

Novartis Institutes for BioMedical Research

CFZ533

Clinical Trial Protocol CCFZ533X2205

**An open label study to evaluate the safety and efficacy of
12 week treatment with CFZ533 in patients with
Graves' disease**

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

Notification of serious adverse events

Refer to [Section 9.2](#) of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and notify the Clinical Trial Leader.).

Contact information is listed in the Site Operations Manual.

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
ATD	antithyroid drug
BMI	Body Mass Index
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CK	creatinine kinase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CTC	Common Toxicity Criteria
CV	coefficient of variation
EC	Ethics Committee
ECG	electrocardiogram
EDC	Electronic Data Capture
ELISA	enzyme-linked immunosorbent assay
FT3	free T3 (triiodothyronine)
FT4	free T4 (thyroxine)
FDA	Food and Drug Administration
GC	germinal center
GCP	Good Clinical Practice
GD	Graves' disease
γ-GT	gamma-glutamyl transferase
h	hour
HIV	human immunodeficiency virus
HUVEC	human umbilical vein endothelial cells
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

i.v.	intravenous
IRB	Institutional Review Board
KLH	keyhole limpet hemocyanin
LFT	liver function test
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
ml	milliliter(s)
NCDS	Novartis Clinical Data Standards
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPD	purified protein derivative
RA	rheumatoid arthritis
RBC	red blood cell(s)
REB	Research Ethics Board
SAE	serious adverse event
s.c.	subcutaneous
SD	standard deviation
SOM	site operations manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TDAR	T cell-dependent antibody responses
TRAb	thyrotropin receptor auto-antibodies
TSH	thyroid stimulating hormone
TSI	thyroid stimulating immunoglobulin
ULN	upper limit of normal
ULOQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization

Pharmacokinetic definitions and symbols

AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Cmax,ss	The observed maximum plasma (or serum or blood) concentration following drug administration at steady state [mass / volume]
Cmin,ss	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
Tmax	The time to reach the maximum concentration after drug administration [time]

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Protocol synopsis

Protocol number	CFZ533X2205
Title	An open label study to evaluate the safety and efficacy of 12 week treatment with CFZ533 in patients with Graves' disease
Brief title	Safety and efficacy study of CFZ533 in Graves' disease patients
Sponsor and Clinical Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	To explore the potential effects of CFZ533, an anti-CD40 antibody, on thyroid function in patients with Graves' disease to determine if CFZ533 has an adequate clinical profile to warrant further clinical development in the disease
Primary Objective	To assess the effects of CFZ533 on thyroid function (TSH, free T4 and total T3) in Graves' disease patients after 12 weeks of treatment
Secondary Objective	To assess the safety and tolerability of CFZ533 for up to 36 weeks
Study design	<p>This is a non-confirmatory, open-label, one treatment arm study in patients with Graves' disease.</p> <p>A total of approximately 15 patients will be enrolled and treated with CFZ533 to ensure approximately 12 completers. For each patient, the study will consist of a screening epoch of up to 28 days, a baseline evaluation, a 12-week treatment epoch, 24-week follow up epoch after the last dosing of CFZ533 on Study Day 85, and a study completion evaluation on Study Day 253. The baseline visit can be skipped and the baseline assessments would be completed prior to the study treatment on Day 1 if Day 1 is scheduled within 7 days of the screening visit. Patients who discontinue the drug before having completed 4 weeks of treatment (including 4 week efficacy and safety evaluations) will be replaced with a newly enrolled patient.</p> <p>Patients who meet the eligibility criteria at screening will be admitted to baseline evaluations. Eligible patients will enter the study to receive treatment with CFZ533 at 10 mg/kg IV infusion over approximately one hour. All IV infusions will take place in a monitored facility. Patients will be monitored closely for at least 2 hours after the completion of IV infusion, at the discretion of the Investigator, for vital signs and adverse events, including development of an injection reaction. Patients will be discharged if the investigator identifies no safety concerns.</p> <p>Eligible patients will visit the study center in the morning of Study Days 1, 15, 29, 57 and 85 for IV administration of CFZ533. PK/PD blood samples will be collected during study center visits prior to the dose and 2-hours post-dose.</p> <p>Patients will return to the site periodically for follow up assessments (safety, PK and PD) as defined in the assessment table. The End of Study visit will take place on Day 253.</p>

