Sponsor: Sanofi **Drug substance(s):** BIVV009	**Study code:** BIVV009-05

Title of the study:

A Phase 1 Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single-Dose and Multiple-Dose BIVV009 in Healthy Japanese Volunteers

Study center(s):

WCCT Global, 5630 Cerritos Ave., Cypress, CA 90630 USA

Study period:

Date first participant enrolled: 09 Feb 2018

Date last participant completed: 10 Aug 2018

Study Status: Completed

Phase of development: 1

Objectives and endpoints:

The primary objectives of Part A and Part B of the study were to evaluate the pharmacokinetics (PK) of single-dose and multiple-dose BIVV009 in healthy Japanese subjects.

The primary endpoints are PK parameters derived from BIVV009 plasma concentrations including but not limited to area under the curve (AUC), clearance (CL), maximum concentration (C_{max}), half life ($t_{½}$), and time to reach maximum concentration (t_{max}) after single and multiple dose administrations.

The secondary objectives and endpoints were to:

- Evaluate the safety and tolerability of BIVV009 in healthy Japanese subjects by assessing adverse events (AEs) and clinically significant abnormalities in laboratory evaluations, systemic lupus erythematosus (SLE) panel testing, vital sign measurements, electrocardiograms (ECGs), and physical examinations.
- Evaluate the pharmacodynamics (PD) of BIVV009 with regard to complement pathway (CP) function in healthy Japanese subjects as measured by Wieslab CP assay, CH50, and total C4.

Exploratory objectives and endpoints included the following:

- Evaluation of the immunogenicity of BIVV009 as measured by the formation of anti-drug antibodies following multiple-dose administration.
- Evaluation of additional parameters of the complement system in healthy Japanese subjects by assessing the levels and activity of complement proteins C1q and C1s.

Methodology:

This was a Phase 1 study designed to evaluate the safety, tolerability, and PK/PD of BIVV009 in healthy Japanese subjects.

The study consisted of 2 parts:

Part A examined 3 different single dose levels of BIVV009. A total of 18 healthy Japanese subjects (6 subjects per dose cohort) were randomized to receive one of the following doses of BIVV009 by intravenous (IV) infusion on Day 1:

- 30 mg/kg (Cohort 1)
- 60 mg/kg (Cohort 2)
- 100 mg/kg (Cohort 3)

Part B examined 2 different multiple doses of BIVV009. A total of 12 healthy Japanese subjects were stratified by weight to receive a total of 3 doses of BIVV009 by IV infusion on Days 1, 8, and 22 as follows:

- 6.5 g BIVV009 for subjects who weighed <75 kg (Cohort 4)
- 7.5 g BIVV009 for subjects who weighed ≥75 kg (Cohort 5)

A minimum of 3 subjects with body weight greater than or equal to 75 kg were required in Cohort 5.

Screening for Part A and Part B ran in parallel. Dosing in Part B began only once safety data through Day 8 were available from the last subject in Part A and there were no ongoing study drug-related serious adverse events in any subjects. Dose cohorts within each part ran in parallel.

Number of participants:

A total of 30 healthy Japanese subjects (18 subjects in Part A and 12 subjects in Part B) were enrolled and administered study drug.

Diagnosis and criteria for inclusion:

Healthy Japanese subjects (20 to 55 years of age) who have lived outside of Japan for less than 5 years and whose parents and grandparents are all Japanese.

Dose groups:

In Part A, subjects were randomized to 1 of 3 single-dose cohorts of BIVV009. In Part B, subjects were stratified by weight to 1 of 2 multiple-dose cohorts of BIVV009.

Duration of treatment: The total time on study for each subject was expected to range from approximately 92 days (Part A) to 141 days (Part B) but may have been shorter depending on the length of the screening period.

Statistical methods:

Pharmacokinetics: BIVV009 concentrations were determined using a validated analytical method. PK parameters were determined by non-compartmental analysis; parameters were to include, but were not limited to, AUC, CL, C_{max}, $t_{1/2}$, and T_{max}. Summary descriptive statistics, figures, and individual listings were presented for all PK parameters by part and dose cohort.
Safety: AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA, v21.0) by system organ class and preferred term. Tabulations of AEs by frequency, relatednesss, and severity were presented. Data were presented by part and dose cohort. Listings were provided for serious adverse events (SAEs). Concomitant medications will be coded using World Health Organization drug enhanced dictionary version (WHODrug B3 Global March 2018). Changes from baseline in clinical laboratory parameters and vital sign measurements were summarized over time using descriptive statistics by part and dose cohort.
Pharmacodynamics: Summary descriptive statistics, figures, and individual listings were presented for all PD biomarkers by part and dose cohort.

