AMENDED CLINICAL TRIAL PROTOCOL 03

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**
Amendment number:	**03**
Compound number (INN/Trademark):	**BIVV020 (Not applicable/Not applicable)**
Brief title:	**A Phase 2a study evaluating BIVV020 in adults with persistent/chronic immune thrombocytopenia (ITP)**
Study phase:	**Phase 2**
Sponsor names:	**Sanofi-Aventis Recherche & Développement** **Local Sponsor for US: Sanofi US. Services Inc**
Legal registered address:	**Sanofi-Aventis Recherche & Développement 1 avenue Pierre Brossolette 91380 Chilly-Mazarin, France** **Local Sponsor for US: Sanofi US Services Inc: 55 Corporate Drive Bridgewater, NJ 08807, USA** **Manufacturer: Same as Sponsor**
Monitoring team's representative name and contact information	[redacted]

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03	all	25 January 2021, Version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02	all	10 December 2020, Version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	all	08 December 2020, Version 1 (electronic 1.0)
Original Protocol	all	03 September 2020, Version 1 (electronic 2.0)

Amended protocol 03 (25 Jan 2021)

This amended protocol 03 (Amendment 03) is not considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Changes in the protocol have been implemented to address MHRA requests.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Section # and Name	Description of Change	Brief Rationale
2.3 Benefit/Risk Assessment	Added information on the benefits and risks of transitioning from sutimlimab to BIVV020	MHRA request
4.2 Scientific rationale for study design	Added information on the rationale for transitioning patients who previously responded to sutimlimab to BIVV020	MHRA request
5.1 Inclusion criteria I05	Restrictions on participant sperm and ova donation added	MHRA request
5.2 Exclusion criteria E08	Participants switching from sutimlimab may be enrolled even with a positive SARS-CoV-2 test, based on the judgement of the Investigator	These participants may be at risk for severe thrombocytopenia if they are unable to receive either sutimlimab or BIVV020
7.1.1 Permanent discontinuation	Added language stating that the replacement of a participant who discontinued from the study will not occur in the case where the participant was discontinued due to a BIVV020-related adverse reaction or safety concern	MHRA request
8.2.2 Vital signs; 8.2.3 Electrocardiograms	Previous requirements for vital signs assessments and electrocardiograms to be conducted prior to clinical laboratory assessments have been changed to recommendations	This order of procedures is not feasible at some sites

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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)

Brief title: A Phase 2a study evaluating BIVV020 in adults with persistent/chronic immune thrombocytopenia (ITP)

Rationale:

Individuals with immune thrombocytopenia (ITP) who are refractory to current therapies may respond to inhibition of the proximal portion of the classical complement pathway (CP). This hypothesis is supported by data obtained using a first-generation CP inhibitor, sutimlimab (BIVV009), which targets the active and inactive conformations of human serine protease complement component 1, s subcomponent (C1s). The current study will assess the efficacy, safety, and tolerability of a second-generation CP inhibitor, BIVV020. BIVV020 selectively targets the activate conformation of C1s and has a prolonged half-life compared to sutimlimab, allowing for subcutaneous (SC) maintenance administration. This study will enroll participants who have received sutimlimab in study TDR16218 as well as participants who have not previously received sutimlimab (naïve participants).

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
Exploratory	
[redacted]	

Overall design:

This is a Phase 2a, open-label, non-randomized, international, multicenter study to evaluate the efficacy, safety, and tolerability of BIVV020 in adults with persistent/chronic primary ITP. The study will enroll approximately 12 participants: up to 6 participants who have received and responded to sutimlimab (BIVV009) in study TDR16218, as well as participants who have not previously received sutimlimab.

The Screening Period will be up to 56 days. Screening begins from the time of the signing of the informed consent form (ICF). For participants receiving sutimlimab in study TDR16218, they may continue to receive sutimlimab during screening, until at least 14 days prior to the first dose of BIVV020, as duration of the PD effect of sutimlimab is approximately 14 days. This period between the final dose of sutimlimab and the first dose of BIVV020 is known as the Transition Period. Enrollment in the study occurs when a participant receives the first dose of BIVV020.

A loading dose of BIVV020 at 50 mg/kg intravenous (IV) will be administered on Day 1, followed by maintenance doses of 600 mg SC weekly starting on Day 8. On Day 1, participants will remain in the clinic for at least 4 hours after the start of investigational medicinal product (IMP) administration. The 600 mg SC dose will be administered as two 2 mL injections. For the first 5 weeks of maintenance therapy, the injections will be performed by the site staff, and participants will receive education on self-administration. At Week 6, the participant (or their caregiver) will perform the injection under the supervision of the site staff. Participants should be observed for 30 minutes after the first 6 SC administrations of IMP.

From Weeks 7 to 12, participants will return to the clinic every other week. During the weeks they are not seen in the clinic, they will administer BIVV020 at home. At clinic visits, participants (or their caregiver) will administer BIVV020 under the supervision of the study staff. Participants may request assistance with the injections from the study staff during these visits. From Weeks 13 to 24, participants will return every 4 weeks and will self-administer BIVV020 under the supervision of study staff at those visits. From Week 25 onward, visits will occur at a minimum of every 8 weeks, and participants will continue to self-administer BIVV020 under the supervision of the study staff during those visits. Clinic visits should be scheduled so that they align as closely as possible with the day the participant typically takes BIVV020. If a participant prefers for drug administration to occur at the site instead of his/her home at any time during the study, this is acceptable.

Phone calls will be performed during the study for site staff to remind participants to take their injections, answer any questions they may have regarding the injections, and to assess adverse events (AEs). From Weeks 7 to 24, phone calls will be performed on weeks that the participants are not seen in the clinic (Weeks 7, 9, 11, 13 to 15, 17 to 19, and 21 to 23). After Week 25, phone calls will be performed approximately 4 weeks after each previous visit. (If a visit during this period occurs within approximately 4 weeks of the prior visit, a phone call is not necessary) Phone calls should continue to occur approximately every 8 weeks after the cessation of treatment, until the End of Study (EOS) visit.

Maintenance injections will continue until the last participant enrolled has completed 52 weeks of treatment. Therefore, the length of maintenance therapy may vary for each participant. The maximum duration of treatment for an individual participant is 104 weeks.

Brief summary: Phase 2

This is a single group treatment, Phase 2a, open-label, single arm study of BIVV020 in male and female participants with persistent/chronic ITP.

Study duration:

- Screening Period: up to 56 days
- Transition Period between last sutimlimab dose and first dose of BIVV020 (for participants who were previously receiving sutimlimab): at least 14 days, included as part of the 56-day Screening Period

Treatment duration: 52 weeks (minimum)

Visit frequency:

- Day 1
- Day 4
- Weeks 1 to 6: Weekly
- Weeks 7 to 12: Every other week
- Weeks 13 to 24: Every 4 weeks
- Weeks 25+: At least every 8 weeks
- End of Study visit: 22 weeks after the last dose of BIVV020

Number of participants:

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.

Intervention groups and duration:

All participants will receive the study intervention.

Study intervention: BIVV020

Investigational medicinal product:

- Formulation: BIVV020 supplied in single use vials containing 750 mg (150 mg/mL; extractable volume of 5 mL)
- Routes of administration: IV loading dose; SC maintenance administration
- Dose regimen: 50 mg/kg IV loading dose, followed by 600 mg SC weekly

Noninvestigational medicinal product: Not applicable

Devices: Not applicable

Posttrial access to study medication:

Participants will continue to receive BIVV020 until the last participant enrolled has completed 52 weeks of treatment. After that time, a long-term extension study may be available for participants to continue to receive BIVV020.

- Interim analysis

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

- Primary endpoint

  The proportion (and number) of responders fulfilling the criteria in the primary endpoint will be presented; the 95% confidence interval for the proportion of responders will be estimated with Clopper-Pearson method.

- Secondary endpoints

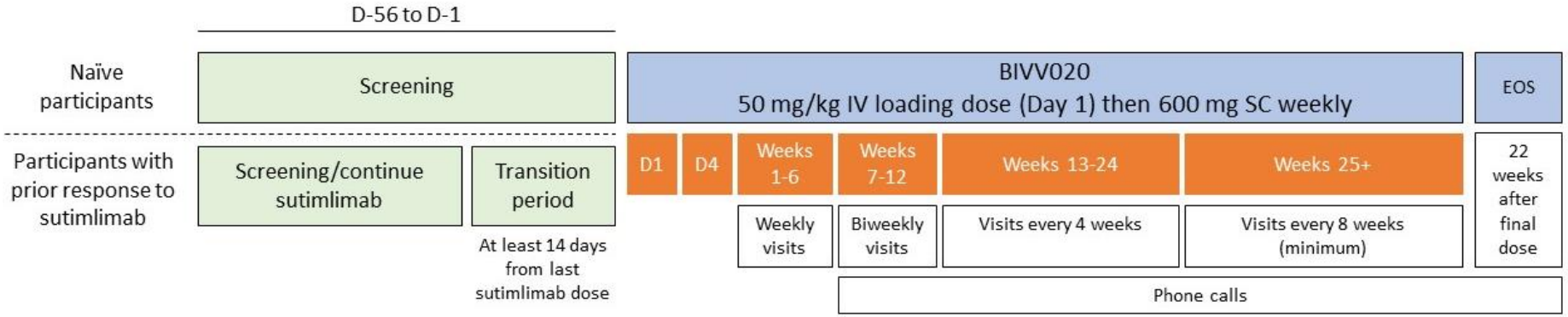
  All secondary endpoints will be summarized using descriptive statistics. For categorical endpoints, number and proportion of participants will be presented; for continuous endpoints, mean, standard deviation, median, and other appropriate statistics will be presented; for time-to-event endpoints, Kaplan-Meier methods will be used to estimate median time-to-event.

Data Monitoring/Other committee:Yes

This study will have a Study Monitoring Committee, comprising at least 2 investigators participating in the study and Sponsor representatives.