Population	The study population will be comprised of male and female patients aged 18 to 65 years old with Graves' disease hyperthyroidism. Approximately fifteen patients will be enrolled with a goal of 12 patients completing the study. Patients may be replaced if they withdraw consent or drop out of the study for reasons other than discontinuation by the investigator due to adverse events, and will be discussed on a case by case basis with the sponsor.
Key inclusion criteria	<ul style="list-style-type: none"> Male and female patients 18 to 65 years of age included. <ul style="list-style-type: none"> Women of child-bearing potential must be willing to use highly effective methods of contraception during the study treatment epoch and for 12 weeks after the last study treatment. Graves' hyperthyroidism (Baskin et al 2002), with the following labs measured at screening: <ul style="list-style-type: none"> TSH<LLN and either FT3>ULN or FT4> ULN Patients must weigh at least 40 kg to participate in the study
Key exclusion criteria	<ul style="list-style-type: none"> History of treatment of Graves' disease with radio-iodine ablation or thyroidectomy and/or current treatment with anti-thyroid drugs (methimazole or propylthiouracil) within one week of starting the study treatment History of hyperthyroidism not caused by Graves' disease (e.g. toxic multinodular goiter, autonomous thyroid nodule, or acute inflammatory thyroiditis) and/or history or presence of thyroid storm (fever, profuse sweating, vomiting, diarrhea, delirium, severe weakness, seizures, markedly irregular heartbeat, yellow skin and eyes (jaundice), severe low blood pressure, and coma). Previous treatment with a B cell-depleting biologic agent or any other immune-modulatory biologic agent within 5 half-lives (experimental or approved). History of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms. History of primary or secondary immunodeficiency, including a positive HIV (ELISA and Western blot) test result. History or evidence of tuberculosis by either of the following tests: <ul style="list-style-type: none"> Positive PPD skin test (size of induration measured after 48-72 hours, and a positive result is defined as an induration of \geq 5mm or according to local practice/guidelines) OR <ul style="list-style-type: none"> Positive QuantiFERON TB-Gold test Plans for immunization with a live vaccine within a 2-month period before enrollment or during the study period. Treatment with immunomodulatory drugs, such as cyclosporine A, methotrexate, and/or cyclophosphamide within 3 months from baseline. Glucocorticosteroid therapy with prednisolone up to 10 mg daily is permitted if patients are on stable dose for more than 3 months before enrollment in the study. Pregnant, breastfeeding females, and women of child bearing potential unless they are using highly effective contraception
Investigational and reference therapy	<ul style="list-style-type: none"> Patients will receive CFZ533 10mg/kg IV infusion on Study Days 1, 15, 29, 57, and 85.

Efficacy/PD assessments	<ul style="list-style-type: none">• TSH• Free T4• Total T3
Safety assessments	<ul style="list-style-type: none">• Physical examinations• ECG• Vital signs (BP, HR, pulse, temperature)• Hematology• Blood chemistry• Urinalysis• Pregnancy test• Blood coagulation panel• Monitoring for AEs/SAEs
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Data analysis	<p>One of the primary aims of this study is to assess the effects of CFZ533 on thyroid function, focusing on TSH, free T4 and total T3 levels, in Graves' disease after 12 weeks of treatment. The effects of CFZ533 on thyroid function will be primarily assessed by the proportion of patients whose TSH levels normalize (>0.35 mU/L) after 12 weeks of treatment. Another important aim of this study is to assess the effects of CFZ533 on free T4 and total T3 after 12 weeks of treatment.</p> <p>One of the main efficacy criteria is to show that the proportion of patients with normalization of TSH (above 0.35 mU/L) after 12 weeks of treatment with CFZ533 is statistically greater than 5%, according to a 1-sided exact test for proportions with a 10% type I error. This will be achieved if we observe at least 3/12 responders since in that case the lower bound of an 80% confidence interval for the proportion of responders will be about 10%. The other two main efficacy criteria are to show that the average free T4 and total T3 levels are significantly reduced after 12 weeks of treatment, according to a 1-sided paired t-test with a 10% type I error.</p>
Key words	<ul style="list-style-type: none">• Graves' disease (GD), hyperthyroidism• CFZ533• CD40, CD154• TSH• T3, T4•

1 Introduction

1.1 Background

Graves' disease (GD) is an autoimmune disorder characterized by hyperthyroidism, diffuse goiter, ophthalmopathy and rarely, dermopathy (Weetman 2000). The underlying pathogenesis of GD is the production of autoantibodies that activate the thyroid stimulating hormone (TSH) receptor in the thyroid gland, leading to hyperthyroidism and associated symptoms. GD affects ~1% of the adult population. Treatment strategies for GD include pharmacotherapy with anti-thyroid drugs (ATD) or thyroid ablation with radioiodine or surgery. Treatment with ATD does not only require long term treatment (12-18 months), but also careful monitoring of patients for side effects such as agranulocytosis and hepatotoxicity (Toft and Weetman 1998; Weetman 2000). In addition, the relapse rate is very high (50-60%) after ATD therapy withdrawal (Izumi et al 2005; Abraham et al 2005). Thyroid ablation with iodine or surgery is associated with complications and results in permanent hypothyroidism and the need for lifetime replacement of thyroid hormone. An ideal treatment for GD would address the underlying auto-immune pathogenesis of the disease, and would restore normal thyroid function.

The CD40-CD154 (CD154 is the CD40L) pathway is thought to play an important role in the pathogenesis of GD by promoting auto-reactive B cell activation, intrathyroidal germinal center (GC) function (Armengol et al 2001), and anti-thyrotropin receptor auto-antibodies (TRAb) production. Furthermore, CD40 expression is increased in the thyroid glands of patients with GD (Hwang et al 2009), and overexpression of CD40 in thyroid glands of transgenic mice increased their susceptibility to experimental autoimmune GD (Huber et al 2012). Furthermore, several single nucleotide polymorphisms in CD40 displayed significant association with GD as well as higher persistent levels of thyroglobulin antibodies and thyroid peroxidase (Jacobson et al 2007, Tomer et al 2002). Collectively these data suggest that blockade of CD40-CD54 interactions could provide a novel therapeutic approach for treating patients suffering GD.

