NCT04669600

STATISTICAL ANALYSIS PLAN

Protocol title:	**A multicenter, Phase 2a, open-label, non-randomized study evaluating the efficacy, safety, and tolerability of BIVV020 in adults with persistent/chronic immune thrombocytopenia (ITP)**
Protocol number:	**PDY16894**
Compound number (INN/Trademark):	**BIVV020 (Not applicable/Not applicable)**
Study phase:	**Phase 2**
Short title:	**A Phase 2a study evaluating BIVV020 in adults with persistent/chronic immune thrombocytopenia (ITP)**
Statistician:	[redacted]
Statistical project leader:	
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Regulatory agency identifier number(s):

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Total number of pages: 30

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VERSION HISTORY

This statistical analysis plan (SAP) for study PDY16894 is based on the protocol dated 25-Jan-2021. There are no major changes to the statistical analysis features in this SAP. The first participant was enrolled on 15 Feb 2021. The SAP is approved before the first interim analysis is conducted.

1 INTRODUCTION

1.1 STUDY DESIGN

This is a Phase 2a, open-label, non-randomized, multicenter study to evaluate the efficacy, safety and tolerability of BIVV020 in adults with persistent/chronic primary ITP.

During the 56-day screening period, prospective participants will have a detailed medical history documented, physical evaluations and blood samples (including platelet count) collected. For participants receiving sutimlimab (BIVV009) in study TDR16218, they may continue to receive sutimlimab during screening, until at least 14 days prior to the first administration of investigational medicinal product (IMP) - BIVV020.

The study will enroll approximately 12 participants: up to 6 participants who have received and responded to sutimlimab (BIVV009) in study TDR16218 (switchers), as well as patients who have not previously received sutimlimab (naïve participants).

A loading dose of BIVV020 at 50 mg/kg intravenous (IV) will be administered on Day 1, followed by maintenance doses of 600 mg subcutaneous weekly starting on Day 8 until the last participant enrolled has completed 52 weeks of treatment. The maximum duration of treatment for a participant is 104 weeks.

The on-site visits will be conducted weekly from Week 1 to Week 6, biweekly from Week 7 to Week 12, every 4 weeks from Week 13 to Week 24, every 8 weeks after Week 24 until the end-of-study (EOS) visit. Platelet counts will be collected during the on-site visits.

1.2 OBJECTIVE AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of BIVV020 on the durability of platelet response in participants with persistent/chronic immune thrombocytopenia (ITP)	• Naïve participants: Proportion of participants with a platelet count ≥50 × 10^9 /L at ≥50% of scheduled visits, or for participants with baseline platelet count <15 × 10^9/L, a ≥20 × 10^9/L increase in platelet count from baseline at ≥50% of scheduled visits, without receiving rescue ITP therapy, as assessed from Week 3 to Week 24 • Participants who previously received sutimlimab: Proportion of participants with maintenance of platelet count ≥30 × 10^9 /L at ≥50% of scheduled visits, without receiving rescue ITP therapy, as assessed from Week 3 to Week 24.

Objectives	Endpoints
Secondary	
• To assess the safety and tolerability of BIVV020	• Standard clinical and laboratory parameters and adverse events
• To assess the pharmacokinetics (PK) of BIVV020	• Plasma concentrations of BIVV020
• To assess the response rate of treatment with BIVV020	• Response rate at Weeks 24 and 52, defined as a platelet count ≥50 × 10^9 /L and a greater than 2-fold increase from baseline, measured on 2 occasions at least 7 days apart, with the absence of bleeding (bleeding is defined as bleeding with a score ≥2 on the WHO bleeding scale), and the lack of combination ITP therapy during this period.
• To assess the time to response	• Time from baseline to first platelet response, defined as greater than or equal to each of the following values: 50 × 10^9 /L and 100 × 10^9 /L (confirmed by 2 measurements at least 7 days apart)
• To assess the effect of treatment with BIVV020 on the requirement for rescue ITP therapy	• Proportion of participants who did not require rescue therapy for an acute episode of thrombocytopenia after Week 3
• To assess the immunogenicity of BIVV020	• Incidence and titer (if relevant) of anti-BIVV020 antibodies
Tertiary/exploratory	

Objectives	Endpoints
[redacted]	

2 SAMPLE SIZE DETERMINATION

Approximately 12 participants will be enrolled. Since there is no statistical hypothesis to be tested in this study, the sample size is not determined statistically.

