A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO ASSESS THE EFFICACY AND SAFETY OF PF-06462700 ADMINISTERED INTRAVENOUSLY AT 40 MG/KG/DAY FOR 4 DAYS IN JAPANESE PARTICIPANTS WITH MODERATE AND ABOVE APLASTIC ANEMIA

Investigational Product Number:	PF-06462700
Investigational Product Name:	Anti-human Thymocyte Immunoglobulin, Equine
United States (US) Investigational New Drug (IND) Number:	Not applicable (N/A)
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	B5411003
Phase:	3

Short Title: A study to assess efficacy and safety of PF-06462700 in Japanese participants with aplastic anemia

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	24 December 2019	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A study to assess efficacy and safety of PF-06462700 in Japanese participants with aplastic anemia

Rationale

PF-06462700 was evaluated as having high medical needs at the 36th meeting of the Study Group on Unapproved and Off-label Drugs of High Medical Need (held on 17 October 2018), and its development was requested by the Research and Development Division, Health Policy Bureau, Ministry of Health, Labor and Welfare (MHLW) on 12 November 2018 for the request contents described below.

The purpose of the study is to assess the efficacy and safety of PF-06462700 administered intravenously at 40 mg/kg/day for 4 days in Japanese participants with moderate and above aplastic anemia for making an approval application in Japan.

The outline of this study was agreed upon with the Pharmaceutical and Medical Device Agency (PMDA) on 27 September 2019.

Objectives, Estimands, and Endpoints

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To investigate the efficacy of PF-06462700 administered intravenously at 40 mg/kg/day for 4 days in Japanese participants with moderate and above aplastic anemia	• Hematologic response at Week 12	Population: Japanese participants with moderate and above aplastic anemia who are at least 2 years of age Variable: Hematologic response at Week 12 Intercurrent events: The efficacy will be evaluated individually for each patient. Therefore, any missing data will not be imputed. All observations after prohibited concomitant medication will be included. Improvement in counts that are dependent upon exogenously administered growth factors or transfusion will not be considered as fulfilling hematologic response criteria in the evaluation. Population-level summary: Due to the limited sample size, summary statistics will not be shown.
Secondary:	**Secondary:**	**Secondary:**
• To investigate the efficacy of PF-06462700 administered intravenously at 40 mg/kg/day for 4 days in Japanese participants with moderate and above aplastic anemia	• Hematologic response at Week 24 • Hematological test values at Day 4 and at Weeks 1, 2, 4, 6, 8, 10, 12 and 24 (Absolute neutrophil count, Platelet count, Reticulocyte count). In case of early termination (ET), at ET and follow-up ET. • Survival status • Transfusion independence at Weeks 12 and 24	Population: Japanese participants with moderate and above aplastic anemia who are at least 2 years of age Variable: Each secondary endpoint Intercurrent events: The efficacy will be evaluated individually for each patient. Therefore, any missing data will not be imputed. All observations after prohibited concomitant medication will be included. Population-level summary: Due to the limited sample size, summary statistics will not be shown.
Safety objective:	**Safety endpoints:**	**Estimands:**
• To investigate the safety of PF-	• Treatment-emergent adverse events	N/A

06462700 administered intravenously at 40 mg/kg/day for 4 days in Japanese participants with moderate and above aplastic anemia	(TEAEs) • Serious AEs (SAEs) and AEs leading to discontinuation • Vital signs • Clinical laboratory values	

Overall Design

Study B5411003 will assess the efficacy and safety of PF-06462700 in participants with moderate and above aplastic anemia. This is a multicenter, open-label, single-arm study. The study will have a maximum duration of approximately 28 weeks. This includes an up to 4-week screening period, a 4-day treatment period and a 24-week follow-up period. This study will enroll the minimum of 3 participants. The study will be initially conducted at 3 sites.

Number of Participants

A minimum of 3 participants will be assigned to the investigational product in the study.

Intervention and Duration

The study will have a maximum duration of approximately 28 weeks. This includes an up to 4-week screening period, a 4-day treatment period and a 24-week follow-up period.

Participants will undergo PF-06462700 skin test. Those with a positive skin test will not be administered PF-06462700.

PF-06462700 will be administered at a dose of 40 mg/kg/day for 4 days. PF-06462700 will be infused intravenously over no less than 4 hours. Infusion times may be extended up to 24 hours (including dilution/preparation time) to improve tolerance if necessary.

Data Monitoring Committee: No

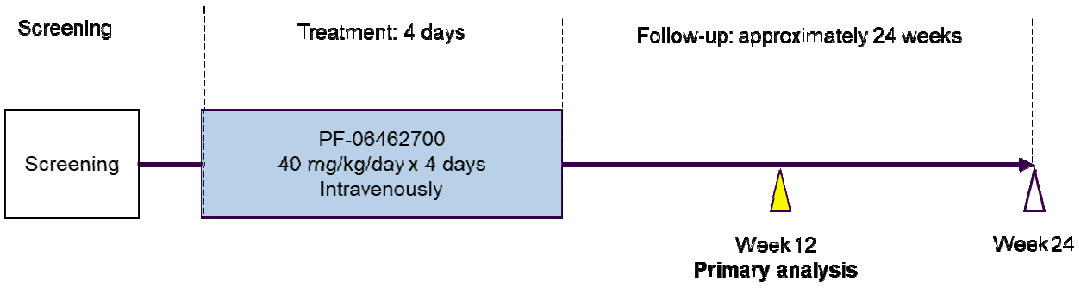
Statistical Methods

The target sample size was determined based on the study feasibility perspective. No statistical testing and inference will be conducted.

All efficacy analyses will be performed on the full analysis set which includes all participants assigned to the investigational product and who take at least 1 dose of investigational product. The hematological response at Week 12, which is the primary endpoint, will be listed individually for each participant. The sample size is limited; therefore, no summary statistics will be shown. All of the secondary endpoints (described in Section 8.1) will also be listed individually for each patient.

All safety analyses will be performed on the safety population which include all participants assigned to the investigational product and who take at least 1 dose of investigational product. The safety result will be listed individually for each patient.