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1.1.1 Relevant data summary

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1.1.1.1 Non-clinical data

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1.1.1.2 Teratogenicity and reproductive toxicity data

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1.1.1.3 Human safety and tolerability data

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1.1.1.4 Human pharmacokinetic data

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1.1.1.5 Human pharmacodynamic data

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1.2 Study purpose

The purpose of the study is to explore the potential effects of CFZ533, an anti-CD40 antibody, on thyroid function in patients with GD to determine if CFZ533 has an adequate clinical profile to warrant further clinical development in GD.

2 Study objectives**2.1 Primary objective**

Objective	Endpoint
<ul style="list-style-type: none">To assess the effects of CFZ533 on thyroid function in Graves' disease (GD) after 12 week treatment	<ul style="list-style-type: none">TSH, free T4 and total T3

2.2 Secondary objective

Objective	Endpoint
<ul style="list-style-type: none">To assess the safety and tolerability of CFZ533 (10 mg/kg IV for 12 weeks) up to 36 weeks	<ul style="list-style-type: none">Adverse events

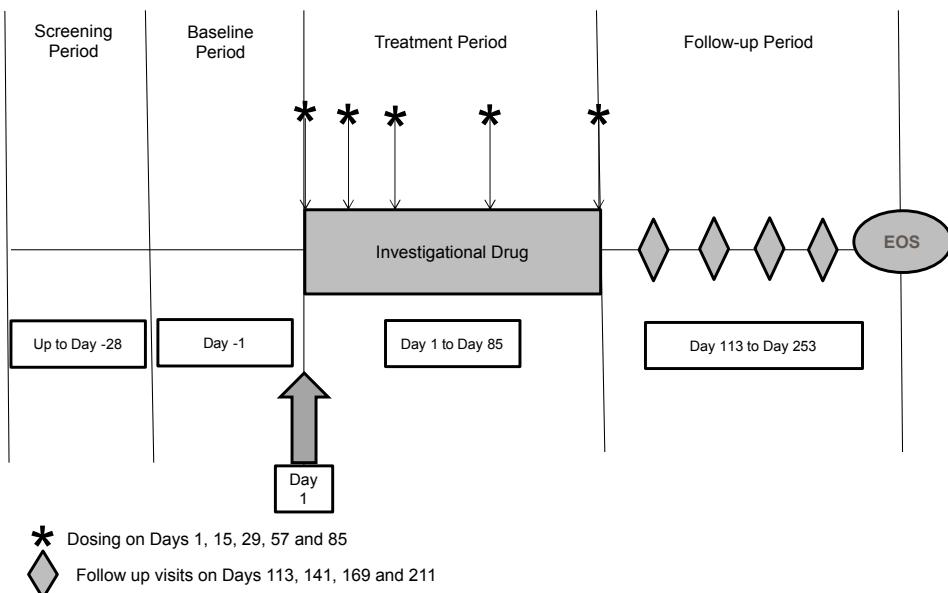
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3 **Investigational plan**

3.1 **Study design**

This is a non-confirmatory, open-label, one treatment arm study in patients with GD.

A total of approximately 15 patients will be enrolled and treated with CFZ533 to ensure approximately 12 completers. For each patient, the study will consist of a screening epoch of up to 28 days, a baseline evaluation, a 12-week treatment epoch, 24-week follow up epoch after the last dosing of CFZ533 on Study Day 85, and a study completion evaluation on Study Day 253. Patients who discontinue the drug before having completed 4 weeks of treatment and 4 week efficacy and safety evaluations will be replaced with a newly enrolled patient. The study completion assessments (End of Study; EOS) should be completed in patients who discontinue the study. The study design is presented in [Figure 3-1](#).

Figure 3-1 Study design

Patients who meet the eligibility criteria at screening will be admitted to baseline evaluations. Baseline evaluations may be started from Day -7 to allow completion of assessments prior to the treatment on Study Day 1. All baseline safety evaluation results must be available prior to dosing and meeting the eligibility criteria. The baseline visit (Visit 99) can be skipped and the baseline assessments would be completed prior to the study treatment on Day 1 (Visit 101) if Day 1 is scheduled within 7 days of the screening visit (Visit 1).

Eligible patients will enter the study to receive treatment with CFZ533 at 10 mg/kg IV over approximately one hour on Study Day 1. Patients will be monitored closely for at least 2 hours, at the discretion of the Investigator, after the completion of IV administration of CFZ533 for vital signs and adverse events, including development of an injection reaction.

Eligible patients will visit the study center in the morning of Study Days 1, 15, 29, 57 and 85 for IV administration of CFZ533. PK/PD blood samples will be collected as defined in the assessment schedule in [Table 8-1](#) and safety assessment will be conducted for 2 hour or longer after completion of each IV infusion, at the discretion of the Investigator. Following satisfactory review of safety data by the Investigator, patients will be discharged from the site on the same day after completion of all assessments, provided there are no safety concerns.