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 2 - Populations for analyses

Population	Description
Enrolled	All participants from screened population who have been allocated to an intervention regardless of whether the intervention was received or not.
Intent-to-treat (ITT)	All exposed participants.
Safety	All enrolled participants who take at least 1 dose (including partial dose) of study intervention.
Pharmacokinetic (PK)	All enrolled and treated participants (safety population) with at least one post-baseline PK sample.
Pharmacodynamic (PD)	All enrolled and treated participants (safety population) with at least one post-baseline PD sample.
ADA	All enrolled and treated participants (safety population) with at least one post-baseline ADA sample.

4 STATISTICAL ANALYSES

Statistical analysis will be performed by Sanofi, using SAS® version 9.3 or higher and, where appropriate, additional validated software. This SAP is based on protocol Version 3, dated 25 January 2021.

4.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, (Q1, Q3 if applicable), minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first IMP administration. For participants enrolled but not treated, the baseline value is defined as the last available value before enrollment. The baseline value for platelet count is defined as the average of the values before the first IMP administration (ie, platelet count collected during the D-56 to D-1 screening period and at 0 hour on D1).

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period (or the screening period)** is defined as the period from the time of the signing of the informed consent form (ICF) to the first IMP administration.
- The **on-treatment period** is defined as the period from the first IMP administration to the last IMP administration +7 days.
- The **post-treatment period** is defined as the period after the on-treatment period.

The **treatment-emergent** (TE) period includes both on-treatment period and post-treatment period.

Analyses of safety will be based on the treatment-emergent period.

4.2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 2 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Enrolled participants
- Enrolled but not exposed participants

- Enrolled and exposed participants
- Participants who completed 24-week, 52-week, and the entire treatment period. A participant is considered as completed 24-week (52-week) treatment period if the participant was treated beyond study day 166 (study day 362 for Week 52).
- Participants who did not complete the 24-week, 52-week, and the entire treatment period and main reason for treatment discontinuation
- Participants who completed the study
- Participants who did not complete the study and main reason for study discontinuation.

In addition, the number (%) of participants screened, enrolled, discontinued treatment, discontinued study early will be provided by country and site.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the enrolled population. Participants impacted by coronavirus disease 2019 (Covid-19) will be summarized upon data availability, such as discontinuation due to Covid-19, protocol deviation due to Covid-19, and visit(s) impacted by Covid-19 as collected in eCRF, etc.

4.3 PRIMARY ENDPOINT(S) ANALYSIS

The primary endpoint is the proportions of participants who met the following criteria:

1. For naïve participants,
   a. a platelet count ≥50 x 10^9/L OR
   b. a ≥20 x 10^9/L increase from baseline if baseline platelet count <15 x 10^9/L

   at ≥50% of scheduled visits from Week 3 to Week 24.

   For switchers, a platelet count >= 30 x 10^9/L at >=50% of scheduled visits from Week 3 to Week 24.

2. No concomitant ITP therapy from Week 3 to Week 24.
   Concomitant medications are defined in Section 5.3. The ITP therapies will be identified by the Sanofi coding group, reviewed by medical, and defined in the programming specifications. The ITP therapies include corticosteroids, thrombopoietin receptor agonists, intravenous immunoglobulin, anti-D immunoglobulin, rituximab, fostamatinib, immunosuppressants (azathioprine, cyclosporin A, mycophenolate mofetil), cyclophosphamide, dapsone, danazol.

The response rate will be summarized for naïve participants, switchers, and total for the ITT along with the 95% exact Clopper-Pearson Confidence Interval (CI).