1.2 SCHEMA

Figure 1 - Graphical study design



D = Day; EOS = end of study; IV = intravenous; SC = subcutaneous

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening/Transition period[a]	Loading dose				Weekly maintenance dosing									End of study
						Weekly clinic visits						Visits every 2 weeks	Visits every 4 weeks	Visits every 8 weeks (minimum)	22 weeks after the final BIVV020 dose
Week		0				1-6						7-12[c]	13-24[d]	25+[e]	
Day	D-56 to D-1	D1	D1	D1	D4[b]	D8	D15	D22	D29	D36	D43	D44 - D85	D86 - D169	D170+	
Hour		0H	1H	4H											
Window					±1 d	±1 d	±1 d	±1 d	±1 d	±1 d	±1 d	±2 d	±3 d	±4 d	±14 d
Informed consent	X														
Inclusion and exclusion criteria[f]	X														
Demography	X														
Medical history	X														
Immunization review/ vaccination[g]	X														
Past and current medical conditions	X														
ECOG status	X														
HIV, hepatitis B and C, and SARS-CoV-2 testing[h]	X														
FSH (if applicable)[i]	X														
Serum creatine kinase	X														

	Screening/Transition period[a]	Loading dose				Weekly maintenance dosing									End of study
						Weekly clinic visits						Visits every 2 weeks	Visits every 4 weeks	Visits every 8 weeks (minimum)	22 weeks after the final BIVV020 dose
Week		0				1-6						7-12[c]	13-24[d]	25+[e]	
Day	D-56 to D-1	D1	D1	D1	D4[b]	D8	D15	D22	D29	D36	D43	D44 - D85	D86 - D169	D170+	
Hour		0H	1H	4H											
Window					±1 d	±1 d	±1 d	±1 d	±1 d	±1 d	±1 d	±2 d	±3 d	±4 d	±14 d
Full physical examination including height and weight[j]	X														X
Weight (predose)		X													
Serum pregnancy test (WOCBP only)	X														
Urine pregnancy test (WOCBP only)		X							X			X[k]	X	X	X
IMP administration[l]															
BIVV020 50 mg/kg IV		X													
BIVV020 600 mg SC						X[m]	X	X	X	X	X	X[n]	X	X	
Safety assessments															
Vital signs[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Abbreviated physical exam[p]		X							X			X[k]	X	X	

	Screening/Transition period[a]	Loading dose				Weekly maintenance dosing									End of study
						Weekly clinic visits						Visits every 2 weeks	Visits every 4 weeks	Visits every 8 weeks (minimum)	22 weeks after the final BIVV020 dose
Week		0				1-6						7-12[c]	13-24[d]	25+[e]	
Day	D-56 to D-1	D1	D1	D1	D4[b]	D8	D15	D22	D29	D36	D43	D44 - D85	D86 - D169	D170+	
Hour		0H	1H	4H											
Window					±1 d	±1 d	±1 d	±1 d	±1 d	±1 d	±1 d	±2 d	±3 d	±4 d	±14 d
Hematology, chemistry, coagulation, and urinalysis[q]	X	X					X		X			X[k]	X[r]	X	X
SLE panel[q]	X								X			X[k]	X	X	X
12-lead ECG	X					X									X
AE review	X	X			X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local site reactions[s]						X	X	X	X	X	X	X	X	X	
Participant diary[t]												X	X	X	
Phone calls[u]												X	X	X	X
Pharmacodynamics[v]															
Platelets[w]			X	X	X	X		X		X	X	X	X	X	X

[redacted]

	Screening/Transition period[a]	Loading dose				Weekly maintenance dosing									End of study
						Weekly clinic visits						Visits every 2 weeks	Visits every 4 weeks	Visits every 8 weeks (minimum)	22 weeks after the final BIVV020 dose
Week		0				1-6						7-12[c]	13-24[d]	25+[e]	
Day	D-56 to D-1	D1	D1	D1	D4[b]	D8	D15	D22	D29	D36	D43	D44 - D85	D86 - D169	D170+	
Hour		0H	1H	4H											
Window					±1 d	±1 d	±1 d	±1 d	±1 d	±1 d	±1 d	±2 d	±3 d	±4 d	±14 d
[redacted]															
Archival PD sample		PX00	PX01			PX02			PX03			PX04[y]	PX05[r]	PX06+	X
DNA sample for future research[x]		X													
Pharmacokinetics/ADA[v]															
BIVV020 plasma samples		P00	P01			P02	P03		P04		P05	P06[y]	P07[r]	P08+	X
Anti-BIVV020 antibodies		PD00							PD01			PD02[y]	PD03[r]	PD04+	X[z]

a The Transition Period applies only to participants who were previously receiving sutimlimab, and is a period of at least 14 days between the last sutimlimab dose and the first dose of BIVV020. This period is included as part of the Screening Period.

b The Day 4 visit may be performed at the participant's home using a home nursing service.

c Visits will occur at Weeks 8, 10, and 12.

d Visits will occur at Weeks 16, 20, and 24.

e Visits will occur at Weeks 32, 40, 48, etc, with phone calls occurring approximately 4 weeks after each visit. Participants will continue to receive BIVV020 until the last participant enrolled has completed 52 weeks of treatment. For the last participant enrolled, a visit should occur at Week 52. Visits should occur around the time a participant is transitioning off BIVV020, even if this visit is less than 8 weeks from the prior visit. The maximum duration of treatment for an individual participant is 104 weeks.

f Inclusion and exclusion criteria should be reviewed on Day 1 prior to enrollment.

g Participants should have documented vaccination against encapsulated bacterial pathogens (*Neisseria meningitidis*, including serogroup B meningococcus [where available]), *Haemophilus influenzae*, and *Streptococcus pneumoniae*) within 5 years prior to enrollment. The participant should receive the vaccine series as early as possible. See Section 8.2.6 for additional details.

h Testing includes HBsAg, HBcAb (IgG and IgM), anti-HCV Ab, and HIV test. Need for SARS-CoV-2 testing to be determined for each site. If SARS-CoV-2 testing is performed, a molecular test should be used.

i FSH testing should be performed in participants with at least 12 months of amenorrhea. See Section 10.4.1.

j Height at screening only.
k To be performed at Weeks 8 and 12 only.
l In addition to the IMP being dispensed in the clinic, the IMP may be dispensed for home administration via DTP services, except if prohibited by local regulatory authorities.
m Injections will be administered by site staff at visits that occur during Weeks 1 to 5. Participants will perform the injection in the clinic on Week 6 under the supervision of study staff.
n At visits that occurs from Week 7 onward, injections will be performed in the clinic by the participants, under the supervision of study staff.
o See Section 8.2.2.
p See Section 8.2.1. Ad-hoc physical exams may be performed at the discretion of the Investigator based on any AEs reported by the participant.
q See Section 10.2 for a list of tests to be performed. Labs should be performed prior to drug administration.
r To be performed at Week 24 only.
s See Section 8.2.7.
t Participants will record IMP administrations in a paper or e-diary when performing administrations at home.
u Phone calls will be performed to remind participants to take their injections, answer any questions they may have regarding the injections, and to assess AEs. From Weeks 7 to 24, phone calls will be performed on weeks that the participants are not seen in the clinic (Weeks 7, 9, 11, 13 to 15, 17 to 19, and 21 to 23). After Week 25, phone calls will be performed approximately 4 weeks after each previous visit. (If a visit during this period occurs within approximately 4 weeks of the prior visit, a phone call is not necessary.) Phone calls should continue to occur approximately every 8 weeks after the cessation of treatment, until the EOS visit.
v To be performed prior to drug administration unless otherwise noted.
w Platelet count should not be performed as a separate test at visits when a complete blood count is performed.
x If participant provided consent for future research.
y To be performed at Week 12 only.
z Participants with positive ADA titers at the last visit of the treatment period will continue to have ADA titers drawn every 8 weeks until titers are decreasing, or until the EOS visit.

Abbreviations: Ab: antibody; ADA: antidrug antibodies; AE: adverse event; D: day; DTP: Direct-to-Patient; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS: End of Study; FSH: follicle stimulating hormone, HIV: human immunodeficiency virus; HB: hepatitis B; HCV: hepatitis C virus; Ig: immunoglobulin; IMP: investigational medicinal product; IV: intravenous; PD: pharmacodynamics; SARS CoV-2: severe acute respiratory syndrome coronavirus 2; SC: subcutaneous; SLE: systemic lupus erythematosus; WOCBP: Women of childbearing potential.

2 INTRODUCTION

BIVV020 is a humanized monoclonal antibody that binds to and selectively inhibits the activated form of human serine protease C1s. BIVV020 is a second generation classical complement inhibitor with a modified mechanism of action compared to its predecessor, sutimlimab in ITP, which binds to the non-activated and activated conformations of C1s. Due to the lower concentration of activated C1s compared to total C1s, BIVV020 is not expected to be cleared rapidly by target-mediated drug disposition, as is the case for sutimlimab. By selectively targeting only the activated conformation of C1s, the clearance of BIVV020 is reduced and its half-life prolonged compared to its predecessor.

The complement system consists of a network of over 30 soluble and membrane-bound plasma proteins that upon activation result in an enzymatic cascade responsible for the clearance of pathogens and immune complexes (1). Along with subcomponents C1r and C1q, C1s sits at the apex of the classical pathway of the complement system. By binding to activated C1s, BIVV020 prevents enzymatic action of the C1 complex on its substrates, complement factors C4 and C2, and thereby blocks formation of the C3 convertase. The result is the inhibition of CP activity proximal to C3, which allows the alternative and lectin pathways to remain functionally intact for the purpose of host defense. The CP has been implicated in many diseases that are driven by the presence of a pathogenic antibody. Immune thrombocytopenia, and particularly ITP that is refractory to other treatments, is one such example.

2.1 STUDY RATIONALE

Individuals with ITP who are refractory to current therapies may respond to inhibition of the proximal portion of the CP. This hypothesis is supported by data obtained using a first-generation CP inhibitor, sutimlimab, which targets the active and inactive conformations of human serine protease C1s. The current study will assess the efficacy, safety, and tolerability of a second-generation CP inhibitor, BIVV020. BIVV020 selectively targets the activated conformation C1s and has a prolonged half-life compared with sutimlimab, allowing for SC maintenance administration.

2.2 BACKGROUND

Immune thrombocytopenia is an autoimmune disorder characterized by immunologic destruction of platelets in response to an unknown stimulus. Immune thrombocytopenia may be either a primary or secondary disorder. Secondary causes of ITP include autoimmune disorders (eg, antiphospholipid antibody syndrome), viral infections (eg, human immunodeficiency virus [HIV], hepatitis C virus [HCV]), and certain drugs. Decreased platelet levels are caused by increased platelet destruction as well as decreased platelet production.

Patients with ITP are typically first treated with oral corticosteroids and intravenous immunoglobulin (IVIg). The goal of treatment is to prevent major bleeding rather than to normalize the platelet count. Splenectomy had been recommended for patients who failed initial

therapy, although given the long-term risks for infection, this recommendation has recently been revisited. Second-line treatment includes azathioprine, cyclosporine A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, rituximab, and thrombopoietin receptor agonists (such as eltrombopag and romiplostim). Each agent has potential toxicities including immune suppression, secondary malignancies, hypertension, and liver dysfunction.

Some ITP patients will be refractory or unresponsive to existing therapy, and it has been postulated that complement-mediated platelet destruction may play a prominent role in these patients. It has been demonstrated that plasma autoantibodies from ITP patients can activate complement on the surface of normal human platelets (2, 3). The proportion of ITP patients whose samples were capable of activating complement consistently was approximately 50% in these studies. The ability of ITP patient autoantibodies to activate complement on the platelet surface was significantly inhibited by the specific CP inhibitor TNT003 (a precursor to sutimlimab), including inhibition of downstream split products of the classical pathway cascade such as C4d and the membrane attack complex C5b-9 (4). Of note, ITP patients with autoantibodies capable of activating complement also have reduced platelet production (2, 4). Due to the characteristics of complement-mediated activation, currently available therapies for ITP would not be expected to be effective in the subset of patients with significant complement-mediated platelet destruction. For example, complement-opsonized particles and blood cells are removed from circulation by the liver, and thus, it would not be expected that splenectomy would be effective in this population, similar to observations in other classical complement-mediated diseases like cold agglutinin disease (CAD) (5). Therefore, it is likely that a proportion of ITP patients, and a substantial proportion of patients with refractory or unresponsive disease, may be amenable to therapy with a CP inhibitor such as BIVV020.

2.3 BENEFIT/RISK ASSESSMENT

The human safety risk from short-term inhibition of the complement system in general appears to be low, based on the experience with 5 approved products in this therapeutic class. Long-term, complement inhibition may increase the risk of infection with encapsulated bacteria, as reflected in the product label for eculizumab (Soliris®), an inhibitor of the terminal portion of the complement system. To mitigate this risk, this study includes an appropriate program of prophylactic vaccinations.