Patients will return to the site periodically for the follow up assessment (safety, PK and PD) on Study Days 113, 141, 169, 211, and 253 as defined in the [Assessment table](#). Days for follow-up visits may be slightly flexible based on the patients' schedule. More information about visit windows can be found in the SOM.

The end of study visit/assessment will occur on Study Day 253, which will include study completion evaluations followed by discharge from the study.

Throughout the study, patients can remain on their standard of care therapies established prior to treatment with study drug, unless outlined otherwise in this protocol, provided that the treatments are maintained at a constant level during the study.

Safety, PK and PD assessment will be taken at various time points as defined in [Table 8-1](#). Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis, pregnancy test, blood coagulation), and adverse event and serious adverse event monitoring. Immunogenicity assessments will be performed before, during and after the treatment period.

3.2 Rationale of study design

GD is an autoimmune disorder, characterized by the presence of circulating thyrotropin receptor auto-antibodies (TRAb), which are thought to be responsible for the development of hyperthyroidism. The interaction of CD40 on B cells with CD154 on T cells plays a key role in the production of TRAb. Additionally, intrathyroidal GCs have been implicated in the pathogenesis of GD ([Armengol et al 2001](#)). CD40 blockade with CFZ533 is expected to reduce the production of TRAb as well as disrupt intrathyroidal GCs. The current pharmacotherapy with anti-thyroid drugs (ATD) for GD requires long term treatment (12-18 months) with high relapse rate (50-60%), at the same time, requires careful safety monitoring during treatment period ([Burch et al 2012](#)). There is no current pharmacotherapy for GD that addresses the underlying pathogenesis, and CFZ533 has the potential to be a novel therapy, addressing the underlying pathogenesis.

The objective of this study is to assess the potential effects of CFZ533 on TSH, which is expected to be normalized Corporate Confidential Information. This will be a non-confirmatory, open-label, one treatment arm study in patients with GD. The rationale and justification for the key design elements are as follows:

Open label: TSH level is recommended as the single best screening test for hyperthyroidism by the American Association of Clinical Endocrinologists ([Baskin et al 2002](#)). The primary PD endpoint, TSH, in patients with GD is objective in nature, and shows very little random fluctuation over time ([Heemstra et al 2008](#)) in the absence of treatment. Another important aim of this study is to assess the effects of CFZ533 on free T4 and total T3 after 12 weeks of treatment. An open label study is therefore considered to be sufficient for the purpose of the planned endpoints.

No comparator: No previous clinical experience with an anti-CD40 blocking agent in patients with GD exists. Given the nature of TSH as described above, the likelihood of observing a response to placebo is very low. Data provided in ([Heemstra et al 2008](#)) regarding the natural variability of TSH levels in this patient population in the absence of treatment were used to predict, via simulations, the proportion of patients treated with placebo that would be expected to rise above 0.3 mU/L within 12 weeks simply due to random variability. This proportion is predicted to be less than 1%. Corporate Confidential Information

Therefore, inclusion of a placebo arm is considered unnecessary.

Patient population: Graves' hyperthyroid patients Corporate Confidential Information

Withholding standard of care treatment: Withholding standard of care treatment for Graves' hyperthyroidism (ATD, radio-Iodine or surgery) for 12 weeks during the clinical study treatment period is justified for two reasons:

- 1) The presence of hyperthyroidism for 12 weeks is unlikely to result in permanent complications, especially when patients are adequately treated with beta blockers (e.g., if the heart rate is controlled)
- 2) A delay of 12 weeks is unlikely to impact the ultimate efficacy and safety of definitive treatment for Graves' hyperthyroidism. Patients will undergo rescue therapy with the standard of care for Graves' hyperthyroidism if they meet the stopping criteria.

3.3 Rationale of dose/regimen, duration of treatment

Dosing rationale

The dosing rationale for this study is determined based on the safety, preliminary PK/PD data from the FIH study, and preclinical pharmacology data. It is further supported by adequate safety multiples from preclinical toxicological studies, relevant PD effects in tissues in non-human primates, and recently disclosed data from ASKP1240 in kidney transplantation.

The dosing regimen of 10 mg/kg Q4W with an additional dose at Day 15 is predicted to maintain the trough plasma concentration of CFZ533 above 50 µg/mL, which is thought to be needed to ensure complete CD40 pathway blockade in target tissues (Figure 3-2). In the thyroid glands of patients with Graves' disease, CD40 expression is increased (Smith et al 1999, Hwang 2009, Mysliwiec et al 2007a, Mysliwiec et al 2007b). The additional dose on Day 15 is needed to overcome efficient target mediated disposition and loss of target saturation in tissues where CD40 expression is increased.

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In [Goldwater et al 2013](#) ASKP1240 demonstrated similar PK properties as compared to CFZ533. Modeling of disclosed PK data from ASKP1240 in Transplantation ([Harland et al 2015](#)) characterized the biology (expression and turnover) of CD40 in conditions where CD40 expression is increased. From a quantitative point of view, the biology of CD40 in GD is not fully characterized, but literature data have confirmed an increase of CD40 expression in these patients. The transplant situation is thought to represent these conditions.