Platelet counts will be summarized by visit. These plots will also be provided:

- Individual platelet count profile: line plot of platelet count by visit for each participant

- Spaghetti plot platelet count by participant
- Median platelet count/change from baseline with by visit

4.4 SECONDARY ENDPOINT(S) ANALYSIS

Participants will continue to receive BIVV020 until the last participant enrolled has completed 52 weeks of treatment. Week 52 is not a scheduled visit and therefore replaced by Week 56 for secondary endpoint(s) analysis. All available data up to Week 56 during the on-treatment period will be included.

The key secondary endpoints include:

The proportion of participants who met the following criteria at Week 24/Week 56:

1. A platelet count ≥50 x 10^9/L and a greater than 2-fold increase from baseline, measured on 2 occasions at least 7 days apart.

2. No bleeding while the platelet counts are maintained above the threshold. Bleeding is defined as bleeding with a score >=2 on the World Health Organization (WHO) bleeding scale (Section 5.5) collected in the eCRF.

3. No concomitant ITP therapy while the platelet counts are maintained above the threshold.

The response rate will be summarized at Week 24 and Week 56 separately for the ITT along with the 95% exact Clopper-Pearson CI.

The proportion of participants who did not require rescue ITP therapy after Week 3 (ie, Week 3 to Week 24, 56, and the end of on-treatment period)

The proportion will be summarized at Week 24, Week 56, and the end of on-treatment period separately for the ITT along with the 95% exact Clopper-Pearson CI.

Time from baseline to first platelet response ≥50 x 10^9/L (confirmed by 2 measurements at least 7 days apart) during 56 weeks of treatment

Time from baseline to first platelet response ≥100 x 10^9/L (confirmed by 2 measurements at least 7 days apart) during 56 weeks of treatment

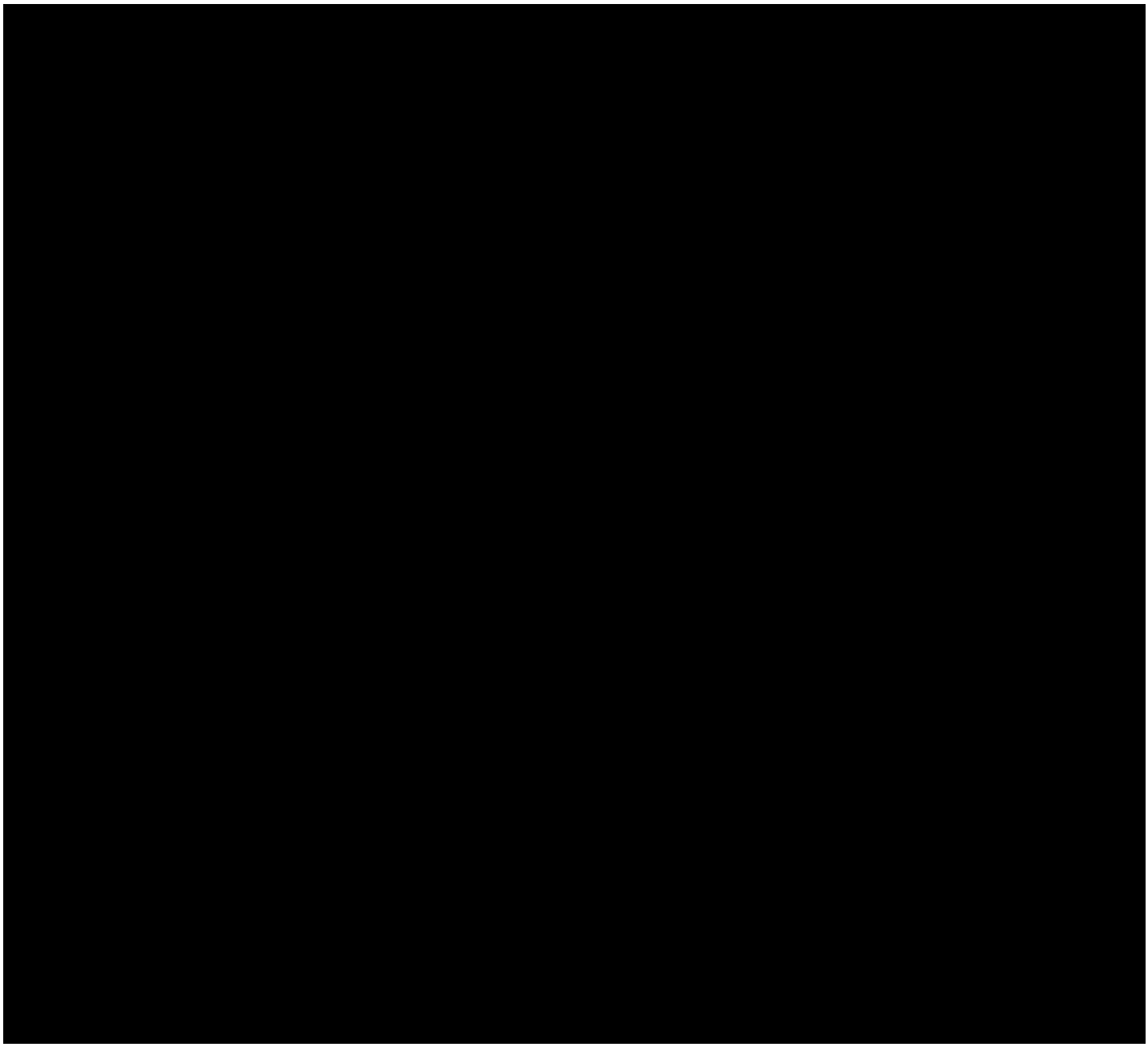
To qualify for the event, both platelet counts have to be ≥50 x 10^9/L (or ≥100 x 10^9/L) and collected ≥7 days apart without any platelet count less than the threshold in between. Platelet counts collected at unscheduled visits are included.

