summarized for all subjects who received a dose of guselkumab and had appropriate samples for detection of antibodies to guselkumab.

All treatment emergent Aes were be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred terms for each dose group of healthy subjects. Laboratory data were to be summarized by type of laboratory test. Descriptive statistics were to be calculated for each laboratory analyte at baseline and at each scheduled time point. Descriptive statistics of QTc intervals, temperature, pulse, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline were to be summarized at each scheduled time point. Abnormal physical examination findings were to be listed.

RESULTS:

STUDY POPULATION: A total of 141 subjects (40 subjects each in the SC lyophilized formulation and PFS-U groups, 41 subjects in the PFS-FID group, and 20 subjects in the IV liquid formulation group) were enrolled and treated in the study. Of these, 5 subjects (1 subject each from the SC lyophilized formulation group and the PFS-FID group and 3 subjects from the PFS-U group) were lost to follow-up and discontinued the study participation. One additional subject in the PFS-FID group discontinued study participation due to other reasons (subject chose not to continue with the study for personal reasons).

The demographic characteristics were generally similar between the treatment groups. Overall, major protocol deviations were reported in 17 subjects. Of the 17 subjects, 14 subjects reported deviations related to the intake of prohibited concomitant medications during the outpatient portion of the study; 2 subjects reported deviations related to birth control (change in the method of birth control in one case and failure to use adequate contraception in the other case), 1 subject reported a deviation related to the study procedure (missed or out of the time window for PK blood draw), and 1 subject reported treatment deviation (received 105 mg of guselkumab due to an error with the pumping device).

PHARMACOKINETIC RESULTS:

- After a single SC administration, guselkumab was absorbed into the systemic circulation with a median T_{max} occurring approximately 5.0 to 5.5 days.
- Guselkumab was eliminated from the circulation with a mean $T_{1/2}$ of approximately 16.6 to 17.2 days after a single 100 mg IV or SC administration.
- The mean V_z value was approximately 6.7 L (97.8 mL/kg) after a single IV administration.
- The CV% of Cmax values ranged from approximately 26% to 46% and the CV% of AUC_{inf} values ranged from approximately 34% to 50%, indicating a large inter-subject variability in systemic exposure to guselkumab after SC administration.
- The systemic exposure (C_{max} and AUCs) of guselkumab were comparable between the liquid formulation (supplied as PFS-U) and the lyophilized formulation: the geometric mean ratios of the C_{max} and AUCs were close to 1 (0.96-0.99) and the 90% Cis of the geometric mean ratios were all within the interval of 0.80-1.25.
- Using the same liquid formation and pre-filled syringe of guselkumab, the SC delivery by the PFS-FID device appeared to result in a slightly higher systemic exposure compared to the PFS-U: the geometric mean ratios of C_{max} and AUCs were 1.18-1.20; the 90% Cis of the geometric mean ratios were within the range of 0.70-1.43.
- The mean absolute bioavailability (F) of guselkumab following a single 100 mg SC administration was estimated to be approximately 47.6%, 48.7%, and 54.9%, respectively, for lyophilized formulation, liquid formulation in PFS-U, and liquid formulation in PFS-FID.
- Following a single IV or SC administration, none (0.0%) of 139 subjects with evaluable serum samples was positive for antibodies to guselkumab during the study period.

Statistical comparisons of exposure parameters (C_{max} and AUC_{0-70d}) of guselkumab in two formulations following a single 100 mg subcutaneous injection

PK Parameter	Treatment Group	N	Geometric Mean	Geometric Mean Ratio (Test/Reference)[a]	90% CI	
C_{max} (µg/mL)	Lyophilized	40	7.385			
	PFS-U	40	7.273	0.985	0.857	1.132
	PFS-FID	41	8.572	1.161	1.011	1.333
AUC_{0-70d}	Lyophilized	39	162.050			
(µg·day/mL)	PFS-U	35	155.569	0.960	0.824	1.119
	PFS-FID	40	186.716	1.152	0.994	1.336

a: Test: liquid formulation with PFS-U or liquid formulation with PFS-FID; Reference: lyophilized formulation

Statistical comparisons of exposure parameters (C_{max} and AUC_{0-70d}) of guselkumab in liquid formulation with two devices following a single 100 mg subcutaneous injection

PK Parameter	Treatment Group	N	Geometric Mean	Geometric Mean Ratio (Test/Reference)[a]	90% CI	
C_{max} (µg/mL)	PFS-U	40	7.273			
	PFS-FID	41	8.572	1.179	1.027	1.353
AUC_{0-70d}	PFS-U	35	155.569			
(µg·day/mL)	PFS-FID	40	186.716	1.200	1.031	1.397

a: Test: liquid formulation with PFS-FID; Reference: liquid formulation with PFS-U