Summary Results:

PHARMACOKINETIC RESULTS:

Geometric Mean Pharmacokinetic Parameters

Cohort	$AUC_{0-\infty}$ (µg*h/mL)	C_{max} (µg/mL)	$t_{1/2}$* (h)	CL (mL/h)	V_{ss} (mL)	Racc
30 mg/kg (N= 6)	88065.59	788.77	84.46	20.91	2186.06	
60 mg/kg (N= 6)	209719.73	1753.66	74.91	19.98	2241.20	
100 mg/kg (N= 6)	563200.93	2556.17	172.48	12.87	3011.11	
6.5 g, Day 1 (N= 9)	404393.99	2357.27	137.37	16.07	3071.63	
6.5 g, Day 22 (N= 9)	1078337.49	3703.10	234.80	6.03	1885.11	1.64
7.5 g, Day 1 (N= 3)	311694.57	2523.04	98.68	24.06	3261.25	
7.5 g, Day 22 (N= 3)	679051.35	3366.79	162.36	11.04	2482.58	1.50

* Arithmetic mean

Source: BIVV009/BIVV009-05/CSR/T-PK-SUM-PARAM-A.SAS, BIVV009/BIVV009-05/CSR/T-PK-SUMPARAM-B.SAS

AUC and C_{max} increased with increasing dose. The mean for $AUC_{0-\infty}$ increased dose proportionally from 30 mg/kg to 60 mg/kg, and more than dose proportionally from 60 to 100 mg/kg, which was demonstrated by a slower clearance and longer $t_{1/2}$ after 100 mg/kg. The mean for C_{max} increased dose proportionally from 30 to 100 mg/kg. For multiple dosing, the PK parameters for both of the doses stratified by weight were similar. The accumulation ratios based on AUC_{0-168} were 1.64 to 1.50 for the 6.5 g and the 7.5 g multiple doses, suggesting moderate accumulation following three doses over 22 days.

PHARMACODYNAMIC RESULTS:

● CP activity was immediately and effectively inhibited to >90% within 0.5 hours by BIVV009 at all dose levels. Dose related differences in the duration of CP activity was observed, with increased single and multiple doses resulting in longer durations of CP inhibition.

● CH50 levels were inhibited for up to 2 weeks following single doses of BIVV009 and up to 2 months following multiple doses.

● There was no correlation between BIVV009 concentrations and C1q levels, and there was no depletion of C1q levels in any of the dose cohorts.

● C1s concentrations decreased for up to 2 weeks following single doses and up to 85 days following multiple doses. The duration of C1s inhibition was dose-related.

SAFETY RESULTS:

Overall, the safety profile of BIV009 in male and female healthy Japanese subjects in Study BIVV009-05 was assessed in 18 subjects in the single dose cohorts and 12 subjects in the multidose cohorts. Part A subjects were between 26-53 years of age with a median age of 39 years and Part B subjects were between 26-56 years of age with a median age of 50 years. BIVV009 was generally well tolerated. The primary safety results included the following:

● No deaths occurred during the study.

● In Part A, there were a total of 4 treatment-emergent adverse events (TEAEs) reported in 4 (22.2%) subjects. Two subjects in Part A (11.1%) experienced a total of 2 TEAEs assessed by the Investigator as related to BIVV009 (both reports of tension headache). In Part B, there were a total of 5 TEAEs reported in 4 (33.3%) subjects. None of the TEAEs in Part B were assessed by the Investigator as related to BIVV009.

● All TEAEs in Part A and Part B were assessed by the Investigator as mild to moderate in severity. No subjects in Part A or Part B experienced a treatment-emergent serious adverse event (TESAE).

● The type and incidence of TEAEs observed in the study were similar to what is expected for a healthy study population. The most common TEAEs observed (incidence ≥10% per study part) were tension headache and viral upper respiratory tract infection, reported in 2 subjects each in Part A and Part B, respectively.

● The pattern of infections reported during the study was typical of the healthy population studied.

● No subjects in Part A or Part B discontinued study drug or the study due to a TEAE.

● There were no TEAEs reported concerning for anaphylaxis or a hypersensitivity reaction associated with BIVV009. However, 2 out of 18 subjects in Part A (11.1%) experienced at least 1 TEAE within 24 hours of the start of study drug infusion. Both subjects experienced 1 TEAE each of tension headache within 24 hours of infusion, which were also assessed by the Investigator as related to BIVV009.

● There were no TEAEs reported concerning for development of autoimmune disease. There were changes from positive to negative and negative to positive in some SLE panel parameters after BIVV009 dosing. None of the reported abnormal SLE panel results were associated with an adverse event. Assessment of SLE panel testing in subjects receiving BIVV009 remains exploratory and the clinical significance is unknown.

● Of 12 Part B subjects evaluated, 3 (25.0%) subjects were positive for anti-drug antibody (ADA) at any time after receiving at least 1 dose of BIVV009 treatment. Assessment of ADA remains exploratory and the clinical significance is unknown.

● No clinically meaningful patterns or trends were observed in abnormalities of hematology or clinical chemistry.

● Overall, there was no apparent clinically meaningful pattern or trend in vital signs, ECGs or physical examinations observed.

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