Kaplan-Meier estimates will be calculated for time to the first of the two qualifying platelet counts. The 25%, median, 75% time to event along with 95% CI will be presented. The Kaplan-Meier survival curve will be presented.

For participants who do not have a platelet response, their time-to-event will be censored:

- at Week 56 for those treated beyond 56 weeks
- at Week 57 (1 week after Week 56) for those who prematurely discontinued the treatment due to any adverse event (AE) or lack of response before Week 56
- at the time of treatment discontinuation for those who prematurely discontinued the treatment before Week 56 due to reasons other than AE or lack of response.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS



[redacted]

4.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 3, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not enrolled) will be provided.

4.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and treatment compliance and summarized within the safety population.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date + 7 days, regardless of unplanned intermittent discontinuations. If the date of the last IMP administration is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized quantitatively and categorically: 1 to 6, 7 to 12, 13 to 24, 25 to 56, 57 to 80, and >80 weeks.

Additionally, the cumulative duration of treatment exposure (expressed in participant-months) will be provided.

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the number of administrations as required by the protocol.

Percentage of treatment compliance for a participant will be defined as the number of administrations that the participant was compliant divided by the total number of administrations that the participant was planned to take from the first IMP administration up to the actual last IMP administration.

Treatment compliance will be summarized quantitatively and categorically: <80%, 80% to 100%, and ≥100%.

4.6.2 Adverse events

General common rules for adverse events

All AEs will be graded according to National cancer institute common terminology for adverse events (NCI-CTCAE) and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the MedDRA (MedDRA) currently in effect at Sanofi at the time of the database lock.

The AEs will be analyzed in the following 2 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs): AEs that developed, worsened or became serious during the treatment-emergent period (including the on-treatment and post-treatment periods defined in Section 4.1).

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a treatment-emergent AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the intensity is missing for 1 of the treatment-emergent occurrences of an AE, the intensity will be assumed as the maximal intensity of the other occurrences of the same event. If the intensity is missing for all the occurrences, the intensity will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase, using the maximum (worst) grade by treatment phase. Summaries

will be provided for all grades combined and for grade ≥3 (including grade 5). Missing grades, if any, will be included in the "all grades" category.