The risks associated with long-term inhibition of the proximal portion of the classical pathway in particular are unknown. Theoretically, such inhibition could increase the risk of systemic lupus erythematosus (SLE) or circulating immune complexes (CIC) disease due to the role of the C1 complex in immune complex clearance, as observed in patients with congenital deficiencies of C1 complex components (C1q, C1s, and C1r). However, pharmacologic inhibition of C1s differs from congenital deficiency of the C1 complex because: 1) congenital C1 complex component deficiency is commonly associated with second mutations in other immune system genes; 2) pharmacologic inhibition of C1s enzymatic function in the C1 complex leaves intact the non-enzymatic function of C1q, which is important for the opsonization and phagocytic removal of apoptotic cells, which protects against autoimmunity; and 3) the phenotype associated with life-long, often total absence of C1 complex structure and function is unlikely to be reproduced by pharmacologic antagonism of C1 enzymatic function in fully developed adults. Nevertheless,

standard clinical biomarkers related to SLE (eg, antibodies to double-stranded DNA [dsDNA]) have been incorporated into the study as safety surveillance measures.

The risk-benefit profile of BIVV020 is supported by nonclinical toxicology studies, data from first-in-human (FIH) studies in healthy adult participants, and the BIVV009 clinical development experience, including preliminary data from an ongoing Phase 1b study of BIVV009 in chronic ITP patients (TDR16218).

Nonclinical toxicology studies did not reveal any target organs for BIVV020. There were no autoimmune findings in a 5-week toxicity study. No binding or cross-reactivity with off-target tissues has been observed. No reproductive or developmental toxicology study has been performed to date. Listed below are the preclinical studies that support the current BIVV020 safety profile:

- Good Laboratory Practice (GLP) 5-week repeat-dose toxicity study (IV and SC) in cynomolgus monkeys with a 4-week recovery period
- GLP 26-week repeat dose toxicity study (IV and SC) in cynomolgus monkeys with an 8-week recovery period
- GLP tissue cross-reactivity study in normal human tissues
- GLP in vitro hemolysis and plasma flocculation study

Results of the recently completed FIH, randomized, double-blind, placebo-controlled study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ascending single and repeated doses of BIVV020 in healthy adult participants (TDU16308-TDR16309) demonstrated that BIVV020 has an acceptable safety and tolerability profile while providing dose-dependent inhibition of CP activity in healthy adult participants.

- No deaths, treatment-emergent serious adverse events (TESAEs) or treatment-emergent severe AEs were reported. Stopping criteria were not met by any participant or cohort. There were no events of serious hypersensitivity and/or anaphylaxis, meningococcal infection, SLE. Preliminary review noted no trend or dose relationship in laboratory data, vital signs, or electrocardiogram (ECG) parameters.
- Two AEs of special interest (AESIs), meeting AESI criteria of alanine aminotransferase (ALT) ≥2 x upper limit of normal (ULN) were reported:
  - An AESI of rhabdomyolysis was reported in 1 subject 7 days after BIVV020 600 mg SC dose (peak creatine phosphokinase = 215 × ULN) and assessed as related to study drug (TDU16308). The subject performed hot yoga and consumed alcohol 2 days prior to the event. The event resolved 15 days later without any corrective intervention. Of note, one non-serious AE of rhabdomyolysis in upper arms due to heavy exertion was also reported in another subject from the placebo cohort (peak creatine kinase = 78.5 × ULN, peak aspartate aminotransferase (AST) = 6.1 × ULN, peak ALT = 1.7 × ULN).

- An AESI of hepatic steatosis (peak ALT value 218 U/l, ULN: 52) was reported in 1 subject after receiving 4 weekly doses of 300 mg SC BIVV020 on Day 55. The event was assessed as related to study drug and resolved 92 days later without any corrective intervention (TDR16309).

Another Sanofi C1s inhibitor, BIVV009, is currently in Phase 3 development for complement mediated diseases, including CAD. BIVV009 is being studied in patients with ITP. As of 11 July 2019, an estimated 162 participants (96 healthy volunteers and 34 patients with CAD as well as 32 patients with other complement-mediated disorders, including ITP as of 11 April 2019) have been exposed to BIVV009 in the clinical development program. BIVV009 appeared to be generally well-tolerated based on the safety data.

As of 11 July 2019, there were no reports of meningococcal infection, SLE, or newly developed autoimmune conditions, serious hypersensitivity and/or anaphylaxis in BIVV009 clinical trials. Serious infections have been reported in BIVV009 clinical trials in patients with CAD, including streptococcal sepsis (*Streptococcus pyogenes*), *Escherichia coli* sepsis, wound infection staphylococcal (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and pneumonia (organism unknown). Overall, the pattern of infections in patients with CAD was consistent with an older, often medically complex patient population, including some patients who received chronic immunomodulatory therapies.

As of 21 June 2020, twelve chronic ITP patients were enrolled in the ongoing BIVV009 study TDR16218. Clinical response, defined by a platelet count greater than 50×10^9/L measured on 2 separate occasions more than 7 days apart, was achieved by 50% of participants, and thrombocytopenia reoccurred during the washout period at the end of Part A. Platelet levels improved again in all patients who qualified for retreatment in Part B to date.

As of 09 April 2020, 12 ITP patients had received at least 1 dose of sutimlimab in the TDR16218 study part A, with 6 patients having received at least 20 weeks of sutimlimab treatment in Part A and 6 patients continuing into the long-term safety extension study Part B. As of 09 April 2020, 4 of these patients had completed an additional 65-85 weeks of sutimlimab treatment in TDR16218 Part B, with an acceptable safety profile and evidence of a sustained therapeutic effect. No new safety concerns were identified with long-term sutimlimab treatment. Four patients continued to receive sutimlimab in study TDR16218 as of 29 September 2020.

Whether inhibition of the proximal portion of the CP may increase the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is unknown. Complement-mediated neutralization has been described for many viral infections, with all pathways (classical, alternative, and lectin) shown to be involved, depending on the particular virus (6). Thus, the effect of CP inhibition on the risk of SARS-CoV-2 infection is unclear. Of note, there is also evidence to suggest that complement activation may play a role in the pathogenesis of the disease (7). If this is indeed the case, complement pathway inhibition may in fact limit the severe manifestations of the disease.

For participants who transition from sutimlimab to BIVV020, the efficacy of BIVV020 is expected to be similar to that of sutimlimab, as both target the same protein, C1s, and inhibit CP. While it is expected that patients who responded to sutimlimab will have a similar response to

BIVV020, there remains the possibility that the response to BIVV020 may differ from that to sutimlimab in some patients. The target-specific and mechanism-related risks are expected to be the same for both sutimlimab and BIVV020. Patients who transition from sutimlimab to BIVV020 will benefit from a decreased burden of drug administration and clinic visits over the course of the study, as sutimlimab is administered intravenously every other week.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BIVV020 may be found in the Investigator's Brochure (IB).

2.3.1 Risk assessment

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention		
Meningococcal infection	Based on the functions of the classical complement pathway and evidence from patients with congenital classical complement deficiencies, or treated with complement inhibitors, BIVV020 may potentially increase risk of meningococcal infection as a result of long-term complement inhibition. **BIVV020 FIH healthy participant experience:** No events of meningococcal infection have been reported. **BIVV009 experience:** No reports of meningococcal infections in BIVV009 clinical trials as of 21 Jun 2020. As of 21 Jun 2020, an estimated 187 participants received BIVV009 in the clinical development program.	Participants will be monitored for meningococcal infection. The risk of meningococcal infection will be described in the ICFs. Participants will be advised to seek medical attention if they develop symptoms concerning for meningococcal infection. To reduce the risk of infection, participants will be required to either demonstrate a proof of documented vaccination against *Neisseria meningitidis* within 5 years of enrollment or comply with the vaccination requirement of the protocol (see Section 8.2.6 for more details).
Serious infections with other encapsulated bacteria	Long-term complement inhibition may potentially increase the risk of serious infections with encapsulated bacteria (eg: *Streptococcus pneumoniae*). **BIVV020 FIH healthy participant experience:** No reports of serious infections with encapsulated bacteria. **BIVV009 experience:** Serious infections have been reported in BIVV009 clinical trials in patients with CAD, although not necessarily with encapsulated organisms. These include streptococcal sepsis (*Streptococcus pyogenes*), *Escherichia coli* sepsis, wound infection staphylococcal (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and pneumonia (organism unknown). Overall, the pattern of infections in patients with CAD was consistent with an older, often medically complex patient population, including some patients who received chronic immunomodulatory therapies.	Participants will be monitored for serious infections with encapsulated bacteria. The risk will be described in the ICFs. Participants will be advised to seek medical attention if they develop symptoms concerning for serious infections with encapsulated bacteria. To reduce the risk of infection, participants will be required to either demonstrate a proof of documented vaccination against encapsulated bacteria within 5 years of enrollment or comply with the vaccination requirement of the protocol (see Section 8.2.6 for more details).
Systemic lupus erythematosus	Long-term CP inhibition could theoretically increase the risk of SLE or CIC disease due to the role of the C1 complex in immune complex clearance, as seen in patients with congenital deficiencies of C1 complex components (C1q, C1s, and C1r). BIVV020	Participants will be monitored for the development of SLE, lupus like syndrome, or other autoimmune diseases. A clinical diagnosis of SLE is

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	inhibits the C1s enzymatic function in the C1 complex. However, pharmacologic inhibition of C1s does not necessarily equate to congenital deficiency of the C1 complex. **Preclinical data:** No autoimmune response (CICC1q; ANAs) was observed in a 5-week repeat-dose toxicity study in cynomolgus monkeys. **BIVV020 FIH healthy participant experience:** No reports of SLE or newly developed autoimmune conditions. **BIVV009 experience:** There were no reports of SLE or newly developed autoimmune conditions in BIVV009 clinical trials as of 21 June 2020. As of 21 June 2020, an estimated 187 participants received BIVV009 in the clinical development program.	an exclusion criterion for all BIVV020 clinical studies. During screening an ANA as well as other autoimmune antibodies will be checked. The Investigator may decide to exclude participants from the study who appear to be at increased risk for autoimmune diseases (aside from ITP). The risk of development of SLE will be described in the ICFs. A panel of standard clinical biomarkers related to SLE (eg, antibodies to double-stranded DNA [dsDNA]) and to CIC disease (eg, measurement of CICs) will be performed at a regular interval during the study. Participants who develop clinical manifestations of SLE or a confirmed SLE diagnosis will be terminated early.
Serious hypersensitivity reactions and/or anaphylaxis	Serious hypersensitivity reactions and anaphylaxis are potential risks with any monoclonal antibody. **BIVV020 FIH healthy participant experience:** No reports of serious hypersensitivity reactions and/or anaphylaxis.	Participants will be monitored during the loading dose infusion of BIVV020 and immediately following infusion for any evidence of a hypersensitivity reaction or anaphylaxis. Additionally, the first 6 maintenance injections of BIVV020 will occur in the clinic. If any signs or symptoms of an allergic reaction are observed during BIVV020 infusion, the infusion must be immediately discontinued, and the participant treated as appropriate.
Coronavirus disease 2019 (COVID-19)	The classical pathway is involved in the neutralization of various viruses. Data is limited regarding SARS-CoV-2 in particular.	The need for SARS-CoV-2 testing during screening will be determined by the Sponsor and the Investigator at each site. Participants will be counseled to avoid situations that may place them at increased risk for COVID-19. If a participant is diagnosed with SARS-CoV-2 during the study, discontinuation of BIVV020 will be determined by the Investigator and Sponsor.
Study intervention: Risks associated with IV infusions and SC injections (including self-administered SC injections)		

Abbreviations: ANA = antinuclear antibody; C1s = complement component 1, s subcomponent; CAD = cold agglutinin disease; CIC = circulating immune complexes; COVID-19 = coronavirus disease 2019; CP = classical complement pathway; FIH = first-in-human; ICF = informed consent form; ITP = immune thrombocytopenia; IV = intravenous; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; SC = subcutaneous; SLE = systemic lupus erythematosus

2.3.2 Benefit assessment

Immune thrombocytopenia patients who are refractory to current therapies have substantial morbidity associated with their disease, including life-threatening bleeding. Treatment with BIVV020 has the potential to improve platelet levels and decrease the risk of bleeding in these patients.