1.2. Schema



1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

	Screening period	Treatment period				Follow-up period								Follow-up of ET case
Visit Identifier[a]	**Screening**	**Day 1[a] (baseline)**	**Day 2**	**Day 3**	**Day 4**	**Day 8 Week 1**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 43 Week 6**	**Day 57 Week 8**	**Day 71 Week 10**	**Day 85 Week 12**	**Day 169 Week 24 or ET**	**Follow up 28 days after ET**
Visit Window	**Day -28 to -1**	**N/A**	**N/A**	**N/A**	**N/A**	**±1 day**	**±1 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**+7 days**
Informed consent/assent	X													
Medical history	X													
Physical examination	X	X			X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X[e]										X	X	
Laboratory														
Hematology	X	X[b]			X	X	X	X	X	X	X	X	X	X
Blood chemistry	X	X[b]			X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X[b]										X	X	X
HBV, HCV, HIV, HTLV-1	X													
EBV, CMV	X						X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Pregnancy test[c]	X	X[b]						X		X		X	X	X
Contraception check[c]	X	X[b]						X		X		X	X	X
12-Lead ECG	X											X	X	
Chest X-ray	X													
Registration		X												
Study treatment														
Skin test		X												

	Screening period	Treatment period				Follow-up period								Follow-up of ET case
Visit Identifier[a]	**Screening**	**Day 1[a] (baseline)**	**Day 2**	**Day 3**	**Day 4**	**Day 8 Week 1**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 43 Week 6**	**Day 57 Week 8**	**Day 71 Week 10**	**Day 85 Week 12**	**Day 169 Week 24 or ET**	**Follow up 28 days after ET**
Visit Window	**Day -28 to -1**	**N/A**	**N/A**	**N/A**	**N/A**	**±1 day**	**±1 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**+7 days**
Investigational treatment administration		X	X	X	X									
Assessments														
Efficacy					X	X	X	X	X	X	X	X	X	
Safety		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant treatment(s)	X	X	→	→	→	→	→	→	→	→	→	→	X	X
Serious and nonserious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	X	X

Abbreviations: Ab = antibody; CMV = cytomegalovirus; EBV = Epstein-Barr virus; ECG = electrocardiogram; ET = Early Termination; HBV = hepatitis B virus, HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV-1 = human T-cell leukemia virus type 1;→ = ongoing/continuous event, WOCBP = woman of childbearing potential.

a. Day relative to start of study treatment (Day 1).
b. Hematology, Blood chemistry, Urinalysis, Coagulation, and Pregnancy test on Day 1 can be omitted, if the interval between Screening visit and Day 1 visit is within 7 days.
c. For WOCBP only. Monthly urine pregnancy tests and contraception check will be performed by the participant between scheduled study visits starting after the Week 12 visit through the Week 24 or ET visit. Site personnel will contact participants (or their legally authorized representative, if appropriate) between study visits to obtain monthly pregnancy test result and ensure this contact and the result of the pregnancy test are recorded in participant source documentation and CRF.
d. EBV DNA or CMV DNA will be performed at Weeks 2, 4, 6, 8,10, 12 and 24, or ET, or Follow-up of ET for any participant who is EBV Ab or CMV Ab positive at screening.
e. If there is body weight data within 3 days before baseline, it can be adopted as a baseline data.

2. INTRODUCTION

PF-06462700 (Brand name in the US: ATGAM) is classified as an immunosuppressant/ immunosuppressive agent. It is the purified, concentrated, and sterile gamma globulin, primarily monomeric immunoglobulin G (IgG), from hyperimmune serum of horses that are immunized with human thymus lymphocytes. PF-06462700 has a strong T-lymphocyte suppressive effect based on non-clinical studies results.

PF-06462700 has been authorized in global markets for more than 30 years where it is registered for 2 indications: 1) treatment of moderate to severe aplastic anemia, and 2) supportive treatment of renal allograft transplantation. In the US, the indication of treatment of moderate to severe aplastic anemia was approved in May 1985. In Europe Union (EU), a marketing authorisation application (MAA) was submitted by the decentralized procedure in 2014 and review is on-going. There are current national authorizations for both indications in the EU Member States Latvia and Slovenia

In Japan, the development was started in 1992 by limiting the targets to aplastic anemia, and the product was designated as an orphan drug in November 1993. Since the number of patients is small, it was difficult to conduct usual phase 2 and phase 3 clinical studies, and therefore, a general clinical study was conducted with 2 dose groups, and then the efficacy and safety in Japanese patients with aplastic anemia were confirmed. After that, for the indication of moderate/severe aplastic anemia with dosage and administration of 10-20 mg/kg per day for 8 days, a drug importing approval application was made by Pharmacia & Upjohn Company Inc. (current: Pfizer Japan Inc.) in [redacted]

PF-06462700 was evaluated as having high medical needs at the 36th meeting of the Study Group on Unapproved and Off-label Drugs of High Medical Need (held on 17 October 2018), and its development was requested by the Research and Development Division, Health Policy Bureau, Ministry of Health, Labor and Welfare on 12 November 2018 for the request contents described below.

Indication	Moderate and above aplastic anemia
Posology	The usual dosage for slow intravenous infusion is 40 mg of anti-human thymocyte immunoglobulin, equine, per 1 kg of body weight once daily, for 4 days.

2.1. Study Rationale

The purpose of the study is to assess the efficacy and safety of PF-06462700 administered intravenously at 40 mg/kg/day for 4 days in Japanese participants with moderate and above aplastic anemia for making a new drug application in Japan.

The outline of the study was agreed upon with the Pharmaceutical and Medical Device Agency (PMDA) on 27 September 2019.

2.2. Background

2.2.1. Mechanism of Action/Indication

The mechanism of PF-06462700-induced immunosuppression has not been definitively determined. However, published data indicate that rapid, reversible depletion of circulating lymphocytes is a consistent finding of PF-06462700 treatment, with greatest effect on T-lymphocytes.[1,2] Lymphocyte depletion may be caused by complement dependent lysis[3,4,5] and/or activation induced apoptosis.[6,7] In addition, immunosuppression may be mediated by the binding of antibodies to lymphocytes, which results in partial activation and induction of T-lymphocyte anergy.[8]

While the mechanism of PF-06462700 in treating aplastic anemia is attributed in large part to its immunosuppressive activity against effector cytotoxic T cells, PF-06462700 has also been shown to directly stimulate growth of hematopoietic stem cells in vitro,[3,6,9] and release hematopoietic growth factors such as interleukin-3 and granulocyte/macrophage colony stimulating factor.[10] Greater sensitivity of peripheral blood mononuclear cells (PBMC) from aplastic anemia patients to these stimulatory actions of PF-06462700 also may account for its efficacy. H^3-thymidine incorporation in vitro in PBMC from both normal volunteers and aplastic anemia patients was increased following incubation with 2.5 or 5 µg/mL of PF-06462700 for 72 hours, indicative of cell proliferation.[8] Cells from patients were more responsive than cells from normal volunteers.[11]

2.2.2. Background of Aplastic Anemia

Aplastic anemia (AA) is a syndrome characterized by a decrease in all blood cells in peripheral blood (pancytopenia) and a decrease in bone marrow cell density (hypoplasia). In fact, there are many diseases that show these laboratory findings, and therefore it is possible to diagnose AA only by excluding other diseases with more definite concepts. It can be said that the essential nature of the disease is a "state of having a characteristic decrease in hematopoietic stem cells despite the absence of effects of myelotoxic drugs."[12]

2.2.2.1. Diagnostic criteria

Table 1 shows the revised diagnostic criteria proposed by the Study Group on Idiopathic Hematopoietic Disorders, Research Program on Rare and Intractable Diseases, Health, Labor and Welfare Sciences Research Grants, which is the diagnostic criteria in Japan.