All AEs will be listed. The AEs that occurred after the first IMP administration (BIVV020) and within the sutimlimab (BIVV009) safety follow-up period (ie, last administration of BIVV009 + 63 days) will be flagged and their relationship to BIVV020 and BIVV009 will be presented.

The AE tables will be sorted as indicated in Table 3.

Table 3 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a]
PT	By decreasing frequency of PTs

a The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any grade ≥3 TEAE
- Any treatment emergent SAE
- TEAE leading to death
- Any TEAE leading to permanent intervention discontinuation
- Any TEAE infection of grade 3 or higher
- Any TEAE thromboembolic event.

The AE summaries of Table 4 will be generated with number (%) of participants experiencing at least one event. The analyses will be performed for all grades combined and for grades ≥3.

Table 4 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
	PT
Common TEAE (≥5%)	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT

Type of AE	MedDRA levels
Treatment emergent SAE	Primary SOC and PT
Treatment emergent SAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent intervention discontinuation	Primary SOC and PT
Pretreatment AE	Overview[a]
	Primary SOC and PT

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent intervention discontinuation

Analysis of deaths

A listing of deaths will be provided.

Analysis of adverse events of special interest (AESIs)

Adverse events of special interest (AESI) will be selected for analyses as indicated in Table 5. Number (%) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 3.

Table 5 - Selections for AESIs

AESIs	Selection
Pregnancy	e-CRF "Pregnancy"
Symptomatic overdose (serious or nonserious) with IMP	e-CRF "Overdose" with "Symptomatic overdose" checked "Yes"
QTc ≥500 ms	e-CRF 12-lead "ECG"
Increase in ALT >3 × ULN	e-CRF "ALT Increase"
Grade 3 or higher anaphylaxis/hypersensitivity reaction per Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grading or an anaphylactic reaction in association with BIVV020 administration	e-CRF "Adverse Events" with 1. "Is the event an AESI" checked "Yes" 2. "Category of Adverse Event" checked "Anaphylaxis/Hypersensitivity" 3. Grade 3 or 4 or 5 4. "Relationship to BIVV020" checked "Related" or missing
Serious autoimmune disease[b]	e-CRF "Adverse Events" with 1. "Is the event an AESI" checked "Yes" 2. "Category of Adverse Event" checked "Autoimmune Disease" 3. "Serious" checked "Yes"
Infections Grade 3 or higher[a]	e-CRF "Adverse Events" with 1. "Is the event an AESI" checked "Yes" 2. "Category of Adverse Event" checked "Infection" 3. "Intensity" checked "Grade 3" or "Grade 4" or "Grade 5"

a AESI "Meningococcal infection" and "Infection due to an encapsulated bacterial organism" are included in Infection.
b Newly diagnosed or potential development of SLE, autoimmune disease or acute flare or chronic worsening of underlying autoimmune disease

4.6.3 Additional safety assessments

4.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECGs) variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets: Red blood cell (RBC) count, Hemoglobin, Hematocrit, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH)
  - White blood cell (WBC) count with differential: WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils
- Clinical chemistry:
  - Metabolism: Glucose (non-fasting), Alkaline phosphatase, Total and direct bilirubin, Total protein
  - Electrolytes: Potassium, Sodium, Calcium
  - Renal function: Blood urea nitrogen (BUN), Creatinine
  - Liver function: Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT), Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)
- Coagulation: prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT)
- Systemic lupus erythematosus (SLE) panel: Antinuclear antibody (ANA), Double-stranded DNA (dsDNA), Anti-La/SSB antibody (SS-B), Anti-Ribonucleoprotein antibody (RNP), Anti-Smith antibody (Sm), Anti-Ro/SSA antibody (SS-A), Anti-Scleroderma antibody (SCL-70), Anti-Chromatin antibody, Anti-Jo-1 antibody, Anti-Centromere B antibody, Circulating immune complexes (CIC)
- Urine electrolytes: Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick, Microscopic examination (if blood or protein is abnormal)
- Vital signs: heart rate, systolic and diastolic blood pressure, respiratory rate, temperature
- ECG variables: heart rate, PR, QRS, QT, and corrected QTc (according to Fridericia).