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Data for another monoclonal antibody that blocks CD40, ASKP1240 - A recent analysis of the disclosed PK/efficacy data from ASKP1240 (Astellas' anti-CD40 antibody) in solid organ transplantation ([Harland et al 2015](#)) indicated that efficient target mediated antibody clearance in tissue could result in loss of CD40 blockade and likely loss of efficacy, as a consequence of a significant increase of CD40 expression in target tissues.

Duration of Treatment

No previous experience with an anti-CD40 blocking agent exists in patients with GD. CFZ533 at 10 mg/kg IV is associated with up to 10 week full receptor occupancy (RO) in patients with RA. Therefore, 12-week treatment with CFZ533 at 10 mg/kg Q4W with an additional dose on Day 15 is anticipated to result in full CD40 RO up to approximately 5 months.

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Therefore, 12-week of treatment with CFZ533 is considered to be necessary and sufficient to test the hypothesis whether or not CFZ533 could be a potential treatment for GD. In addition, follow up duration may be extended up to 365 days (52 weeks) if clinically relevant efficacy was observed during the treatment period or up to 5-month of full CD40 RO. The clinical relevant efficacy is referring to normalization of TSH after 12 week treatment with CFZ533. Another important endpoints are effects of CFZ533 on free T4 and total T3 after 12 weeks of treatment. Extended follow up of a patient will be terminated when a standard of care rescue therapy is initiated for treating Graves' hyperthyroidism.

3.4 Rationale for choice of comparator

Not applicable.

3.5 Purpose and timing of interim analyses/design adaptations

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3.6 Risks and benefits

3.6.1 Potential benefit

Based on the established role of both B cells and T cells in the pathogenesis of Graves' disease, CFZ533 has a potential to become a novel therapy to address the underlying pathogenesis. CFZ533 has never been used in patients with Graves' disease. Therefore, no statement can be made of its efficacy for patients participating in this study at this stage.

3.6.2 Potential risks associated with CFZ533 administration and their mitigation

Currently, limited data exists regarding the use of agents that block the CD40/CD154 pathway. Preclinical and Phase 1 data for CFZ533 as well as data from compounds acting on the same pathway (i.e., CD40-CD154) have been taken into account to estimate the potential risks associated with CFZ533. The risks to patients in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, avoidance of prohibited treatments and overall adherence to terms outlined in this protocol. The current IB (Section 6, Investigator Guidance) also provides detailed instructions regarding the risks and their mitigation.

Acute hypersensitivity

Hypersensitivity or infusion reactions can manifest with itching, flushing, headache, nausea/vomiting, hypotension, urticaria, bronchospasm, or angioedema.

In this study, CFZ533 will be administered as an intravenous infusion where such hypersensitivity reactions can still occur. Patients will be monitored for at least 2 hours after the completion of CFZ533 IV infusion at each visit.

Immunogenicity

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Extrapolation of immunogenicity risks from healthy subjects to Graves' disease patients is unknown and blood samples will be collected during this trial to assess the immunogenicity.

Infections

Subjects treated with CFZ533 may be at an increased risk of infection. CD40 ligation is linked to the functional activity of antigen presentation, as well as T-cell priming, B-cell differentiation, antibody production and immune memory.

Administration of CFZ533 is expected to result in general immunosuppression with a decreased capacity to mount a response to novel immunogens, including those of bacterial, viral, fungal and parasitic origin when full receptor occupancy has been achieved.

Although the ability to mount a primary immune response will be affected by CFZ533, the memory B-cell repertoire and immune recall response should remain intact and protective. In addition, subjects will have adequate preformed antibody to maintain protective humoral response for extended periods of time (months).

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In patients receiving weekly to bi-monthly administration of the parent antibody lucatumumab, the rate of infection was very low and similar to control, supporting these stated hypotheses. Patients with current, active or latent infection susceptible to reactivation will be excluded from entry into the present clinical study.

The risk of infection may increase if CFZ533 is combined with steroids or strong immunosuppressive drugs. Patients who are HIV-positive or have taken immunomodulatory drugs, such as cyclosporine A, methotrexate, and/or cyclophosphamide within 3 months at the baseline will be excluded.

Patients enrolled in the current study will be monitored regularly and carefully for signs and symptoms which might indicate a severe infection. Patients will be informed to contact the study physician if they present with signs and symptoms of an infection such as fever, nausea, myalgia, headache, arthralgia, chills, diarrhea, stiff neck, and malaise for further assessment and treatment if necessary.

Lymphadenopathy

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The investigator should pay special attention to lymph nodes in patients during physical assessments including unusual lymphadenopathy in the absence of infection.

Lymphoproliferative disorders

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The clinician should monitor hematology regularly for changes consistent with a lymphoproliferative disorder.

Pregnancy

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

Thrombosis

It has been shown that monoclonal antibodies that bind to CD154 (CD40L), the natural ligand to CD40, are associated with a risk of thrombosis in both clinical studies and non-clinical studies in primates. Accordingly, the potential risk of thromboembolic events with CFZ533 has been thoroughly investigated during the process of development.