Internationally, AA is diagnosed only when 2 or more of the 3 criteria [hemoglobin < 10 g/dL, neutrophils< 1,500/µL, and platelets < 100,000/µL] are met and the bone marrow is hypoplastic.[13]

Table 1. Diagnostic criteria for aplastic anemia (Revised in 2016) [12]

1. Clinical findings include anemia, bleeding tendency, and sometimes pyrexia.
2. At least 2 of the following 3 criteria are met:
   [1] Hemoglobin level < 10 g/dL, [2] Neutrophils < 1,500/μL, [3] Platelets < 100,000/μL
3. No other diseases that can cause pancytopenia. Other diseases commonly causing pancytopenia include leukemia, myelodysplastic syndrome, myelofibrosis, paroxysmal nocturnal hemoglobinuria (PNH), megaloblastic anemia, cancer bone marrow metastasis, malignant lymphoma, multiple myeloma, hypersplenism (cirrhosis, portal hypertension, etc.), systemic lupus erythematosus, hemophagocytic syndrome, and infection.
4. The following test findings increase the certainty of diagnosis:
   1) No increase in reticulocytes or immature platelets.
   2) Bone marrow aspiration findings (including clot specimens) show decreased nucleated cells in severe cases.
      In non-severe cases, there may be no decrease in nucleated cells depending on the puncture site, but megakaryocytes have decreased.
      When cells remain, erythroblasts often show dysplasia, but granulocytic dysplasia is not prominent.
   3) Bone marrow biopsy findings show decreased hematopoietic cell percentage.
   4) Increased serum iron levels and decreased unsaturated iron binding capacity.
   5) MRI of the thoracolumbar spine shows decreased hematopoietic cells and increased adipose tissue.
   6) Blood cells in paroxysmal nocturnal hemoglobinuria plasma are detected.
5. When making a diagnosis, aplastic anemia is suspected according to 1. and 2., other diseases are excluded according to 3., and the diagnosis is more definite according to 4. Diagnosis of aplastic anemia is basically based on exclusion of other diseases. However, in non-severe cases, it is difficult to differentiate from myelodysplastic syndrome with no increase in blast cells/ringed sideroblasts or chromosomal abnormality because morphological abnormality is often observed in bone marrow cells. Therefore, the treatment policy should be determined according to the pathological condition. Laboratory findings that may be useful in determining whether the patient has bone marrow failure due to immune pathology (immunosuppressive therapy is easy to become effective) include increases in PNH-type cells and cells with loss of HLA Class I alleles, and high plasma thrombopoietin levels (320 ng/mL).

2.2.2.2. Severity criteria

Since the prognosis and treatment policy of AA vary greatly depending on the severity, the severity should be determined according to the degree of cytopenia. In Japan, the severity is divided into 5 grades: very severe, severe, slightly severe, moderate, and mild (Table 2). Cases with a neutrophil count of less than 200/μL are called the very severe form because they have a high risk of severe infection or bleeding. The very severe form includes cases with an increase in neutrophils to some extent in response to granulocyte colony-stimulating factor (G-CSF) and the “fulminant type” in which there is no response to G-CSF and virtually no neutrophils.[14]

Table 2. Severity criteria for aplastic anemia (Modified in 2017) [12]

Stage 1	Mild	No blood transfusion is required other than the following:
Stage 2	Moderate	
	a	Two or more of the following criteria are met, and no red blood cell transfusion is required.
	b	Red blood cell transfusion is required, but the frequency is less than 2 units per month. Reticulocytes < 60,000/μL Neutrophils < 1,000/μL Platelets < 50,000/μL
Stage 3	Slightly severe	Two or more of the following criteria are met, and transfusion of 2 units or more of red blood cells is required every month. Reticulocytes < 60,000/μL Neutrophils < 1,000/μL Platelets < 50,000/μL
Stage 4	Severe	Two or more of the following criteria are met: Reticulocytes < 40,000/μL Neutrophils < 500/μL Platelets < 20,000/μL
Stage 5	Very severe	In addition to neutrophils < 200/μL, at least 2 of the following criteria are met: Reticulocytes < 20,000/μL Platelets < 20,000/μL

2.2.2.3. Epidemiology

The number of medical service recipients in Japan (prevalence) is approximately 11,000 in 2014 with a prevalence rate of 8.7 (/100,000 population). The number of incidence cases from 2004 to 2012 was approximately 9,500 (about 1,000 people per year), the incidence rate was estimated to be 8.2 (/1 million person-years)[15]. The sex ratio (female/male) of the incidence rate was 1.16, with a peak in both men and women in their 10s to 20s and 70s to 80s, and with a greater peak in the elderly. The incidence rates in western countries are reported to be 1.5 to 2.5 (/1 million person-years).[16,17] The incidence rate in Japan is higher than these rates.[12]

2.2.2.4. Treatments

Treatments of aplastic anemia in Japan include supportive therapy and treatment aimed at hematopoietic recovery.[12]

2.2.2.4.1. Supportive therapies

Supportive therapies include blood transfusion (red blood cell transfusion, platelet transfusion, granulocyte transfusion) when anemia or thrombocytopenia is severe or associated with moderate or severe clinical symptoms, G-CSF administered when the neutrophil count is less than 500/μL and infection is concurrently present, and iron chelation therapy.[12]

2.2.2.4.2. Treatments aimed at hematopoietic recovery

Treatments aimed at hematopoietic recovery include (1) immunosuppressive therapy [Cyclosporine, anti-thymocyte globulin (ATG)], (2) anabolic steroid therapy (Methenolone

acetate, Danazol), and (3) hematopoietic stem cell transplantation. Treatment guidelines by severity have been shown.[12]

2.2.3. Clinical Overview

Brief descriptions of completed clinical studies are provided below. In this section, ATGAM and/or horse-ATG mean PF-06462700.