2.3.3 Overall benefit: risk conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with BIVV020 are justified by the anticipated benefits that may be afforded to participants with persistent/chronic ITP.

3 OBJECTIVES AND ENDPOINTS

Table 2 - 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.
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

Objectives	Endpoints
Exploratory	
[redacted]	

3.1 APPROPRIATENESS OF MEASUREMENTS

The efficacy endpoints for this study are measures of platelet response and ITP disease severity. Regarding the primary endpoint, achieving a platelet count $\geq 50 \times 10^9$/L is known to reduce the risk of bleeding; for patients with a baseline platelet count $<15 \times 10^9$/L, an increase of $\geq 20 \times 10^9$/L would be considered clinically significant. For patients who previously received sutimlimab, the endpoint seeks to demonstrate that a response due to sutimlimab is maintained with BIVV020.

4 STUDY DESIGN

4.1 OVERALL DESIGN

- This is a Phase 2a open-label, non-randomized, international, multicenter study to evaluate the efficacy, safety, and tolerability of BIVV020 in adults with persistent/chronic primary ITP.
- The study will enroll approximately 12 participants: up to 6 participants who have previously received and responded to sutimlimab (BIVV009) in study TDR16218, as well as participants who have not previously received sutimlimab.
- The Screening Period will be up to 56 days. Screening begins from the time of the signing of the ICF. For participants receiving sutimlimab in study TDR16218, they may continue to receive sutimlimab during screening, until at least 14 days prior to the first dose of BIVV020, as duration of the PD effect of sutimlimab is approximately 14 days. This period between the final dose of sutimlimab and the first dose of BIVV020 is known as the Transition Period.
- Enrollment in the study occurs when a participant receives the first dose of BIVV020.
- A loading dose of BIVV020 at 50 mg/kg IV will be administered on Day 1, followed by maintenance doses of 600 mg SC weekly starting on Day 8. On Day 1, participants will remain in the clinic for at least 4 hours after that start of IMP administration.
- The 600 mg SC dose will be administered as two 2 mL injections. For the first 5 weeks of maintenance therapy, the injections will be performed by the site staff, and participants will receive education on self-administration. At Week 6, the participant (or their caregiver) will perform the injection under the supervision of the site staff. Participants should be observed for 30 minutes after IMP administration for the first 6 SC administrations.
- Starting at Week 7, the injections will be performed by the participant or caregiver at home. From Weeks 7 to 12, participant will return to the clinic every other week. At clinic visits, participants (or their caregiver) will administer BIVV020 under the supervision of the study staff. Participants may request assistance with the injections from the study staff during these visits.
- From Weeks 13 to 24, participants will return every 4 weeks and will self-administer BIVV020 under the supervision of study staff at those visits. From Week 25 onward, visits will occur at a minimum of every 8 weeks, and participants will continue to self-administer BIVV020 under the supervision of the study staff during those visits. Clinic visits should be scheduled so that they align as closely as possible with the day the participant typically takes BIVV020.
- If a participant prefers for drug administration to occur at the site instead of his/her home at any time during the study, this is acceptable.

- Phone calls will be performed during the study for site staff to remind participants to take their injections, answer any questions they may have regarding the injections, and to assess AEs. From Weeks 7 to 24, phone calls will be performed on weeks that the participants are not seen in the clinic (Weeks 7, 9, 11, 13 to 15, 17 to 19, and 21 to 23). After Week 25, phone calls will be performed approximately 4 weeks after each previous visit. (If a visit during this period occurs within approximately 4 weeks of the prior visit, a phone call is not necessary.) Phone calls should continue to occur approximately every 8 weeks after the cessation of treatment, until the EOS visit.
- Maintenance injections will continue until the last patient enrolled has completed 52 weeks of treatment. Therefore, the length of maintenance therapy may vary for each participant. The maximum duration of treatment for an individual participant is 104 weeks.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is designed to evaluate BIVV020 in patients with persistent/chronic primary ITP. These patients have failed prior therapies and have few available treatment options. Patients who are currently enrolled in study TDR16218 and have responded to sutimlimab will have the option of transitioning to this study. In this study, those patients will be able to receive the study drug subcutaneously, as opposed to intravenously, which was the case for sutimlimab.

For patients transitioning from sutimlimab to BIVV020, the switch to BIVV020 is expected to result in a decreased burden of drug administration while maintaining the same efficacy and risk profile as sutimlimab. Both BIVV020 and sutimlimab are monoclonal antibodies that target the same protein, C1s, and inhibit the classical complement pathway. The major difference between the 2 molecules is that BIVV020 has mutations that enhance FcRN binding, leading to an improved PK profile versus sutimlimab. In addition, BIVV020 demonstrates high affinity and specificity for the active form of C1s, whereas sutimlimab binds to both the inactive and active forms. BIVV020 has a high affinity (10^{-9} M) and specificity for the active form of human C1s, and is a potent ($IC_{50} = 10^{-8}$ M) and complete (100%) inhibitor of serum classical complement pathway activity, but not alternative or lectin pathway activity. The active form of C1s is required for the progression of the classical complement pathway. BIVV020 binds only this form, thereby requiring a lower dose compared to sutimlimab. BIVV020 demonstrates these improvements over sutimlimab, while inhibiting the classical complement pathway in effectively the same manner. Thus, patients who responded to sutimlimab are expected to have a similar response to BIVV020.

Participant convenience was taken into consideration in the design of this study. At the start of the study, the injections will be administered by the study staff. This will ensure that the participants are receiving the injections appropriately and will allow them to become familiar with the injection procedures. Education on self-administration will also be provided during this time. As the study progresses, the injections will be administered to a greater extent at home, which will minimize the time spent traveling to the clinic. However, when coming in for clinic visits, the participants will self-administer the injections under the supervision of the study staff to ensure that the administrations are being performed correctly.

The maximum duration of treatment for an individual participant is 104 weeks. As of 29 September 2020, 4 ITP patients have received sutimlimab for approximately 2 years with maintained efficacy and an acceptable safety profile. No new safety concerns associated with long-term sutimlimab treatment have been identified.

Platelet levels, which constitute the primary efficacy endpoint of the study, are a direct measure of disease activity.

4.2.1 Participant input into design

Participants were not involved in the design of the study. Nonetheless, this study has a reduced visit burden compared to the study from which some of the participants will be enrolled, TDR16218.

4.3 JUSTIFICATION FOR DOSE

The dose level and dosing regimen proposed for this study were derived from modeling and simulation based on data [redacted]. A population PK/PD model was developed using [redacted] and BIVV020 systemic exposure. The initial IV loading dose of 50 mg/kg, and the subsequent maintenance dose of 600 mg SC once weekly, were chosen to [redacted].

The proposed 600 mg once weekly SC dose is [redacted].

The selected loading dose of 50 mg/kg [redacted].

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study including the EOS visit.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all the following criteria apply:

Age

I 01. Male and female participants ≥18 years of age at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Confirmed diagnosis of primary ITP; for participants who previously received sutimlimab in study TDR16218, a response to sutimlimab must have been obtained, as defined by platelet count ≥30 × 10^9/L on 2 visits at least 7 days apart.

I 03. For participants who have not previously received sutimlimab: persistent/chronic ITP (ITP lasting for ≥6 months) and all the following conditions:

a) Platelet count ≤30 × 10^9/L on 2 occasions at least 5 days apart during the Screening Period;

b) Lack of an adequate platelet count response (as defined by maintenance of sustained platelet count ≥30 × 10^9/L in the absence of bleeding) to at least 2 ITP treatments, 1 of which was a thrombopoietin receptor agonist. Other ITP treatments include: IVIg, anti-D immunoglobulin, corticosteroids, splenectomy, rituximab, cyclophosphamide, azathioprine, danazol, cyclosporin A, mycophenolate mofetil, or fostamatinib.

c) If receiving weekly thrombopoietin receptor agonist dosing, the last dose must have been administered ≥7 days before the first dose of BIVV020. If receiving daily thrombopoietin receptor agonist dosing, the last dose must have been administered ≥24 hours before the first dose of BIVV020.

d) If applicable, concurrent administration of ITP medications (eg, corticosteroids, IVIg, azathioprine, danazol, cyclosporin A, mycophenolate mofetil, or thrombopoietin receptor agonists) is acceptable provided the patient has been on a stable dose for at least 1 month. See Section 6.8 for additional details.

e) If previously dosed with rituximab, the last dose of rituximab must have been administered at least 12 weeks before the first dose of BIVV020.

f) If previously dosed with cyclophosphamide, the last dose of cyclophosphamide must have been administered at least 4 weeks before the first dose of BIVV020.

I 04. Documented vaccinations against encapsulated bacterial pathogens (*Neisseria meningitidis*, including serogroup B where available, *Haemophilus influenzae*, and *Streptococcus pneumoniae*) within 5 years of enrollment, or as specified in Section 8.2.6.

Contraception

I 05. All contraceptives use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- Male participants must be surgically sterile for at least 90 days or agree when sexually active with female partners of childbearing potential to use a male condom with spermicide for the duration of the study and for 52 weeks after the last dose of BIVV020. Additionally, sperm donation is not allowed during the study and for 52 weeks after the last dose of BIVV020.
- Female participants must be post-menopausal, surgically sterile, or be established on (≥3 months prior to screening) and agree to continue to use the same highly effective method of birth control in conjunction with male barrier contraception (eg, male condom with spermicide) during their participation in the study and for 52 weeks after the last dose of BIVV020. Highly effective methods of contraception include intrauterine device (IUD; Mirena®), established use of oral, implanted, or transdermal hormonal method of contraception associated with inhibition of ovulation, bilateral tubal ligation, or permanent birth control via the Essure procedure. Participants who practice true abstinence, because of the participant's lifestyle choice (ie, the participant should not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are NOT acceptable methods of contraception. Additionally, ova donation is not allowed during the study and for 52 weeks after the last dose of BIVV020.

Informed Consent

I 06. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of the protocol which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Clinically significant medical history or ongoing chronic illness that would jeopardize the safety of the participant or compromise the quality of the data derived from his/her participation in the study.

E 02. Clinically relevant infection within the month prior to enrollment.

E 03. History of venous or arterial thrombosis within the year prior to enrollment.

E 04. Clinical diagnosis of SLE.

E 05. Secondary ITP from any cause including lymphoma, chronic lymphocytic leukemia, and drug-induced thrombocytopenia.

E 06. Positive hepatitis B surface antigen (HBsAg) or active HCV infection. For patients with an isolated positive anti-HBc antibody, hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR) must be negative at Screening. Patients who have undergone hepatitis C antiviral therapy may be enrolled if they are documented to be HCV RNA negative on at least 2 occasions separated by at least 3 months (including 1 RNA test at least 6 months after completion of antiviral therapy) and are also HCV RNA negative at Screening.

E 07. HIV infection.