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Although the risk is hypothetical, hematologic and coagulation parameters will be regularly monitored in the current study.

Systemic inflammation and potential kidney injury

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Although not expected in this clinical study, the investigator will monitor for signs, symptoms and laboratory results consistent with clinically significant inflammation as well as for changes in renal function and signs of acute kidney injury as per local practice.

Vaccination

Vaccination of patients during treatment with CFZ533 and prior to clearance of the antibody is likely to result in therapeutic failure (i.e., non-protective antibody titers) due to the pharmacologic activity of CFZ533. For patients participating in this study, all vaccinations should be up to date based on local guidelines. Administration of live attenuated agents will be prohibited in patients receiving CFZ533 treatment in this study.

There may be other unknown risks to CFZ533 which may be serious and unforeseen.

Blood samples will be collected frequently during the study either via venipuncture or cannula. Approximately 460 mL of blood is planned to be collected over the study duration (~36-week) from each patient. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

4 Population

The study population will be comprised of male and female patients 18 to 65 years of age with Graves' disease hyperthyroidism.

To ensure 12 completers, a total of approximately 15 patients will be enrolled to participate in this study.

The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Patient selection is to be established by checking through all inclusion/exclusion criteria at screening and/or baseline. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a patient from enrollment into the study.

Replacement patients will be enrolled to replace patients who discontinue the study for reasons other than safety before having completed 4 weeks of treatment and 4 week efficacy and safety evaluations.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria at screening:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients 18 to 65 years of age included.
 - Women of child-bearing potential must be willing to use the highly effective methods of contraception (definition in Exclusion criteria #24) during the study treatment epoch and for 12 weeks after the last study treatment.

3. Graves' hyperthyroidism ([Baskin et al 2002](#)) with the following labs measured at screening:
 - TSH<LLN and either FT3>ULN or FT4> ULN
4. Patients must weigh at least 40 kg to participate in the study
5. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
6. Patients have received up to date required vaccinations based on local guidelines.

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are NOT eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Use of other investigational drugs within 5 half-lives prior to first treatment.
2. History of hypersensitivity to vaccines, the study drug or to drugs of similar chemical classes (e.g. IgG₁-related biologic agents).
3. History of treatment of Graves' disease with radio-iodine ablation or thyroidectomy.
4. Current treatment with anti-thyroid drugs (methimazole or propylthiouracil) within one week of starting treatment. Discontinuation of ATD must not have been for the sole purpose of qualifying for this study; rather it should have been based on clinical considerations (e.g. lack of efficacy or safety/tolerability issues with ATD).
5. History of hyperthyroidism not caused by Graves' disease (e.g. toxic multinodular goiter, autonomous thyroid nodule, or acute inflammatory thyroiditis).
6. History or presence of thyroid storm (fever, profuse sweating, vomiting, diarrhea, delirium, severe weakness, seizures, markedly irregular heartbeat, yellow skin and eyes (jaundice), severe low blood pressure, and coma).
7. Previous treatment with a B cell-depleting biologic agent or any other immunomodulatory biologic agent (experimental or approved) within 5 half-lives prior to first treatment.
8. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
9. Significant illness which has not resolved within two weeks prior to initial dosing.
10. History of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms, including current, active or latent infection susceptible to reactivation.
11. History of primary or secondary immunodeficiency, including a positive HIV (ELISA and Western blot) test result at screening.
12. A positive Hepatitis B surface antigen or Hepatitis C test result at screening.
13. History or evidence of tuberculosis by either of the following tests at screening:
 - Positive PPD skin test (size of induration measured after 48-72 hours, and a positive result is defined as an induration of $\geq 5\text{mm}$ or according to local practice/guidelines) **OR**

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- Positive QuantiFERON TB-Gold test

14. A negative Epstein Barr virus (EBV) test (as defined in the laboratory manual) at screening.

15. Any of the following abnormal laboratory values at screening (may be repeated one time for a single outlying value):

- Total white blood count (WBC) outside of the range $2.0-15.0 \times 10^9/L$
- Absolute neutrophil count $<1.5 \times 10^9/L$
- Lymphocyte count $<0.8 \times 10^9/L$
- Platelets $< 100 \times 10^9/L$
- Hemoglobin $< 9.0 \text{ g/dl}$

16. Severe liver disease or liver injury as indicated by abnormal liver function tests at screening:

- Any **single parameter** of ALT, AST, γ -GT, must not exceed $>5 \times$ the upper limit of normal (ULN);
- alkaline phosphatase (ALP) must not exceed $>5 \times$ the upper limit of normal (ULN);
- serum total bilirubin (TBL) must not exceed $>1.8 \times$ the upper limit of normal (ULN) except if the elevation is due to Gilbert's syndrome.

If necessary, laboratory testing may be repeated on one occasion (as soon as possible) prior to randomization, to rule out any laboratory error.

17. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).

18. Donation or loss of 400mL or more of blood within eight (8) weeks prior to initial dosing or longer, if required by local regulation.

19. Plans for immunization with a live vaccine within a 2-month period before enrollment or during the study period.

20. History or evidence of drug or alcohol abuse within the 6 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening.