2.2.3.1. Overseas clinical studies

2.2.3.1.1. Study 3-197[18], ※1

OBJECTIVE: To evaluate the efficacy of ATGAM for the treatment of aplastic anemia.

STUDY DESIGN: A randomized controlled study in which subjects are randomized to receive ATGAM or control treatment (supportive therapy alone). Subjects assigned to the control group were allowed to receive ATGAM at 3 months after initiation of study treatment.

TARGET PATIENTS: Patients with moderate to severe aplastic anemia who were not candidates for bone marrow transplantation.

DOSING REGIMEN FOR ATGAM: 20 mg/kg/day for 8 days.

SAMPLE SIZE: ATGAM group: N=21; Control group: N=20.

PRIMARY ENDPOINT: Response at 3 months after initiation of study treatment.

KEY RESULTS: The hematologic response rate at 3 months was statistically significantly higher in ATGAM group than in control group (47% vs 6%; $p<0.01$). In the patients treated with ATGAM including 11 patients in the control group who were treated with ATGAM after 3 months, the survival rate at 24 months was 62%. Fever, chills, and erythematous or urticarial rash were seen in all ATGAM treated patients. Platelet counts decreased during ATGAM infusion and daily platelet transfusions were necessary. Serum sickness occurred in all patients within 6 to 18 days of ATGAM initiation and was well-controlled with standard therapy. Three patients experienced transient hypotension.

2.2.3.1.2. Study 3-198

OBJECTIVE: To compare the response of ATGAM plus androgen in combination with HLA-mismatched transplantation or without HLA-mismatched transplantation.

STUDY DESIGN: An open-label, non-randomized controlled study in which subjects are assigned to receive either ATGAM plus androgen in combination with mismatched

※1 The results of Study 3-197 shown in the technical report by the sponsor and those in the published report (Champlin, 1983) are inconsistent because they have evaluated treatment response according to different definitions.

transplantation of bone marrow or only ATGAM plus androgen, according to the availability of an appropriate donor.

TARGET PATIENTS: Patients with severe aplastic anemia who were not candidates for bone marrow transplantation.

DOSING REGIMEN FOR ATGAM: 16 mg/kg/day for 10 days.

SAMPLE SIZE: with mismatched transplant: N=24; without mismatched transplant: N=18.

PRIMARY ENDPOINT: Response at 3 months a with mismatched transplant after initiation of study treatment.

KEY RESULTS: The hematologic response rates at 3 months in patients receiving mismatched transplant in addition to ATGAM plus androgen and in those treated with only ATGAM plus androgen were similar (43% and 44%, respectively). The survival rates at 12 months in those with mismatched bone marrow transplant and in those without it were 83% and 59%, respectively. The most commonly reported adverse events were rash, fever, arthralgias, chills, headache, myalgia and pruritus.

2.2.3.1.3. Study 5000[19]

OBJECTIVE: To compare the response of ATGAM with or without androgen.

STUDY DESIGN: A randomized, double-blind, controlled study in which subjects are randomized to receive either ATGAM plus androgen or ATGAM plus placebo.

TARGET PATIENTS: Patients with moderate to severe aplastic anemia who were not candidates for bone marrow transplantation.

DOSING REGIMEN FOR ATGAM: 20 mg/kg/day for 8 days.

SAMPLE SIZE: ATGAM plus androgen: N=26; ATGAM plus placebo: N=27.

PRIMARY ENDPOINT: Response at 6 months after initiation of study treatment.

KEY RESULTS: The hematologic response rates at 6 months in the ATGAM plus androgen group and ATGAM plus placebo group were similar (42% and 44%, respectively). The survival rates at 24 months in the ATGAM plus androgen group and ATGAM plus placebo group were 55% and 50%, respectively (when analyzed in only patients with severe disease). Adverse reactions in both groups were comparable and included rash, chills, gastrointestinal disturbances, and joint pain during ATGAM infusion, as well as symptoms of serum sickness in

all patients. Five patients had asymptomatic sinus bradycardia; six patients required antihypertensive therapy. Alanine transaminase or alkaline phosphatase levels increased to >2 times the upper limits of normal in 7 patients receiving ATGAM plus androgen, and in 9 patients receiving ATGAM plus placebo.

2.2.3.1.4. National Institutes of Health (NIH)-initiated clinical study[1]

OBJECTIVE: To compare the efficacy and safety of ATGAM and rabbit-ATG in aplastic anemia.

STUDY DESIGN: A randomized controlled study in which subjects are randomized to receive ATGAM or rabbit-ATG.

TARGET PATIENTS: Patients with severe aplastic anemia.

DOSING REGIMEN FOR ATGAM: 40 mg/kg/day for 4 days, DOSING REGIMEN FOR rabbit-ATG: 3.5 mg/kg/day for 5 days.

SAMPLE SIZE: N=60/group.

KEY ENDPOINT: Hematologic response at 6 months after initiation of treatment.[*1]

KEY RESULTS: The response rate at 6 months in the ATGAM group (68%) was significantly higher than that in the rabbit-ATG group (37%). The 3-year survival in the ATGAM group (96%) was significantly higher than that in the rabbit-ATG group (76%). As expected from the patient characteristics of the population in this study, the most frequently reported AEs were infections in both treatment groups. Mortality or disease exacerbation leading to study discontinuation was reported in 2 subjects treated with ATGAM and 9 subjects with rabbit-ATG. Serious adverse events (SAEs) for which at least 2 subjects were reported in the ATGAM group included neutropenic fever (negative cultures) (23 events), neutropenic fever (positive cultures) (17), upper respiratory infection (5), serum sickness, menorrhagia, Clostridium difficile infection, and tonsillitis/pharyngitis (2 each).

2.2.3.2. Japanese clinical study

2.2.3.2.1. An Upjohn (currently, Pfizer)-initiated clinical study[20]

OBJECTIVE: To evaluate the efficacy and safety of ATGAM in the treatment of aplastic anemia.

STUDY DESIGN: An open-label, two-arm, randomized controlled study in which subjects are randomized to receive either ATGAM 10 mg/kg/day or 20 mg/kg/day.

TARGET PATIENTS: Patients with moderate to severe aplastic anemia who were not candidates for bone marrow transplantation.

DOSING REGIMEN FOR ATGAM: 10 or 20 mg/kg/day for 8 days.

SAMPLE SIZE: ATGAM 10 mg/kg/day: N=25; 20 mg/kg/day: N=25.

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*[1] Response was declared if the subject no longer met the criteria of severe aplastic anemia (hypoplasia of bone marrow (<30%) and fulfilment of at least 2 of the three conditions, neutrophil count $<0.5\times10^9$/L, reticulocyte count $<60\times10^9$/L, and platelet count $<20\times10^9$/L).