E 08. Positive SARS-CoV-2 molecular test (if coronavirus disease [COVID-19] testing required). Note: Participants switching from sutimlimab may be enrolled even with a positive SARS-CoV-2 test, as per the judgement of the Investigator.

E 09. Pregnant or lactating women.

E 10. Eastern Cooperative Oncology Group (ECOG) performance status >2.

E 11. Sensitivity to any of the study interventions, or components thereof, or other allergy that, in the opinion of the Investigator, compromises participation in the study.

Prior/concomitant therapy

E 12. Use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), or anticoagulants within 1 week prior to enrollment.

Prior/concurrent clinical study experience

E 13. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug (with the exclusion of sutimlimab) within 30 days or 5 half-lives, whichever is greater, prior to enrollment.

Diagnostic assessments

E 14. Hemoglobin level <10 g/dL.

E 15. White blood cells (WBCs) or neutrophil counts outside of normal limits, if considered clinically significant by the Investigator. Elevated WBC/absolute neutrophil count (ANC) attributed to steroid treatment is acceptable.

E 16. Prothrombin time/international normalized ratio (PT/INR) or activated partial thromboplastin time (aPTT) outside of the normal limits, if considered clinically significant by the Investigator.

Other exclusions

E 17. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 18. Participants not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 19. Participants who are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the International Council for Harmonisation - Good Clinical Practice (ICH-GCP Ordinance E6).

E 20. Any specific situation during study implementation/course that may raise ethics considerations.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/STUDY INTERVENTION ADMINISTRATION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9) and should be considered for screening/enrollment/administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 3 - Overview of study interventions administered

Intervention label	BIVV020
Intervention name	BIVV020, humanized anti-C1s monoclonal antibody
Type	Drug
Dose formulation	BIVV020 supplied in single use vials containing 750 mg (150 mg/mL; extractable volume of 5 mL)
Unit dose strength(s)	750 mg/5 mL
Dosage level(s)	50 mg/kg IV loading dose, followed by 600 mg SC weekly
Route of administration	IV loading dose; SC maintenance administration
Use	Experimental
IMP or NIMP	IMP
Packaging and labeling	Details are provided in the Pharmacy Manual.
Current/Former name(s) or alias(es)	Not Applicable

Table 4 - Arms and associated interventions

Arm name	BIVV020
Associated interventions (intervention label[s])	Details are provided in the Pharmacy Manual

An intravenous (IV) loading dose of BIVV020 at 50 mg/kg will be administered on Day 1, and will be followed by maintenance doses of 600 mg SC weekly starting on Day 8. For the first 5 weeks of maintenance therapy, the injections will be performed by the site staff, and participants will receive education on self-administration. At Week 6, the participant (or their caregiver) will perform the injection under the supervision of the site staff. Starting at Week 7, the injections will be performed by the participants or caregiver at home. See Section 4.1 for additional details regarding the locations for IMP administration over the course of the study.

6.1.1 Intravenous loading dose administration

- The loading dose of BIVV020 at 50 mg/kg IV will be administered on Day 1.
- Infusion of the BIVV020 IV preparation should be done using a large volume infusion pump.

- Approximately 50 mL of dosing solution and approximately 60 mL of flush will be administered. An infusion pump will be programmed to deliver 90 mL at a rate of 150 mL/hr. Any excess volume over 90 mL will remain in-line to account for IV dead space. The total time for infusion will be approximately 45 minutes.
- The total time of dose preparation (vial puncture) to completion of administration may not exceed 4 hours.
- Participants will remain in the clinic for at least 4 hours after the start of IMP administration.
- The administration process is to be documented in the source document worksheet or within the administration/dosing logs.

Further details can be found in the Pharmacy Manual.

6.1.2 Subcutaneous dose administration

- The 600 mg SC dose will be administered in 2 injections; each injection will be 2 mL.
- Depending the study visit, SC administration my be performed at the site or by the patient/caregiver at home. In case of home administration, a Patient Diary should be used to record administration details.
- The recommended injection sites include:
  - Abdomen (except for the 2 inch [~5 cm] radius area around the navel). This is the preferred location.
  - Top of thighs.
  - Outer area of upper arm (by caregivers only).
- The SC injections should be given consecutively, but may be spaced apart by up to 30 minutes. A different site for each injection should be used (eg different locations on the abdomen).
- The total time of dose preparation (vial puncture) to completion of administration may not exceed 4 hours.
- Participants should be observed for 30 minutes after IMP administration for the first 6 SC administrations.

Further details can be found in the Pharmacy Manual.

BIVV020 may be supplied at the site or from the Principal Investigator/site/Sponsor to the participant via a Sponsor-approved courier company (direct-to-patient [DTP]) where allowed by local regulations and agreed upon by the participant. The participant/Investigator can refuse this option. Details are provided in the Pharmacy Manual.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9).

A complete description of BIVV020 and its proper handling will be provided in the Pharmacy Manual available to the clinical site. The appropriate number of kits will be dispensed as necessary for the periods between visits (please refer to SoA Section 1.3). Storage conditions and use-by-end date (when required by country regulations) are part of the label text.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received. Any discrepancies must be reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may administer it at clinic visits. All study intervention stored at the sites must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.7).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

Additional information regarding treatment allocation, preparation and dispensation are available in the Pharmacy Manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

- IMP accountability:
  - Intervention units are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract).

- The Investigator counts the number of vials, etc, remaining in the returned packs, and fills in the Intervention Log Form.
- The Investigator records the dosing information on the appropriate page(s) of the case report form (CRF).
- The monitor in charge of the study then checks the CRF data by comparing them with the IMP which he/she has retrieved and intervention log forms.

Starting at Week 7, the injections will be performed by the patient or caregiver, either at home or in the clinic at scheduled visits. When participants self-administer the study intervention at home, they will be provided with a paper diary or e-diary to record their administrations.

The date and time of each dose administered in the clinic will be recorded in the source documents and recorded. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of BIVV020 units dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5 DOSE MODIFICATION

Not applicable.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Participants will continue to receive BIVV020 until the last participant enrolled has completed 52 weeks of treatment. After that time, a long-term extension study may be available for participants to continue to receive BIVV020. If a long-term extension study is available, the follow up period for this study may not be applicable or may be modified as per the long-term extension study.

6.7 TREATMENT OF OVERDOSE

The Sponsor does not recommend specific treatment for an overdose, as there is no specific antidote. However, any supportive medical treatment may be administered, based on evaluation and clinical findings.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor immediately.
2. Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.

3. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study intervention if requested by the Sponsor (determined on a case-by-case basis).
4. Document appropriately in the CRF.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements, and rescue medication) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Vaccinations such as seasonal influenza vaccines and other recommended vaccines and booster vaccinations are permitted as per local standard of care, investigator discretion, and local labels.

Concurrent administration of ITP medications (corticosteroids, IVIg, azathioprine, danazol, cyclosporine A, mycophenolate mofetil, or thrombopoietin receptor agonists) is acceptable provided the patient has been on a stable dose for at least 1 month. This applies for both new patients and patients who were previously receiving sutimlimab in Study TDR16218.

Corticosteroids, thrombopoietin receptor agonists, and IVIg are permitted, if the follow requirements are met:

A) Corticosteroids: the first dose of BIVV020 may be dosed only ≥4 days after a steroid pulse (single dose of >0.5 mg/kg prednisone equivalent or an increase in prednisone equivalent dose from prior levels) for acute ITP treatment
B) Thrombopoietin receptor agonists: If receiving weekly thrombopoietin receptor agonist dosing, the last dose must have been administered ≥7 days before the first dose of BIVV020. If receiving daily thrombopoietin receptor agonist dosing, the last dose must have been administered ≥24 hours before the first dose of BIVV020. Thrombopoietin receptor agonists may be restarted by the Investigator if a participant has an insufficient response to BIVV020.
C) Intravenous Ig (IVIg): the first dose of BIVV020 must be dosed ≥1 day after a dose of IVIg. A single dose of IVIg is allowed during the study; additional doses after the first dose must be approved by the Sponsor.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 Rescue medicine

Rescue medicines given for acute episodes of thrombocytopenia/bleeding, such as steroid pulse/bolus, thrombopoietin receptor agonists, or platelet transfusion are allowed (see above for guidance on IVIg). Additionally, increasing the dose of concomitant ITP medications to prevent or treat bleeding due to low platelet counts is allowed and would be considered rescue therapy.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently/definitely discontinue the study intervention. If this occurs, a new participant may be enrolled to replace the one who was discontinued, unless the permanent discontinuation was due to a BIVV020-related adverse reaction or safety concern.

The Investigator/Sponsor must permanently discontinue dosing with BIVV020 in a participant if any of the following participant-level stopping rules are met:

- Pregnancy in a participant while receiving study drug.
- Change in compliance with inclusion/exclusion criteria that is clinically relevant and affects patient's safety.
- Intake of non-permitted concomitant medications that might affect participant's safety or study assessments/objectives.
- An allergic reaction, including an anaphylactic reaction, in association with BIVV020 administration.
- SLE or any other immune complex disease.
- Meningococcal infection.
- Occurrence of AEs that, in the opinion of Investigator/Sponsor, may jeopardize patient safety or data integrity. These include, but are not limited to, abnormal liver tests and abnormal QTc, meeting the stopping criteria (see Section 7.1.2, Section 7.1.3, Appendix 6, Section 10.6).
- Lack of efficacy (see Section 7.1.4).
- Participant misses more than 3 consecutive doses of BIVV020 without Investigator approval. If a participant misses 3 consecutive doses and the Investigator believes the participant should remain in the study, a protocol for BIVV020 re-initiation may be considered, in consultation with the Sponsor.

Handling of participants after permanent intervention discontinuation

If study intervention is definitively discontinued, the participant should continue to be followed for an additional 22 weeks. The procedures listed for the EOS visit as per the SoA should be performed at the final visit.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the electronic case report form (eCRF) when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in the ALT algorithm in Appendix 6 (Section 10.6) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

7.1.3 QTc stopping criteria

In the event of prolongation of QTc interval (automatic measurement) ≥500 ms or increase from baseline >60 ms, confirmed by a manual reading by the Investigator or a physician delegated by the Investigator using the Fridericia formula for correcting QT, the participant should be placed under supervision in a specialized setting. Investigational medicinal product administration must be stopped and appropriate blood samples collected. Subsequent ECG monitoring of the participant should then be performed on a regular and clinically responsible basis until the QTc interval returns to a safe value as determined by the Investigator in agreement with the Sponsor. Investigational medicinal product may be restarted at the discretion of the Investigator (in agreement with the Sponsor) once the QTcF returns to a safe value.

7.1.4 Lack of efficacy (relapse or sustained lack of improvement) stopping criteria

The study intervention may be discontinued due to a lack of response. Determination for treatment discontinuation in this case will be made by the Investigator and Sponsor.

7.1.5 Thrombocytosis

BIVV020 should be discontinued if a participant's platelet count is >450 × 10^9/L. BIVV020 may be restarted when the platelet count is ≤150 × 10^9/L. The procedure for BIVV020 re-initiation must be discussed with the Sponsor prior to re-dosing.

7.1.6 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (described in Appendix 9 [Section 10.9]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

If a participant is diagnosed with COVID-19, the decision to temporarily discontinue the study treatment will be made by the Sponsor and Investigator. Once the patient is fully recovered, the decision to restart treatment will be determined by the Investigator and Sponsor.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, following procedures for the EOS visit (see SoA [Section 1.3]).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to continue to be followed for an additional 22 weeks. The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be reallocated (retreated) in the study. Their study identification numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management or from Study TDR16218 (if available) and obtained before signing of the ICF may be utilized for screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be within a safe limit for human clinical trials as recommended by the local Institutional Review Boards and Ethics Committees. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

8.1 EFFICACY ASSESSMENTS

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3). The primary efficacy endpoint is determined by platelet counts, which will be assessed by a central lab.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- An abbreviated physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

- Ad-hoc physical exams may be performed at the discretion of the Investigator based on any AE reported by the participant and need not be limited to the time points listed in the SoA.