Data below the lower limit of quantitation (LLOQ)/detection limit will be replaced by half of the LLOQ, data above the upper limit of quantification (ULOQ) will be replaced by ULOQ value.

Quantitative analyses

For all laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each planned visit, the last value during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock (Section 5.6). For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable. For parameters defined as efficacy endpoints, PCSA summaries will not be provided.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

4.7 OTHER ANALYSES

BIVV020 concentrations will be described in the PK population for each planned visit (D1 – 0H, D1 – 1H, D8, D15, D29, D43, Week 12, Week 24, every 8 weeks starting from D170, 22 weeks after the final BIVV020 dose), using the following descriptive statistics: mean, standard deviation, geometric mean, coefficient of variation, median, minimum, and maximum.

All concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics excepted for the geometric mean and associated coefficient of variation for which they will be considered as missing.

4.7.1 Immunogenicity analyses

Participant's antidrug antibodies (ADA) status, response variable (see definitions below) will be summarized in the ADA population.

Sample status (negative, positive, inconclusive) and titers will also be described overtime using descriptive statistics.

The impact of positive immune response on efficacy, PK and safety variables may be further explored, depending on ADA incidence.

Participant's ADA status

- Participants with **pre-existing ADA** correspond to participants with ADAs present in samples drawn before first IMP administration. Participants with missing ADA sample at baseline will be considered as without pre-existing ADA.
- Participants with **treatment-emergent ADA** correspond to participants with at least one treatment-induced/boosted ADA.
  - Participants with **treatment-induced ADA** correspond to participants with ADAs that developed during the treatment-emergent period and without pre-existing ADA (including participants without pre-treatment samples).
  - Participants with **treatment-boosted ADA** correspond to participants with pre-existing ADAs that are boosted during the treatment-emergent period to a significant higher titer than the baseline. A 3-fold serial dilution schema is used during titration, so at least a 9-fold increase of titer values will be considered as significant.
- Participants **without treatment-emergent ADA** correspond to participants without treatment-induced/boosted ADA during the treatment-emergent period.
- Participants **with inconclusive ADA** are defined as participants which cannot irrefutably be classified as with or without treatment-emergent ADA.

ADA response variable:

- **ADA incidence** is defined as the proportion of participants found to have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response (treatment-boosted ADAs) at any time point during the treatment-emergent period.

4.8 INTERIM ANALYSES

An interim analysis (IA) will be conducted when approximately 12 participants have each been treated for 15 weeks.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA:	antidrug antibodies
AE:	adverse event
ALT:	alanine aminotrasferase
ANA:	antinuclear antibody
aPTT:	activated partial thromboplastin time
AST:	aspartate aminotrasferase
ATC:	anatomic category, anatomic or therapeutic category
BMI:	body mass index
BUN:	blood urea nitrogen
CI:	Confidence Interval
CIC:	circulating immune complexes
Covid-19:	coronavirus disease 2019
[redacted]	[redacted]
dsDNA:	double-stranded DNA
ECG:	electrocardiogram, electrocardiogram
eCRF:	electronic case report form
EOS:	end-of-study
HGLT:	high level group term
HLGT:	high-level group term
HLT:	high-level term
IA:	interim analysis
ICF:	informed consent form
IMP:	investigational medicinal product
INR:	international normalized ratio
ITP:	immune thrombocytopenia
ITT:	Intent-to-treat, intent-to-treat
IV:	intravenous
LLOQ:	lower limit of quantification
LLT:	lower-level term
MCH:	mean corpuscular hemoglobin
MCV:	mean corpuscular volume
MedDRA:	medical dictionary for regulatory activities
NCI-CTCAE:	National cancer institute common terminology for adverse events, National cancer institute common terminology for adverse events
PCSA:	potentially clinically significant abnormality, potentially clinically significant abnormality
PD:	pharmacodynamics
PK:	pharmacokinetic
PT:	preferred term
RBC:	red blood cell