21. Treatment with immunomodulatory drugs, such as cyclosporine A, methotrexate, and/or cyclophosphamide within 3 months from baseline. Glucocorticosteroid therapy with prednisolone up to 10 mg daily is permitted if patients are on stable dose for more than 3 months before enrollment in the study.

22. History or presence of coronary artery disease, ventricular or atrial arrhythmias (including atrial fibrillation) with the exception of sinus tachycardia controlled with beta-blockers.

23. Pregnant or breast-feeding women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

24. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 12 weeks after stopping medication. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (i.e., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception)
- Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment)
- Male sterilization (at least 6 m prior to screening). The vasectomized male partner should be the sole partner for that subject
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

25. Sexually active males must use a condom during intercourse while taking CFZ533 and for 12 weeks after stopping the investigational medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

26. Treatment with amiodarone within 9 months of starting treatment in this study.

Note: In the case where a safety laboratory assessment at screening and initial baseline is outside of the range specified above, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the patient is excluded from the study.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for study patients

During recruitment, screening/informed consent review, and baseline visit, the patients must be informed and reminded of the following restrictions:

5.1 Contraception requirements

Please refer to exclusion criteria ([Section 4](#)) for details of contraception requirements for the study.

5.2 Prohibited treatment

Use of the treatments displayed in the table below is NOT allowed after the start of study drug until the end of study evaluation.

Table 5-1 Prohibited treatment

Medication	Action to be taken
Iodine (radioactive or cold)	Withdrawal may be required on a case-by-case basis
Methimazole	
Propylthiouracil	
Amiodarone	
Live vaccinations	Withdrawal immediately

Patients may continue the medications that had been taken before enrolling in this study and may take medications that are permitted per protocol. Doses may be titrated if deemed necessary by their physicians.

5.3 Dietary, fluid, smoking, and other restrictions

Patients should maintain their usual diet and life habits during the entire study.

6 Treatment

6.1 Study treatment

Details on the storage and management of study medication and instructions for prescribing and taking study treatment are outlined in Section 3 of the Site Operations Manual (SOM).

6.1.1 Investigational treatment

The investigational drug, CFZ533 will be available as lyophilisate in dose strength of 150 mg. CFZ533 will be packed and labeled under responsibility of drug supply management department of Novartis and will be supplied to the Investigator sites as open label bulk supply.

6.2 Treatment arms

Patients will receive CFZ533 intravenously at 10 mg/kg over approximately one hour on Study Day 1, Day 15, Day 29, Day 57, and Day 85.

6.3 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions are not permitted UNLESS safety finding(s) warrant it at the discretion of the investigator (See [Section 7.4](#)).

6.4 Treatment assignment

All patients who are eligible to participate in the study will be assigned to study treatment (see Site Operations Manual for more details). The investigator will enter the treatment number on the CRF.

6.5 Treatment blinding

This is a non-confirmatory, open-label, one treatment arm study.

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6.6 Emergency breaking of assigned treatment code

Not applicable.

6.7 Treatment exposure and compliance

The IV infusion will be given at the study site, therefore, compliance is ensured. In addition, pharmacokinetic exposure will be measured in all patients treated with CFZ533, as detailed in [Section 8.5](#).

6.8 Recommended treatment of adverse events

Parenteral administration of monoclonal antibodies can be associated with acute, severe reactions (occurring within the first few hours post dose) secondary to hypersensitivity, immunogenicity, or ADCC-mediated cell depletion.

Injection site reactions can also be noted during or after subcutaneous administration and are usually less severe than infusion reactions, however, may still require medical attention and treatment.

In this study, CFZ533 will be administered as an intravenous infusion.

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In the

event of a hypersensitivity reaction, **stop the infusion**. Assess and treat for anaphylaxis, if indicated, and initiate supportive care per local practice. Fluids, vasopressors, corticosteroids, antihistamines, bronchodilators, and oxygen should be on hand.

Patients will be monitored at the site for at least 2 hours or longer after the completion of IV infusion at the discretion of the Investigator to ensure adequate safety monitoring. In case of any signs of an acute reaction, clinical treatment will be provided as determined by the treating physician on a case-by-case basis and depending on the severity. For the management of allergic reaction, anaphylaxis and cytokine release, it is recommended to follow the guidelines by the National Cancer Institute Common Toxicity Criteria ([CTCAE 2010](#)).

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.9 Rescue medication

Patients may receive standard of care treatment for Graves' hyperthyroidism at the discretion of the investigator in case of worsening of the disease. Patients will be discontinued from the study in this case as described in [Section 7.1](#). Rescue medication is to be provided by the study center or personal physician.

Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF after start of study drug.

6.10 Concomitant treatment

Patients may be treated with any medications that are not listed as prohibited treatment, as standard of care for their medical conditions by their physicians. Use of beta-blockers for treating the symptoms of Graves' disease during participation in this study is permitted at the discretion of the treating physician. Medication, amount and frequency of use must be recorded.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug.

Administration of acetaminophen is acceptable at the discretion of treatment physicians, but must be documented.