8.2.2 Vital signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be performed sitting and preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- If possible, vital signs should be performed prior to the collection of clinical laboratories.

8.2.3 Electrocardiograms

- Twleve-lead ECGs will be obtained at the time points defined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The readout should include date, time, participant study ID, signature of the research physician, and at least 3 complexes for each lead. This printout will be retained at the site.
- If possible, ECGs should be performed prior to the collection of clinical laboratories.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. These tests will be performed by a central lab, except for serum and urine pregnancy tests, which will be performed locally.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE, as per the guidelines in Section 10.3.1. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.4.1 Additional testing in case of hypersensitivity/allergic reaction

If a participant exhibits signs of a hypersensitivity/allergic reaction during study drug administration, the study drug should be stopped immediately, and medical treatment provided, as appropriate.

In case of a suspected anaphylactic reaction, the following labs may be obtained at the discretion of the Investigator, and after discussion with the Sponsor:

- Approximately 30 to 120 minutes after the start of symptoms: blood draw for antidrug antibodies (ADA), tryptase, IL-6, plasma histamine, CICs, and complement levels (CH50). A follow-up tryptase level should be obtained approximately 8 days following the reaction. Further characterization of the ADA response might be performed.
- 24-hour urine collection for methylhistamine analysis (ideally collection should be started within 6 hours of onset of symptoms).

8.2.4.2 Additional testing in case of suspected rhabdomyolysis

If a participant exhibits signs or symptoms which may be indicative of rhabdomyolysis during study drug administration, including, but not limited to: muscle pain in the extremities or back, excessive muscle weakness or trouble moving arms and legs, dark red or brown urine or decreased urination, the following labs should be obtained:

- Serum creatine kinase.
- Hepatic function panel.

8.2.5 Pregnancy testing

Serum and urine pregnancy testing will be performed as per the SoA (Section 1.3) by local labs.

8.2.6 Vaccinations against encapsulated bacteria

In the event a participant does not have documented vaccination against encapsulated bacterial pathogens (*N meningitidis*, including serogroup B meningococcus [where available], *H influenzae*, and *S pneumoniae*) within 5 years prior to enrollment, vaccination must be initiated as early as possible during the Screening Period. Vaccination series must be completed as per current regional guidelines for patients with persistent complement deficiency, and in accordance with their respective labels, as applicable. Where no regional guidelines are available for patients with persistent complement deficiency, vaccinations should include meningococcal conjugate, meningococcal serogroup B, 13-valent pneumococcal (PCV13), 23-valent pneumococcal (PPSV23), and *H influenza* type b vaccines, where available, and administered as per regional guidelines.

All vaccination series should be initiated as early as possible and completed at least 2 weeks prior to the first BIVV020 administration. For participants who have not previously received pneumococcal vaccines, PCV13 should be given first and PPSV23 at least 8 weeks after the dose of PCV13. Participants must be advised that vaccination may not completely prevent infections with encapsulated organisms and that they should immediately report fevers or other symptoms consistent with acute infection to the Investigator.

Patients who develop symptoms consistent with an infection due to encapsulated bacterial pathogens during the study period will have a blood sample collected to test for confirmation of infection.

8.2.7 Injection site reactions

Injection site reactions should be documented by the Investigator as per the SoA (Section 1.3). These include pain, tenderness, erythema/redness, swelling, induration, and itching. If the Investigator considers an injection site reaction an AE, the appropriate source form should be completed.

8.2.8 Phone calls

Phone calls will be performed during the study for site staff to remind participants to take their injections, answer any questions they may have regarding the injections, and to assess AEs. From Weeks 7 to 24, phone calls will be performed on weeks that the participants are not seen in the clinic (Weeks 7, 9, 11, 13 to15, 17 to 19, and 21 to 23). After Week 25, phone calls will be performed approximately 4 weeks after each previous visit. (If a visit during this period occurs within approximately 4 weeks of the prior visit, a phone call is not necessary.) Phone calls should continue to occur approximately every 8 weeks after the cessation of treatment, until the EOS visit.

8.2.9 Participant diary

At-home IMP administration will be recorded in a participant diary (paper or e-diary).

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.6.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until the EOS visit, at the time points specified in the SoA (Section 1.3).

For participants transitioning from the TDR16218 sutimlimab study, additional considerations and requirements for AE/SAE reporting are required. All AEs/SAEs that began during the TDR16218 study that are ongoing at the EOS visit in TDR16218 and at ICF signature in PDY16894 must be reported again during the PDY16894 study screening period in the PDY16894 clinical trial database as AEs and as per the SAE reporting procedures outlined in Section 10.3.4. A follow-up SAE report for study TDR16218 should also be submitted for ongoing SAEs when participants sign the ICF for PDY16894.

New AE/SAEs that begin after ICF signature in the PDY16894 study must be reported per the standard AE/SAE reporting procedures in Section 10.3. If the AE/SAE occurred within 9 weeks of the last dose of sutimlimab, the event must include an assessment of causality between the AE/SAE and sutimlimab.

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE and AESI data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and AESIs (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the IB.
- Suspected unexpected serious adverse reactions (SUSARs) are reported to regulatory authorities, Investigators, and IRBs/IECs as follows:
  - For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days.
  - For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR, or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and in female partners of male participants will be collected after the start of study intervention and until the end of the study.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy (after obtaining the appropriate informed consent for female partners of male participants).
  - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.6 Adverse event of special interest

Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy
  - Pregnancy occurring in a female participant entered in the study or in a female partner of a male participant entered in the study. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or nonserious) with IMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic vials or syringe counts) and defined as at least twice the intended dose within the intended therapeutic interval/visits, adjusted according to the tested drug.
  - Infusion: increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
  - Of note, asymptomatic overdose is to be reported as a standard AE.
- QTc ≥500 ms
- Increase in ALT >3 × ULN (see Appendix 6, Section 10.6)
- Other project specific AESIs
  - Grade 3 or higher allergic reaction per Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grading or an anaphylactic reaction in association with BIVV020 administration.
  - Newly diagnosed or potential development of SLE, autoimmune disease or acute flare or chronic worsening of underlying autoimmune disease.
  - Meningococcal infection.
  - Infection due to an encapsulated bacterial organism.

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 PHARMACOKINETICS

8.4.1 Sampling times

The sampling times for blood collection can be found in the SoA (Section 1.3)

8.4.2 Sample handling procedure

Special procedures for collection, storage, and shipment are provided in the laboratory manual.

8.4.3 Bioanalytical methods

Details of bioanalytical methods can be found in the laboratory manual.

8.4.4 Pharmacokinetic parameters

Plasma concentrations of BIVV020 will be obtained. This data may be included in a population PK analysis.

Pharmacokinetic samples could be used for testing analytical method performance such as comparability and incurred sample reproducibility.

8.5 GENETICS AND/OR PHARMACOGENOMICS

Participants may provide consent for future research to be performed utilizing their samples. This may include DNA analysis (See Section 8.9 and Section 10.5).

8.6 BIOMARKERS

- Collection of biological samples for biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3):

- Samples will be tested to evaluate their association with the observed clinical responses.
- In addition, samples will be stored and analysis may be performed on additional biomarkers related to the complement pathway to evaluate their association with observed clinical responses.
- Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to the mechanism of action of BIVV020.
- Samples collected for biomarker analyses and their derivatives will be stored for a period of up to 5 years after last patient last visit for potential re-analyses.

8.7 IMMUNOGENICITY ASSESSMENTS

Antibodies to BIVV020 will be evaluated in plasma samples collected from all participants according to the SoA (Section 1.3). Additionally, plasma samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Plasma samples will be screened for antibodies binding to BIVV020 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to BIVV020 and/or further characterize the immunogenicity of BIVV020.

The detection and characterization of antibodies to BIVV020 will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study intervention will also be evaluated for BIVV020 plasma concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit, at a facility selected by the Sponsor to enable further analysis of immune responses to BIVV020.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects.

Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research).

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

A participant’s coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

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

9.2 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 5 - Populations for analyses

Population	Description
Screened	All participants who signed the informed consent form (ICF).
Enrolled	All participants from the screened population who receive at least 1 dose (full or partial) of study intervention.
Intention to Treat (ITT)	All participants who receive at least 1 dose (full or partial) of study intervention.
Safety	All participants who receive at least 1 dose (full or partial) of study intervention.
Pharmacokinetic (PK)	All participants who receive at least 1 dose (full or partial) of study intervention with sufficient sample data.
Pharmacodynamic (PD)	All participants who receive at least 1 dose (full or partial) of study intervention with sufficient sample data to assess PD parameters.
PK/PD	All enrolled participants in the PK population with at least 1 time-matched PK/PD parameter.

9.3 STATISTICAL ANALYSES

The Statistical Analysis Plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.3.1 General considerations

- Common definitions of baseline.
- General methods (eg, how the continuous variables will be summarized).

The baseline value is defined as the last non-missing assessment before the first dose of study drug.

Unless otherwise specified, analyses will be performed based on the populations described above; safety analysis will be performed based on the safety population; PK, PD, and PK/PD analyses will be performed using the respective populations as defined in Section 9.2.

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period from enrollment up to the first dose of study intervention. Demographics, baseline disease characteristics, medical history, and prior therapy including prior ITP therapy use will be summarized based on data collected in this period.
- The **treatment-emergent (TE) period (or the study treatment period) for efficacy** and exposure analysis is defined as the period from the first study intervention administration to the last study intervention administration +7 days.
- The **safety analysis period** is defined as the period from the first study intervention administration to the EOS visit. Safety summaries will be based on this period.

9.3.2 Primary endpoint

The primary endpoint is described in Section 3.

The number and proportion of participants meeting the responder criteria will be presented; the 95% confidence interval of the proportion of responders will be estimated using Clopper-Pearson method. Missing data will not be imputed in the statistical analysis. If a patient discontinues study treatment prior to Week 3, the patient will be considered as a non-responder. If a patient discontinues the study treatment after Week 3 and prior to Week 24, his or her responder status will be assessed using the available data between Week 3 and Week 24.

9.3.3 Secondary endpoints

The secondary endpoints are described in Section 3.

For the continuous secondary endpoints (clinical and laboratory parameters, PK parameters), summary statistics by visit including sample size, mean and standard deviation, median, minimum and maximum will be presented for the actual value and the change from baseline, if applicable.

For the time-to-event endpoint (ie, time to first platelet response), Kaplan-Meier method will be used to estimate the proportion of participants with response at different study day, and the median time to response. Participants with no response will be censored at the date of the last platelet count assessment.

For the responder endpoint (ie, participants who did not require rescue therapy for an acute thrombocytopenia episode after Week 3), the number and proportion of such participants will be presented, along with the 95% confidence interval of the proportion estimated using Clopper-Pearson method.

9.3.4 Exploratory endpoints

[redacted]

9.3.5 Safety analysis

9.3.5.1 Adverse events

Treatment-emergent adverse events (TEAEs) are AEs that develop after the first study drug administration in the safety analysis period. All AEs in the study include TEAEs and AEs that develop prior to the first study drug administration and continue into the safety analysis period. All deaths in the study will be reported.