RNP:	Anti-Ribonucleoprotein antibody
SAP:	statistical analysis plan
SCL-70:	Anti-Scleroderma antibody
SD:	standard deviation
SGOT:	serum glutamic-oxaloacetic transaminase
SGPT:	serum glutamic-pyruvic transaminase
SLE:	systemic lupus erythematosus
Sm:	Anti-Smith antibody
SOC:	system organ class
SOC:	system organ class
SS-A:	Anti-Ro/SSA antibody
SS-B:	Anti-La/SSB antibody
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event, treatment-emergent adverse event
ULOQ:	upper limit of quantification
WBC:	white blood cell
WHO:	World Health Organization
WHO-DD:	World Health Organization - drug dictionary, World Health Organization drug dictionary, World Health Organization-drug dictionary

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

Not applicable.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history will be summarized using descriptive statistics in the exposed population.

Demographic and baseline characteristics

- age in years as quantitative variable and in categories (<65, ≥65)
- gender (Male, Female)
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown)
- ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)
- height (cm), weight (kg), body mass index (BMI) (kg/m^2).

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

The time (in years) from the date of ITP diagnosis to the date of first IMP administration will be summarized.

Medical and surgical history will be coded to a PT and associated primary SOC using the MedDRA currently in effect at Sanofi at the time of database lock.

The proportion of participants who had documented vaccines within 5 years and who have received vaccination during the study will be summarized. The vaccines include meningococcal vaccine, S. pneumoniae vaccine, and H. influenza vaccine. The type of the vaccine will be summarized.

Prior or concomitant medications

All medications will be coded using the World Health Organization-drug dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any interventions received by the participant concomitantly to the IMP during the on-treatment period.
- Post-treatment medications are those the participant took in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior, concomitant, and post-treatment non-ITP medications will be summarized for the ITT population, by anatomic and therapeutic level. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on incidence in intervention group. Therapeutic classes are sorted by decreasing frequency within each anatomic class. In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Prior ITP, concomitant non-rescue ITP, and concomitant rescue ITP therapies/medications will be summarized separately by the ATC level 4 chemical class and medication name. All ITP therapies will be listed with rescue ITP therapies flagged.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Study Day

Study Day is defined as days relative to the date of first IMP administration (ie, D1 as in the protocol). The Study Day of an event is calculated as

- (date of event – date of first IMP administration + 1), if the event is on or after the first IMP administration;
- (date of event – date of first IMP administration), if the event is prior to the first IMP administration.

The date of the first IMP administration is Study Day 1.

Analysis windows for time points

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy, safety, PK and ADA variables.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

Table 6 - Analyses window definition

Scheduled visit post baseline	Targeted study day
D1	1
D4	4 (+/-1)
D8	8 (+/-1)
D15	15 (+/-1)
D22	22 (+/-1)
D29	29 (+/-1)
D36	36 (+/-1)
D43	43 (+/-1)
Week 8	57 (+/-2)
Week 10	80 (+/-2)
Week 12	85 (+/-2)
Week 16	113 (+/-3)

Scheduled visit post baseline	Targeted study day
Week 20	141 (+/-3)
Week 24	169 (+/-4)
Week 32	171 (+/-4)
Week 40	281 (+/-4)
Every other 2 weeks until the until the last participant enrolled has completed 52 weeks of treatment	

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG and ADA will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

5.5 APPENDIX 5 WHO BLEEDING SCALE

Coded Grade of Bleeding	Decoded Grade of Bleeding
1	Petechiae
2	Mild blood loss
3	Gross blood loss
4	Debilitating blood loss

5.6 APPENDIX 6 CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Parameter	PCSA	Comments
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Parameter	PCSA	Comments
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Parameter	PCSA	Comments
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm >90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	
QTc	Absolute values (ms) >450 ms >480 ms >500 ms Increase from baseline Increase from baseline]30-60] ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula. Absolute values categories are cumulative QTc >480 ms and ΔQTc >60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.

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