KEY ENDPOINT: Hematologic response at 6 months after initiation of treatment.[*2]

KEY RESULTS: Among 56 patients enrolled, 35 were included in the Efficacy Analysis Set, and 50 in the Safety Analysis Set. Overall, the percentage of patients who achieved moderate to marked hematologic improvement at 6 months after initiation of treatment was 28.6%, and that for mild to marked improvement was 42.9% (Moderate to marked improvement rate in the 10 mg/kg/day group: 21.1%; that in the 20 mg/kg/day group: 37.5%). Adverse reactions commonly reported for ATG and anti-lymphocyte globulin (ALG) products, including pyrexia, rash, headache/chills, and arthralgia were frequently reported in this study with one patient experiencing anaphylaxis; all of these events were manageable with an intervention.

2.2.3.2.2. A Prospective Study for Aplastic Anemia by the Investigative Research Team for Idiopathic Disorders of Erythropoiesis (a specific disease), the Ministry of Health and Welfare[21]

OBJECTIVE: To evaluate the efficacy of immunosuppressive therapy in aplastic anemia.

STUDY DESIGN: An open-label study.

TARGET PATIENTS: Patients with aplastic anemia (only those with severe disease were treated with ATGAM). Patients were initially treated with high doses of methylprednisolone, and then steroid-resistant patients were treated with ATGAM or with ALG.

DOSING REGIMEN FOR ATGAM: 40 mg/kg/day for 4 days.

SAMPLE SIZE: A total of 184 patients, including 13 treated with ATGAM.

KEY ENDPOINT: Hematologic response at 1 month after initiation of treatment.[*3]

KEY RESULTS: Among 13 ATGAM-treated patients, 1 patient achieved a good response, 3 did a minimal response, and 9 did no response at one month. Although only 1 patient

[redacted]

*2 1. Marked Improvement (case in which the severity as assessed per the "Severity Criteria for Aplastic Anemia of the Investigative Research Team for Idiopathic Disorders of Erythropoiesis (a specific disease), the Ministry of Health and Welfare" has changed from severe to mild or from severe to moderate or from moderate to mild, and hemoglobin level has increased ≥2 g/dL without transfusion), 2. Moderate Improvement (case in which the severity has unchanged from severe or from moderate, and hemoglobin level has increased ≥2 g/dL without transfusion), 3. Mild Improvement (case in which the severity has changed from severe to moderate or from moderate to mild, and hemoglobin level has not increased ≥2 g/dL without transfusion), 4. No Response (other cases)

*3 1. Good Response (case in which the severity as assessed per the "Severity Criteria for Aplastic Anemia of the Investigative Research Team for Idiopathic Disorders of Erythropoiesis (a specific disease), the Ministry of Health and Welfare" has changed from severe to mild or from severe to moderate or from moderate to mild, and hemoglobin level has increased ≥2 g/dL without transfusion), 2. Partial Response (case in which the severity has unchanged from severe or from moderate, and hemoglobin level has increased ≥2 g/dL without transfusion), 3. Minimal Response (case in which the severity has changed from severe to moderate or from moderate to mild, and hemoglobin level has not increased ≥2 g/dL without transfusion), 4. No Response (other cases)

responded to ATGAM at 1 month, 1 of 3 patients with minimal response and 6 of 9 patients with no response achieved good response at 8 to 32 weeks. Thus, ATGAM was effective in Japanese patients with aplastic anemia as well.

2.3. Benefit/Risk Assessment

In this section, eATG means PF-06462700.

eATG has strong suppressive effects on T-lymphocyte based on results from non-clinical studies. The mechanism of eATG-induced immunosuppression has not been definitively determined. Published data indicate that rapid, reversible depletion of circulating lymphocytes is a consistent finding following administration of eATG, with greatest effect on T-lymphocytes. Lymphocyte depletion may be caused by complement dependent lysis and/or activation-induced apoptosis. In addition, immunosuppression may be mediated by the binding of antibodies to lymphocytes, which results in partial activation and induction of T-lymphocyte anergy.

Immune-mediated reactions

In rare instances, serious immune-mediated reactions have been reported with the use of eATG. Clinical signs associated with anaphylaxis, other infusion associated reactions, and serum sickness have been reported. Based on the mechanism of action of eATG, there is a potential risk of cytokine release syndrome.

A systemic reaction such as a generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis precludes any additional administration of eATG.

Infection

Monitor patients carefully for concurrent infection. Some studies have suggested an increase in the incidence of cytomegalovirus infection in patients receiving eATG[22]. Some physicians have found that it may be possible to reduce this risk by decreasing the dosage of other immunosuppressive agents which might be administered concomitantly with eATG.

In common with products derived from, or purified with human blood components, the possibility of transmission of some infectious diseases should be borne in mind.

Renal or hepatic impairment

In patients with aplastic anemia and other hematologic abnormalities who have received eATG, abnormal tests of liver function and renal function have been observed.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PF-06462700 may be found in the investigator's brochure, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To investigate the efficacy of PF-06462700 administered intravenously at 40 mg/kg/day for 4 days in Japanese participants with moderate and above aplastic anemia	• Hematologic response at Week 12	Population: Japanese participants with moderate and above aplastic anemia who are at least 2 years of age Variable: Hematologic response at Week 12 Intercurrent events: The efficacy will be evaluated individually for each patient. Therefore, any missing data will not be imputed. All observations after prohibited concomitant medication will be included. Improvement in counts that are dependent upon exogenously administered growth factors or transfusion will not be considered as fulfilling hematologic response criteria in the evaluation. Population-level summary: Due to the limited sample size, summary statistics will not be shown.
Secondary:	**Secondary:**	**Secondary:**
• To investigate the efficacy of PF-06462700 administered intravenously at 40 mg/kg/day for 4 days in Japanese participants with moderate and above aplastic anemia	• Hematologic response at Week 24 • Hematological test values at Day 4 and at Weeks 1, 2, 4, 6, 8, 10, 12 and 24 (Absolute neutrophil count, Platelet count, Reticulocyte count). In case of ET, at ET and follow-up ET. • Survival status • Transfusion independence at Weeks 12 and 24	Population: Japanese participants with moderate and above aplastic anemia who are at least 2 years of age Variable: Each secondary endpoint Intercurrent events: The efficacy will be evaluated individually for each patient. Therefore, any missing data will not be imputed. All observations after prohibited concomitant medication will be included. Population-level summary: Due to the limited sample size, summary statistics will not be shown.
Safety objective:	**Safety endpoints:**	**Estimands:**

• To investigate the safety of PF-06462700 administered intravenously at 40 mg/kg/day for 4 days in Japanese participants with moderate and above aplastic anemia	• Treatment-emergent adverse events (TEAEs) • Serious AEs (SAEs) and AEs leading to discontinuation • Vital signs • Clinical laboratory values	N/A

4. STUDY DESIGN

4.1. Overall Design

Study B5411003 will assess the efficacy and safety of PF-06462700 in participants with moderate and above aplastic anemia. This is a multicenter, open-label, single-arm study. The study will have a maximum duration of approximately 28 weeks. This includes an up to 4-week screening period, a 4-day treatment period and a 24-week follow-up period. This study will enroll the minimum of 3 participants. The study will be initially conducted at 3 sites.