SAFETY RESULTS: Overall, 95 (67.4%) of the 141 subjects reported at least 1 TEAE. The highest incidence (85.0%) of TEAEs was reported in the smallest treatment group (n=20), the IV liquid formulation group, with the most frequently reported TEAEs (reported in >20% of subjects in the treatment group) observed in the SOCs of Nervous System Disorders, Musculoskeletal and Connective Tissues Disorders, Respiratory, Thoracic and Mediastinal Disorders, General Disorders and Administration Site Conditions, Gastrointestinal Disorders and Reproductive System and Breast Disorders. The incidence of TEAEs was 55.5%, 65.0%, 73.2% in the SC lyophilized formulation group, PFS-U group, and PFS-FID group, respectively. In these treatment groups, the most frequently reported TEAEs (reported in >20% of subjects in any of the treatment group) were observed in the SOCs of General Disorders and Administration Site Conditions, Nervous System Disorders, Gastrointestinal Disorders, and Skin and Subcutaneous Tissue Disorders.

For all treatment groups in this study, the most frequently reported TEAEs (reported in ≥5.0% of subjects in total population) were headache (18.4%), injection site erythema (14.2%), nausea (9.2%), induration and cough (each reported by 6.4% of subjects), injection site pain, erythema, and pruritus (each reported by 5.7% of subjects), and feeling hot, dizziness postural, myalgia, and oropharyngeal pain (each reported by 5.0% of subjects).

The majority of the TEAEs were mild to moderate in intensity. No treatment-emergent deaths or discontinuations due to Aes occurred during the study. Two subjects; 1 each in the SC lyophilized formulation group and the IV liquid formulation group reported treatment-emergent SAEs of spontaneous abortion during the study.

Overall, 65 (46.1%) subjects reported TEAEs reasonably related to study agent and 28 subjects (19.9%) reported TEAEs reasonably related to medical devices. Incidence of TEAEs reasonably related to study agent and medical device was higher in the PFS-FID group (58.5% and 43.9%, respectively) compared with other groups (52.5% and 17.5%, respectively, in the PFS-U group; 27.5% and 7.5%, respectively, in the SC lyophilized formulation group).

Aes of special interest included injection-site reaction Aes, infections and infusion reactions. Overall, 34 subjects (28.1%) reported injection-site reaction Aes during the study. Incidence of injection-site reaction Aes was higher in the PFS-FID group (51.2%) compared with the other groups (25.0% and 7.5% in the PFS-U and SC lyophilized formulation group). The median time to start an AE, relative to study agent administration, was faster in the PFS-FID group (2.0 minutes) compared with the PFS-U and SC lyophilized formulation groups (9.0 minutes in both the groups). The median duration of Aes was longer in the PFS-U group (162.5 minutes) compared with the PFS-FID group (100.5 minutes) and the SC lyophilized formulation group (98.0 minutes). The most commonly reported injection site Aes (reported in ≥3.0% of subjects in total population) were injection site erythema (25 subjects [20.7%]), injection site induration (14 subjects [11.6%]), followed by injection site pain (10 subjects [8.3%]). All injection-site reactions were mild in intensity except one event of pain in extremity, which was moderate in intensity.

Overall, 12 subjects (8.5%) reported treatment-emergent Aes in the SOC of Infections and Infestations during the study. The incidence of treatment-emergent Aes in the SOC of Infections and Infestations was low in the IV liquid formulation group and the SC lyophilized formulation group (1 subject [5%] and 2 subjects [5.0%]), respectively) compared to other 2 treatment groups (3 subjects [7.5%] in the PFS-U group, and 6 subjects [14.6%] in the PFS-FID group). The most commonly reported treatment-emergent infections (reported in ≥1.4% of the total population) were oral herpes, upper respiratory tract infection and urinary tract infection (each reported in 2 subjects [1.4%]). Four subjects in the IV liquid formulation group reported infusion reactions during the study. All treatment-emergent infections and infusion reactions were mild to moderate in intensity.

No TEAEs related to laboratory test results were reported during the study. There was no clinically significant effect on ECG parameters and vital signs measurements reported during the study.

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

CONCLUSIONS:

- The systemic exposure (C_{max} and AUCs) of guselkumab were comparable between the liquid formulation (supplied as PFS-U) and the lyophilized formulation.
- Using the same liquid formation, the SC delivery by the PFS-FID device resulted in a slightly higher (approximately 18% to 20%) systemic exposure compared to the PFS-U.
- The mean absolute bioavailability (F) of guselkumab following a single 100 mg SC administration was estimated to be approximately 47.6%, 48.7%, and 54.9%, respectively, for lyophilized formulation, liquid formulation in PFS-U, and liquid formulation in PFS-FID.
- Guselkumab, administered as an IV infusion or SC injection, was well-tolerated in healthy subjects. When administered as a SC injection, the incidence of injection-site reaction Aes was higher in the PFS-FID group (51.2%) compared with the other groups 25.0% and 7.5%, respectively, in the PFS-U and SC lyophilized formulation group). No significant safety issues were observed and no significant clinically significant changes in laboratory values, vital signs, and ECGs were observed.

Disclaimer

Information in this posting shall not be considered to be a claim for any product, whether marketed or under development. In case of a marketed product, some of the information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.