An overall summary table will be provided with numbers and proportions of participants with at least one of the following events (not limited to):

- TEAE and TESAE
- Related TEAE and TESAE
- TEAE Grade 3 or higher
- TEAESI
- TEAE infection of Grade 3 or higher and TESAE infection
- Discontinuation of study treatment and/or withdrawal from study due to a TEAE
- Death

Additional summaries, including but not limited to, the incidence of TEAEs and TESAEs by system organ class (SOC) and preferred term, and by relationship to study intervention.

9.3.5.2 Laboratory variables and vital signs

For laboratory parameters, 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.

For vital signs, descriptive statistics for results and changes from baseline will be provided for each visit during the safety analysis period. the number and percentage of participants with potentially clinically significant vital signs will be provided.

9.3.6 Other analysis

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

9.4 INTERIM ANALYSES

An interim analysis will be performed when approximately 12 patients have each been treated for 15 weeks.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki (2013) and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR]).
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so, designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and

- The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participants and answer all questions regarding the study, including what happens to the participant when his/her participation ends.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s).Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only

by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study,
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,

- Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Review Committees

Study Monitoring Committee

The Study Monitoring Committee (SMC) will comprise at least 2 investigators participating in the study as well as Sponsor representatives from clinical and pharmacovigilance functions. The SMC will meet quarterly to review safety data and can make recommendations about early study closure or changes to the conduct of the study.

Safety Management Team

Participant safety will be continuously monitored by the Sponsor's internal safety team, which includes safety signal detection, comprehensive cross-functional characterization, and monitoring of the product safety profile at any time during the study as per the Internal Sponsor Safety Management Team (SMT) charter (BTD-010790).

All safety data collected will be summarized and reviewed by the Sponsor's internal safety team for agreement of next steps.

Based on the review of safety data, enrollment in the study may be paused or the study may be stopped.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the “EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations”.

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of CRFs will be provided.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study hold

A dosing and enrollment hold will occur if there is >1 participant with a Grade 4 or higher TEAE, unless determined to be clearly unrelated to IMP or attributable to an underlying pre-existing disease or condition. The hold may be lifted if the benefit/risk ratio of the study is still deemed to be favorable by the Study Monitoring Committee and applicable regulatory and ethical bodies.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 6 will be performed by the central laboratory unless otherwise specified.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Additional tests may be performed at any time during the study as deemed necessary by the Investigator or required by local regulations.
- Pregnancy testing (serum and urine) will be performed locally.
- SARS-CoV-2 testing, if applicable, will be performed through the central lab.

Table 6 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices (at minimum):
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	White blood cell (WBC) count with differential:
	WBC
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry	
	Blood urea nitrogen (BUN)
	Creatinine
	Glucose (non-fasting)
	Potassium
	Sodium
	Calcium
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase[a]
	Total and direct bilirubin
	Total protein

Laboratory tests	Parameters
Coagulation	
	Prothrombin time (PT)/international normalized ratio (INR) Activated partial thromboplastin time (aPTT)
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)
Other	
	Serum creatine kinase (CK) (at Screening only) Follicle-stimulating hormone (FSH) (at Screening only, if indicated; see Section 10.4.1) CH50
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	• Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) will be performed locally
Other screening tests	• FSH (as needed in women of non-childbearing potential only) • Serology (human immunodeficiency virus [HIV] antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody [HBcAb] immunoglobulin [Ig] G and IgM, and hepatitis C virus antibody) • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) molecular test (if applicable)

NOTES:
a If alkaline phosphatase is elevated, consider fractionating.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of the participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during interview with the participant and by review of available medical records at the next visit.
- Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned.

Events <u>meeting</u> the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the judgement of the Investigator and are not related to progression of underlying disease. For example:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc)
  - Development of drug dependence or drug abuse
  - Suicide attempt or any event suggestive of suicidality
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions
  - Cancers diagnosed during the study or aggravated during the study (if judged as unusual or significant by the Investigator)
  - Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (if judged unusual or significant by the Investigator).

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

Adverse events will be graded according NCI-CTCAE v5 and classified by SOC/preferred term according the last available version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

For AEs not included in the NCI CTCAE, the Investigator will be required to assess the intensity of the adverse drug/biologic experience using the CTCAE general guideline:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered women of childbearing potential (WOCBP) (fertile) from the time of menarche until becoming postmenopausal, unless permanently sterile.

- A postmenopausal state is defined as when a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range should be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2 Contraception guidance

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below in Table 7.

Table 7 - Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[a] *Failure rate of <1% per year when used consistently and correctly*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation - (oral, intravaginal, or transdermal) • Progestogen-only hormone contraception associated with inhibition of ovulation - (oral or injectable)
Highly effective methods that are user independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation - Intrauterine device (IUD) - Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Essure procedure
Vasectomized partner *Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not and less than 1 year after vasectomy, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

NOTES:
a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

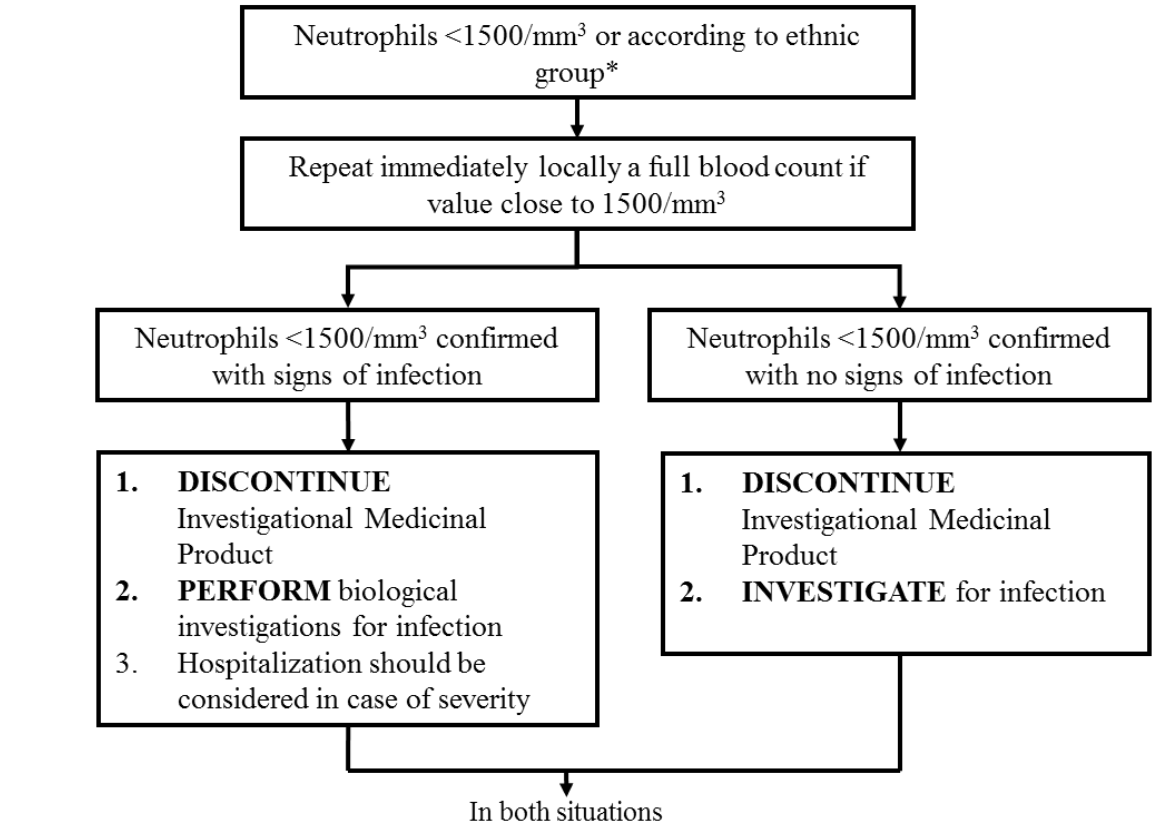
10.5 APPENDIX 5: GENETICS

Future use/analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for possible future DNA analysis from consenting participants.
- While there are no planned DNA analyses in this study, future research related to the complement pathway, ITP, and related diseases may use DNA samples collected from this study, if the participant provides consent. They may also be used to develop tests/assays including diagnostic tests related to complement pathway inhibitors and ITP. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to BIVV020 or study interventions of this class to understand study disease or related conditions.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on BIVV020 continues but no longer than 15 years or other period as per local requirements.

10.6 APPENDIX 6: SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

NEUTROPENIA

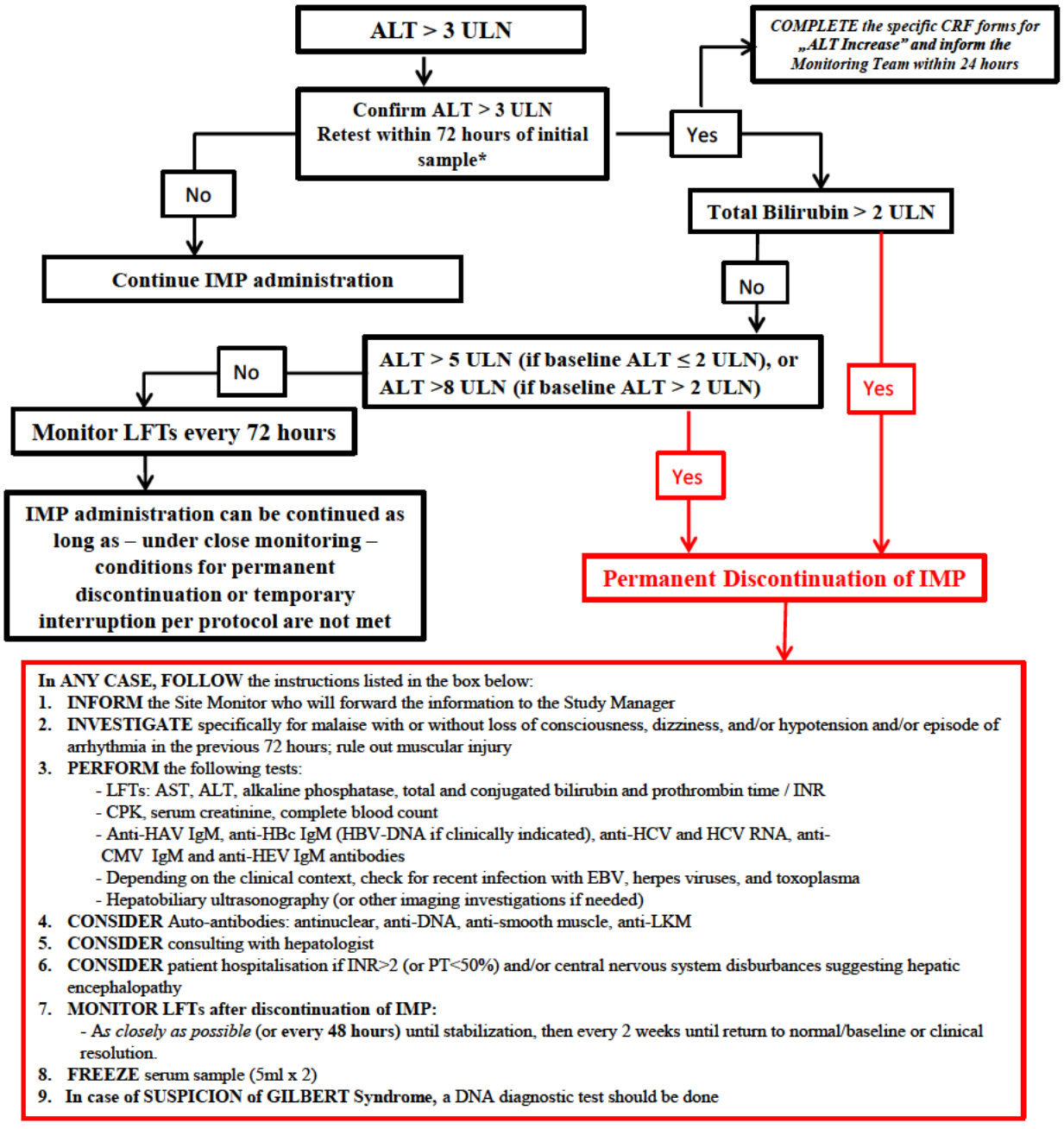


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - Infectious serologies to be performed locally, according to clinical symptoms / medical history
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