To be eligible to enroll in this study, participants must have moderate and above aplastic anemia at screening visit. The full list of eligibility criteria for the study is included in Section 5.

Screening will occur within 28 days prior to the first dose of study drug to confirm that participants meet enrollment criteria for the study. Eligible participants will be administered to this investigational drug intravenously at 40 mg/kg/day for 4 days.

4.2. Scientific Rationale for Study Design

This study's objectives are to investigate the efficacy and safety of PF-06462700 administered intravenously at 40 mg/kg/day for 4 days in each of Japanese patients with aplastic anemia. The study design of this study was set according to the study design of the NIH-initiated clinical study[1]. Since this disease is a serious and rare disease, the target sample size was set to be 3 subjects from the viewpoint of feasibility, and the study was designed as a single-arm, open-label study in a group treated with PF-06462700. This study design was agreed upon with PMDA on CCI [redacted].

4.3. Justification for Dose

Based on the development request for this drug by the Research and Development Division, Health Policy Bureau, Ministry of Health, Labor and Welfare (MHLW), the dosage and administration intravenously of 40 mg/kg/day for 4 days should be selected for this study. This dosage and administration is the same as the NIH-initiated study demonstrated that PF-06462700 provided a significantly higher 6-month haematologic response and 3-year survival rate than comparable treatment with rabbit-ATG.

4.4. End of Study Definition

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

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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 of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 2 years and more, inclusive, at Visit 1 (Screening).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Have a clinical diagnosis of aplastic anemia by bone marrow aspiration/biopsy findings and/or magnetic resonance imaging (MRI) etc.

4. Must meet the following criteria of moderate and above aplastic anemia (Stage 2b and above, see Table 2):

Informed Consent:

5. Capable of giving signed informed consent/assent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD)/assent document and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Eligible and willing to have a sibling allogeneic stem cell transplantation.

2. Evidence of a myelodysplastic syndrome (except for refractory cytopenia in children), as well as other primitive marrow disease.

3. History or clinical suspicion of congenital aplastic anemia (Fanconi anemia, Congenital keratosis, etc).

4. History of malignant tumors with active disease within 5 years from study participation.

5. Participants who are clearly infected with hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and human T-cell leukemia virus type 1 (HTLV-1).

6. Pregnant or breast-feeding participants.

7. Participants with severe hepatic, renal or cardiac failure, or any other life-threatening concurrent [aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or total bilirubin values >5 × upper limit of normal (ULN), and/or creatinine value >2 × ULN].

8. Participants with hypersensitivity such as shock after skin test of this study drug.

9. Participants with uncontrolled severe infection (pneumonia, sepsis, etc).

10. Participants who received live vaccine or live attenuated vaccine within 6 weeks prior to the first dose of study drug.

11. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

12. Prior immunosuppressive therapy with lymphocyte-depleting agents/therapies, including both non-B-cell selective and B-cell-depleting agents (e.g., alefacept, alemtuzumab, rituximab). However, participants previously treated with rATG may enroll.

13. Previous history of stem cell transplantation.

Prior/Concurrent Clinical Study Experience:

14. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product used in this study (whichever is longer).

Diagnostic Assessments:

15. Baseline 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (e.g., baseline corrected QT [QTc] interval >450 msec, complete left bundle branch block [LBBB], signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

Other Exclusions:

16. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to the investigational product in the study. 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 details, eligibility criteria, and any serious adverse event (SAE).

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

6. STUDY INTERVENTION

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.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention Administered

Intervention Name	PF-06462700
Type	Biologic
Dose Formulation	Concentrate for solution for infusion
Unit Dose Strength	5 mL ampoules containing 50 mg PF-06462700 per mL
Dosage Level	40 mg/kg/day for 4 days
Route of Administration	Intravenously
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in open label carton which includes 5 ampoules. Each carton will be labeled as required per country requirement.

6.1.1. Administration

Participants will undergo PF-06462700 skin test. Those with a positive skin test will not be administered PF-06462700.

PF-06462700 will be administered at a dose of 40 mg/kg/day for 4 days. PF-06462700 will be infused intravenously over no less than 4 hours. Infusion times may be extended up to 24 hours (including dilution/preparation time) to improve tolerance if necessary.

6.1.2. Skin test

To identify those at greatest risk of systemic anaphylaxis, skin test for potential recipients is strongly recommended before commencing treatment. A conservative, conventional approach would first employ epicutaneous (prick) testing with undiluted eATG. If the subject

does not show a wheal 10 minutes after pricking, proceed to intradermal testing with 0.02 mL of a 1:1000 volume/volume (v/v) saline dilution of eATG with a separate saline control injection of similar volume. Read the result at 10 minutes: a wheal at the eATG site 3 or more mm larger in diameter than that at the saline control site (or a positive prick test) suggests clinical sensitivity and an increased possibility of a systemic allergic reaction should the drug be dosed intravenously.

The predictive value of this test has not been proven clinically. Allergic reactions such as anaphylaxis have occurred in patients whose skin test is negative. Also, skin test done as described above will not predict for later development of serum sickness. In the presence of a locally positive skin test to eATG, serious consideration to alternative forms of therapy should be given. The risk to benefit ratio must be carefully weighed. If therapy with eATG is deemed appropriate following a locally positive skin test, treatment should be administered in a setting where intensive life support facilities are immediately available and a physician familiar with the treatment of potentially life threatening allergic reactions is in attendance.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the investigational product manual (IP manual).

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. See the IP manual for storage conditions of the study intervention once diluted.

8. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (e.g., at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

Detailed instructions for PF-06462700 on how to prepare the investigational product for administration are provided in the current IP Manual. The investigational product will be dispensed at each visit from Day 1 to Day 4. A qualified staff member (e.g. physician, nurse, pharmacist, medical staff) will dispense the investigational product, in quantities appropriate for the study visit schedule.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

Registration will be performed centrally by the sponsor or designee for all participants. Following full assessment and determination that the participant meets all eligibility criteria, the investigator or designee will fax or email a complete the registration form to the sponsor or designee. The sponsor or designee will assign a participant identification number, which will be used on all case report form (CRF) pages and other trial-related documentation or correspondence referencing that participant and fax or email to the site.

No participant shall receive investigational product until the investigator or designee has received the above information from the sponsor or designee: confirmation of the participant's enrollment.

6.4. Study Intervention Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

6.5. Concomitant Therapy

Medications/treatments that are taken in the screening period (after informed consent is obtained and before the first dose of study intervention) as well as any medications/treatments taken for the treatment of aplastic anemia at any time prior to the screening visit will be documented as prior medications/treatments. Medications/treatments taken after the first dose of study intervention has been administered will be documented as concomitant medications/treatments. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) 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

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

6.5.1. Permitted Concomitant Medications

For the purposes of this protocol, dietary supplements are defined as vitamins, minerals, and purified food substances with pharmaceutical properties. Vitamins, minerals and purified food substances are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis).

A participant who is receiving a permitted concomitant medication for any reason must be on a locally-approved medication and dose for the treated indication, and this must be documented on the case report form (CRF).

Participants should report any changes to permitted medications during the study to the investigator as soon as they occur. Medication changes must be documented in the participant's record and CRF.

Unless a prohibited medication or treatment, participants may be administered any other medications necessary for the treatment of concomitant medical disorders as deemed necessary by the treating physician. Following Day 1, addition of concomitant medications or any change in the dosage should be limited to those considered medically essential.

Premedication is recommended for all participants, consistent with institutional guidelines, and may include an antihistamine, anti-inflammatory agent, or pain reliever.

It is available to administer the following drugs according to the patient's condition with reference [Reference Guide for Management of Aplastic Anemia, Revised in 2018] or institutional guidelines:

- Cyclosporine
- Corticosteroid (e.g. prednisolone)
- Diphenhydramine and acetaminophen
- Iron chelation therapy
- Antibacterial, antifungal and antiviral drugs
- Blood transfusion (erythrocyte, platelet transfusion)

6.5.2. Permitted Concomitant Medications only when necessary

The following medications are permitted to use only when necessary.

- G-CSF
- Elthrombopag, Lomiprostim
- Anabolic steroids

6.5.3. Prohibited Concomitant Medications

Participants will abstain from all prohibited medications as described below in this section. Medically necessary medications should not be discontinued without prior evaluation of acceptable alternatives, including consultation with prescribing health professional.

Participants should be instructed at each visit to contact the study site investigator promptly if there are any intended changes or additions to concomitant medications.

Prohibited Concomitant Medications/Treatments:

The following medications and treatments are prohibited for use during the study. Participants who are treated with any prohibited medication or treatment during the course of the study may be discontinued after discussion with the sponsor. NOTE: Examples provided do not represent an all-inclusive list of medications and treatments. If there is a question about whether a particular medication is prohibited, the medication should be discussed with the sponsor.

- Medications and treatments that could affect aplastic anemia:
  - ATG (horse or rabbit)

- Lymphocyte-depleting agents/therapies, including both non-B-cell selective and B-cell-depleting agents (e.g., alefacept, alemtuzumab, rituximab)
- Immunosuppressants except for cyclosporine A, corticosteroids (e.g., azathioprine, methotrexate, sulfasalazine, mycophenolate mofetil).

- Medications with potential safety concerns:
  - Investigational drugs
  - Live (attenuated) vaccines: prohibited within the 6 weeks prior to the first dose of study intervention, during the study, and for 6 months after the last dose of study intervention.

6.6. Dose Modification

Dose modification of the study intervention is not permitted in this study.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue investigational product. If investigational product is permanently discontinued, the participant will remain in the study to be evaluated for the assessments at the Early Termination (ET) and Follow-up visits (per Schedule of Activities (SoA)).

Note that discontinuation of investigational product does not represent withdrawal from the study.

See the Schedule of Activities (SoA) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

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, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the Schedule of Activities (SoA) for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are assigned to the investigational product and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

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.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1: Regulatory, Ethical, and Study Oversight Considerations.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the Schedule of Activities (SoA). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

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 (e.g., blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive

actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

The total blood sampling volume for individual participants in this study is approximately 60 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

8.1.1. Hematologic response

Hematologic response at Weeks 12 and 24

"Effective" when 2 or more of the following criteria:

- Absolute neutrophil count ≥ 500/μL
- Platelet count ≥ 20,000/μL
- Reticulocyte count ≥ 60,000/μL

Improvement in counts that are dependent upon exogenously administered growth factors or transfusion will not be considered as fulfilling response criteria.

For subjects of Stage 2b or 3 (see Table 2) at the baseline*, hematological response will be "effective" when the above-mentioned criteria are met, and Stage is improved at the same time. (*If the baseline assessment is omitted [Section 1.3], severity at the screening will be referred.)

8.1.2. Hematological test values

Hematological test values (absolute neutrophil count, platelet count and reticulocyte count) will be evaluated at Weeks 12 and 24. These values will also be evaluated at Day 4 and at Weeks 1, 2, 4, 6, 8 and 10. In case of early termination (ET), these values will be evaluated at ET and follow-up for ET.

8.1.3. Transfusion independence

Transfusion independence will be evaluated at Weeks 12 and 24.

8.1.4. Survival status

During the study period, the survival status of each participant will be recorded.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (SoA). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Physical Examinations

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Weight (kgs) will be measured and recorded in the source document at various time points according to Schedule of Activities (SoA).

8.2.2. Vital Signs

Vital signs will be measured with the participant in a semisupine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.

8.2.3. Electrocardiograms

12-Lead ECGs should be collected at times specified in the Schedule of Activities (SoA) section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

If a postdose QTc interval remains ≥30 msec from the baseline **and** is >450 msec; or an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 6: ECG Findings of Potential Clinical Concern.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2: Clinical Laboratory Tests for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, 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 or medical monitor.

If such 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 assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

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

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in woman of childbearing potential (WOCBP) at the times listed in the Schedule of Activities (SoA). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the investigational product/study treatment. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

AEs 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 to pursue and obtain adequate information both to determine the outcome and to assess whether it

meets the criteria for classification as an SAE or that caused the participant to discontinue the study intervention/study (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through the last study visit (Week 24 visit or Follow-up visit of ET case).

For participants who are screen failures, the active collection period ends when screen failure status is determined.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek 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.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

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: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading 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/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the last study visit (Week 24 visit or Follow-up visit of ET case).