***** For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.3.1 is met.

INCREASE IN ALT

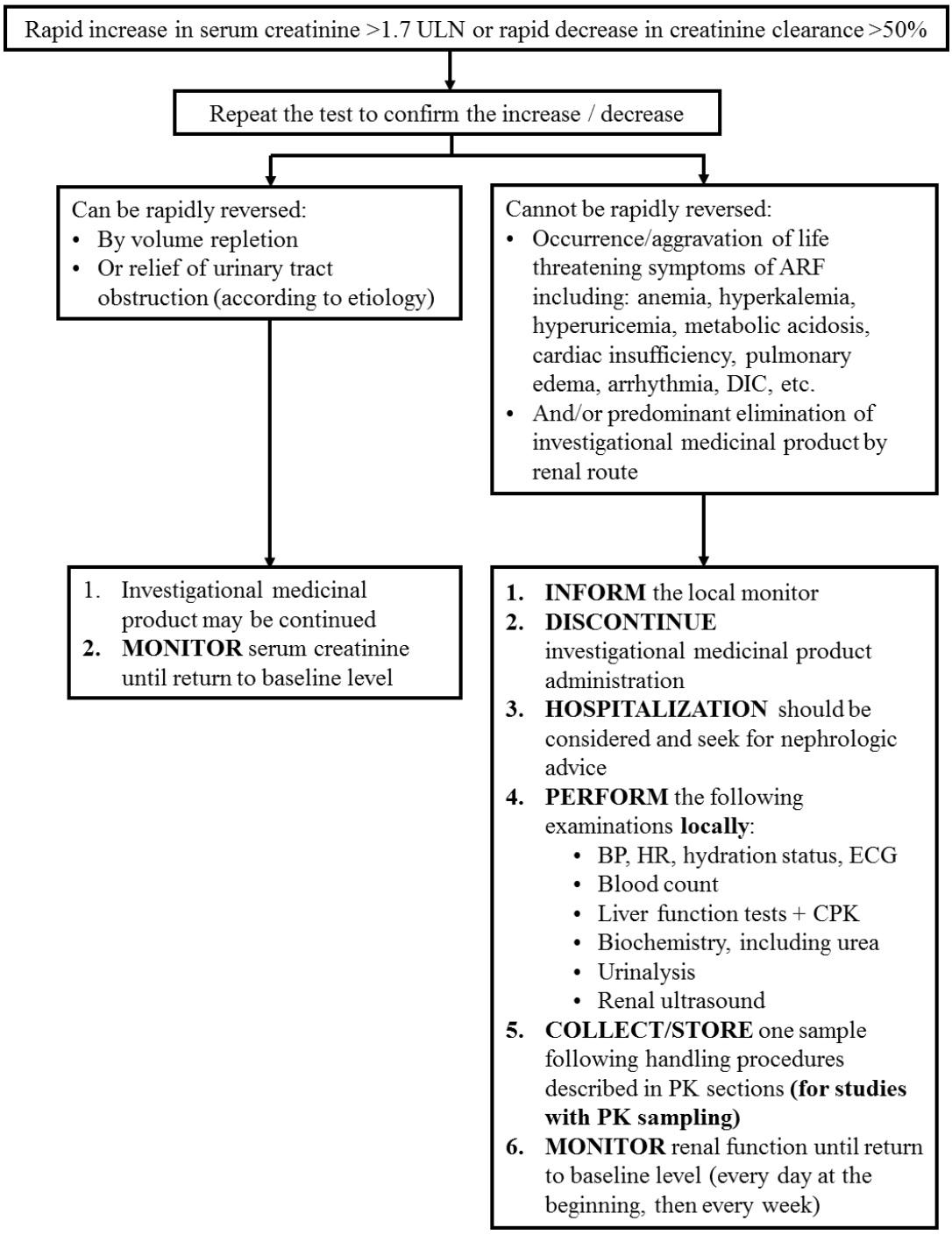


In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours**) until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
Note:
"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
See Section 8.3 for guidance on safety reporting.
Normalization is defined as ≤ ULN or baseline value, if baseline value is > ULN.

INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.3.1 is met.

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained).

Study intervention

If a participant has to stop BIVV020 due to a regional or national emergency (eg, COVID-19), re-initiation of the study intervention can only occur once the Investigator has determined, according to his/her best judgement, that 1) BIVV020 did not contribute to the occurrence of the concerned adverse event and 2) the selection criteria for the study are still met (refer to Section 5). Re-initiation of the study intervention will be done under close and appropriate clinical/and or laboratory monitoring and in consultation with the Sponsor.

Study assessments and procedures

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/administration of study intervention may be temporarily delayed.

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety and/or efficacy data.
- If onsite visits are not possible, visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed when central labs cannot be performed due to a government declared national emergency.

Statistical analyses

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

Informed consent

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs).

10.10 APPENDIX 10: ABBREVIATIONS

ADA:	antidrug antibodies
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
C1s:	complement component 1, s subcomponent
CAD:	cold agglutinin disease
COVID-19:	coronavirus disease 2019
[redacted]	[redacted]
CRF:	case report form
CTCAE:	Common Terminology Criteria for Adverse Events
DTP:	direct to patient
ECG:	electrocardiogram
eCRF:	electronic case report form
EOS:	end of the study
FIH:	first-in-human
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
GLP:	Good Laboratory Practice
HCV:	hepatitis C virus
HIV:	human immunodeficiency virus
HRT:	hormonal replacement therapy
IB:	investigator's brochure
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
IRB:	institutional review board
ITP:	immune thrombocytopenia
IV:	intravenous

IVIg:	intravenous immunoglobulin
PCSA:	potentially clinically significant abnormality
PCV13:	13-valent pneumococcal
PD:	pharmacodynamics
PK:	pharmacokinetics
PPSV23:	23-valent pneumococcal
PT:	prothrombin time
SAE:	serious adverse events
SAP:	statistical analysis plan
SARS-CoV-2:	serious acute respiratory syndrome coronavirus 2
SC:	subcutaneous
SLE:	systemic lupus erythematosus
SoA:	schedule of activities
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reactions
TEAE:	treatment-emergent adverse event
TESAE:	treatment-emergent serious adverse event
ULN:	upper limit of normal
WBC:	white blodd cells

10.11 APPENDIX 11: PROTOCOL AMENDMENT HISTORY

This is the third amendment of the protocol. Changes to the protocol for amended protocol 03 are summarized before the Table of Contents. Changes to the protocol for amended protocols 01 and 02 are summarized in this section.

Amended protocol 02 (10 December 2020)

This amended protocol 02 (Amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Changes in the protocol have been implemented to address requests received from the US Food and Drug Administration as well as additional corrections and clarifications.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities	Pre-dose weight added on Day 1	Weight needed for loading dose
1.3 Schedule of activities, footnote **g**; 8.2.6 Vaccinations against encapsulated bacteria	Titers may not be used in lieu of documentation of prior vaccination	Clear titer cutoffs associated with protection do not exist for most of the required vaccines
5.1 Inclusion criteriion I03	For participants who have not previously received sutimlimab, one of their prior treatments must have been a thrombopoietin receptor agonist	US FDA request
6.8 Concomitant therapy	Clarification that vaccinations, such as the seasonal influezna vaccine, are permitted during the study	Clarification
6.8.1 Rescue medicine	Clarification that a dose increase in a concomitant ITP medication is considered rescue therapy	Clarification
8.2.4.1 Additional testing in case of hypersensitivity/allergic reaction	Clarification of testing to be performed in case of hypersensitivity/allergic reaction	Some of the lab tests listed in the prior version were difficult to perform and of unclear utility
8.3.1 Time period and frequency for collecting AE and SAE information	Additional information for participants transitioning from study TDR16218	For these participants there are additional requirements and considerations for AE/SAE reporting
10.1.9 Study and site start and closure	Addition of a dosing and enrollment hold for toxicity	US FDA request
10.2 Appendix 2: Clinical Laboratory Tests	Thrombopoietin removed from clinical chemistry panel	Test not essential for study and cannot be performed through the central lab
Throughout	Additional clarifications and corrections to typography and formatting	Clarification and consistency with document standards

Amended protocol 01 (08 December 2020)

Changes for amended protocol 01 (08 December 2020) were considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR AMENDMENT 01

Changes in protocol amendment 01 were implemented to address requests received in a Voluntary Harmonisation Procedure communication.

PROTOCOL AMENDMENT 01 SUMMARY OF CHANGES

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Overall design; 1.3 Schedule of activities, footnote **e**; 2.3 Benefit/Risk assessment; 4.1 Overall design; 4.2 Scientific rationale for study design	Addition of a maximum duration of treatment of 104 weeks per participant, and also noted long-term safety profile for sutimlimab, another compound with a similar mechanism of action.	Added limit as a safety measure, and added further information to support likelihood of long-term safety
1.1 Synopsis, Overall design; 4.1 Overall design, 6.1.2 Subcutaneous dose administration	Specified that participants should be observed for 30 minutes after IMP administration for the first 6 SC administrations	Additional safety monitoring
1.1 Synopsis, Data Monitoring/Other committee; 10.1.5 Review Committees	Added mention of Data Monitoring Committee to synopsis, renamed “Data Monitoring Committee” subheading as “Study Monitoring Committee,” and added a brief description of the Data Monitoring Committee, which will include at least 2 investigators participating in the study	Increased safety monitoring
1.3 Schedule of activities; 5.1 Inclusion critierion I05	Male and female participants are now required to continue contraception until 52 weeks after the last dose of BIVV020. A urine pregnancy test was added to the End of Study visit for women of child-bearing potential.	Required contraception extended due to the prolonged half-life of BIVV020
6.1 Study interventions administered (new subsections 6.1.2 and 6.1.3	Additional details for IMP administration added	Health authority request
6.2 Preparation/handling/ storage/accountability	Added statement referring to the Pharmacy Manual for procedure details	Clarification
6.8 Concomitant therapy	Clarification that thrombopoietin agonists may be restarted by the Investigator after BIVV020 administration if a participant has an insufficient response to BIVV020	Clarification
new section added: 7.1.5 Thrombocytosis; subsequent subheadings renumbered	A new section was added to specify that BIVV020 should be discontinued if platelet counts rise above 450 x 10^9/L	Added guidance for thrombocytosis
10.1.1 Regulatory and ethical considerations	Clarification that the Declaration of Helsinki guidelines referenced are the most recent guidelines from 2013	Clarification

Section # and Name	Description of Change	Brief Rationale
10.4.2 Contraceptive guidance	Double-barrier contraception removed as a highly effective contraceptive method	Double barrier contraception is not considered to be highly effective as per the Clinical Trial Facilitation Group

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