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

None

8.3.7. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of PF-06462700 greater than 40 mg/kg/day within a 24-hour time period will be considered an overdose.

There is no specific antidote or specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic (PD) parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

Banked biospecimens for Genetics are not collected in this study.

8.7.3. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

In this study, no formal hypothetical testing will be conducted. The target sample size was determined based on study feasibility perspective. No statistical testing and inference will be conducted.

9.1.1. Estimands

The hematologic response at Week 12 in the target population:

- Population: Japanese participants with moderate and above aplastic anemia who are at least 2 years of age
- Variable: Hematologic response at Week 12

- Intercurrent events:

  The efficacy will be evaluated individually for each patient. Therefore, any missing data will not be imputed. All observations after prohibited concomitant medication will be included. Improvement in counts that are dependent upon exogenously administered growth factors or transfusion will not be considered as fulfilling hematologic response criteria in the evaluation.

- Population-level summary: Due to the limited sample size, summary statistics will not be shown.

9.2. Sample Size Determination

A sufficient number of participants will be screened to achieve 3 participants assigned to investigational product. It is acceptable to assign to investigational product more than 3 subjects.

The target sample size was determined based on the study feasibility perspective. No statistical testing and inference will be conducted.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.
Full analysis set (FAS)	All participants assigned to investigational product and who take at least 1 dose of investigational product. For participants who discontinue study and/or receive blood transfusion or prohibited concomitant medication, any missing data will not be imputed and all observations after blood transfusion or prohibited concomitant medication will be included in the analysis.
Safety	All participants assigned to investigational product and who take at least 1 dose of investigational product.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

All efficacy analyses will be performed on the FAS.

Endpoint	Statistical Analysis Methods
Primary	• Hematologic response at Week 12: The result will be listed individually for each patient. No summary statistics will be provided. Any missing data will not be imputed.
Secondary	• The result of the all secondary endpoints (described in Section 8.1) will be listed individually for each patient. No summary statistics will be provided. Any missing data will not be imputed. • As for hematological test values, the values on each timepoint will be plotted individually. Any missing data will not be imputed.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population. Due to the limited small sample size, the safety result of each patient will be listed individually.

Statistical Analysis Methods
The results of safety assessments and adverse events (described in section 8.2 and 8.3) through week 24 will be listed individually for each participant.

9.4.3. Other Analyses

N/A

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct clinical reviews of the data during the course of the study for the purpose of safety assessment, and/or supporting clinical development.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

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 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), and other relevant documents (e.g., advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, 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/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and

of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators 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 participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative defined as parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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 ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

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

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (clinical study report [CSR] synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator

is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (e.g., 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 the monitoring plan and contracts.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

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.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion 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. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified

between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. 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 site.

Data reported on the CRF or entered in the electronic CRF (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.

Definition of what constitutes source data can be found in the Study Monitoring Plan.

10.1.8. Study and Site Closure

The sponsor 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 upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor

30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will 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 of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 3. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Reticulocyte count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine Glucose (fasting) Calcium Sodium Potassium Chloride AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	Glucose (qual) Protein (qual) Blood (qual)	At screening only: • FSH[a] • Pregnancy test (β-hCG)[b] • Hepatitis B core antibody, surface antibody and surface antigen (HBV DNA if necessary) • Hepatitis C antibody (HCV RNA if antibody is positive) • HIV • HTLV-1 • EBV antibody (EBV DNA if antibody is positive and conduct at Week 2 and after) • CMV antibody (CMV DNA if antibody is positive and conduct at Week 2 and after)

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; FSH = follicle-stimulating hormone; HBV = hepatitis B virus, HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV-1 = human T-cell leukemia virus type 1; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; qual = qualitative; RBC = red blood cell; RNA = ribonucleic acid; WBC = white blood cell.

a. For confirmation of postmenopausal status only.
b. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or institutional review board/ethics committee (IRB/EC). Serum or urine β-hCG for female participants of childbearing potential.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: 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.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting 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. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "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 an AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> 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 (e.g., 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence 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 that 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 detained (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 preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent 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 (e.g., 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 in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All

Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. 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 Pfizer Safety.
- 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

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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 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 investigator's brochure (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 to the sponsor. 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 to the sponsor.**
- 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.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE 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 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 healthcare professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- 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 Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety 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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become 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 Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

The potential risk of exposure to PF-06462700 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the no-observed-adverse-effect level (NOAEL) for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[23]

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

- Documented hysterectomy;
- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

- A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen 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.

10.4.4. Contraception Methods

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation*.
2. Intrauterine device (IUD).
3. Intrauterine hormone-releasing system (IUS).
4. Bilateral tubal occlusion.
5. 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, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - oral;
    - intravaginal*;
    - transdermal*;
    - injectable*.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral*;
    - Injectable*.

8. 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 intervention. 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.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action*.

10. Male or female condom with or without spermicide.

11. Cervical cap*, diaphragm, or sponge with spermicide*.

12. A combination of male condom with either cervical cap*, diaphragm, or sponge with spermicide* (double-barrier methods).

    *: These methods are not approved or not certificated in Japan.

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (e.g., because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (e.g., because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (e.g., a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on

preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (Tbili) elevations (>2 × ULN) by several days or weeks. The increase in Tbili typically occurs while AST/ALT is/are still elevated above 3 × ULN (i.e., AST/ALT and Tbili values will be elevated within the same laboratory sample). In rare instances, by the time Tbili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to Tbili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and Tbili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a Tbili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** Tbili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of Tbili above the normal range: Tbili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and Tbili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and Tbili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (e.g., biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and Tbili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: i.e., rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de

pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.7. Appendix 7: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AA	aplastic anemia
Abs	absolute
AE	adverse event
ALG	anti-lymphocyte globulin
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
AV	Atrioventricular
β-hCG	beta-human chorionic gonadotropin
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EMA	European Medicines Agency
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Term
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HTLV-1	human T-cell leukemia virus type 1
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LBBB	left bundle branch block
LFT	liver function test
MAA	marketing authorisation application
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MHLW	Ministry of Health, Labor and Welfare
MRI	magnetic resonance imaging
msec	millisecond
N/A	not applicable
NIH	National Institutes of Health
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
PBMC	peripheral blood mononuclear cell
PCD	primary completion date
PD	pharmacodynamic(s)
PMDA	Pharmaceutical and Medical Device Agency
PNH	paroxysmal nocturnal hemoglobinuria
PT	prothrombin time
PVC	premature ventricular contraction/complex
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure

Abbreviation	Term
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
v/v	volume/volume
WBC	white blood cell
WOCBP	woman of childbearing potential

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