Should a patient have an incidental and limited need for a medication to be taken within the restricted pre-dose timeframe (e.g. acetaminophen for a headache, antibiotic prophylaxis prior to dental surgery, etc.), the sponsor should be advised, as administration of any concomitant medication may require the patient to be replaced. Decisions regarding replacements will be discussed with the sponsor on a case-by-case basis.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the amount of single doses and units, the dosing frequency, route of administration, the start and discontinuation dates, and the medical reason for the therapy.

7 Discontinuation and study completion

7.1 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time.

The investigator **must** discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment **must** be discontinued under the following circumstances:

- Patient withdraws consent
- Pregnancy
- Grade 3 or higher allergic reaction
- Acute, Grade 3 or higher infection as judged by the Investigator

The study treatment should be discontinued if:

- Clinically significant worsening of Graves' disease, eg. beta-blocker unable to control the symptoms of hyperthyroidism, at the discretion of the Investigator.
- New onset atrial fibrillation or angina.
- On balance, the investigator believes that continuation would be detrimental to the patient's well-being.

Discontinuation of study treatment will be at the discretion of the Investigator, under the following circumstances:

- Use of prohibited treatment as per [Section 5.2](#).
- Any other protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see [Section 7.3](#)). Where possible, they should return for the assessments defined in the [Assessment table](#). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them as specified in [Section 7.2.1](#). Patients who discontinue the drug before having completed 4 weeks of treatment and 4 week efficacy and safety evaluations will be replaced with a newly enrolled patient.

7.2 Study completion and post-study treatment

Each enrolled patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last patient completes their End of Study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

After the study participation, the patients will continue to be treated by his/her general practitioner according to the local standard clinical management related to the underlying disease.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them to appropriate ongoing care.

7.2.1 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents actions taken to contact the patient (e.g. dates of telephone calls, registered letters, etc). A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.3 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore **and** does not want any further visits or assessments **and** does not want any further study related contact **and** does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

7.4 Study stopping rules

Following a review of the adverse event(s), a decision to permanently discontinue enrollment will be made jointly by the Investigator and Sponsor. The following stopping rules, based on potential preclinical findings, will serve as the basis for placing the study on hold or terminating the study.

- Two (2) or more patients experience study-drug related SAEs
- Three (3) or more treatment-related AE, CTCAE Grade 3 or higher.
- Two (2) or more patients experience CTCAE Grade 3 or higher leukopenia (WBC <1.0 x 10⁹/L)
- Two (2) or more patients experience CTCAE Grade 3 or higher thrombocytopenia (platelets <25 x 10⁹/L)
- One (1) patient experiences cytokine release syndrome
- One (1) patient has a treatment-related thromboembolic event of CTCAE Grade 3 or higher
- Two (2) or more patients experience:
 - Emergent hypogammaglobinemia defined as $\geq 50\%$ reduction in total serum IgG or IgM concentration from baseline
 - Severe systemic infection or opportunistic infection that requires treatment, e.g., sepsis, mycosis, pneumonia.
- The principal investigator or the Sponsor considers that the number and/or severity of AEs justify discontinuation of the study.
- The sponsor unilaterally requests it.

7.5 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, patients should be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

Table 8-1 Assessment schedule

Patients should be seen for all visits on the designated day, with the assessments performed as per schedule, within the allowed “visit/assessment window” specified in the Site Operations Manual.

Study Phase	Screening	Baseline	Treatment								Follow-up				EOS visit		
			V101		V102		V103		V104		V199		V201	V202	V203	V204	
Visit Numbers ¹	V1	V99 ¹²														V299	
Study Day(s)	Up to -28	-1	1		15		29		57		85		113	141	169	211	253
Time (post-dose)	-	-	0h ⁹	1h ⁹	-	-	-	-	-								
Informed consent	X																
Inclusion / Exclusion criteria	X	X ²															
Medical history/current medical conditions	X																
Demography	X																
Hepatitis and HIV Screen	X																
TB Test ¹⁰	X																
EBV Screen	X																
Alcohol Test and Drug Screen	X																
Blood Pressure and Pulse Rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X		X		X		X			X		X			X	X	X
Body temperature	X	X	X		X		X		X		X		X	X	X	X	X
Body height	X																
Body weight	X	X ¹³					X		X		X		X		X		X
ECG evaluation	X	X	X		X		X		X		X		X	X	X	X	X
Pregnancy test	X	X ¹³			X		X		X		X		X		X		X
Dose administration			X		X		X		X		X						
Blood chemistry ⁴	X	X	X				X				X		X		X		X

Study Phase	Screening	Baseline	Treatment								Follow-up				EOS visit		
Visit Numbers ¹	V1	V99 ¹²	V101		V102		V103		V104		V199		V201	V202	V203	V204	V299
Study Day(s)	Up to -28	-1	1		15		29		57		85		113	141	169	211	253
Time (post-dose)	-	-	0h ⁹	1h ⁹	-	-	-	-	-								
Corporate Confidential	X	X	X				X				X		X		X		X
Hematology	X	X	X		X		X		X		X		X		X		X
Urinalysis	X	X	X				X				X		X		X		X
Cytokine assessment			X	X	X	X	X	X	X	X	X	X					
Coagulation Panel		X ¹³		X		X		X		X		X	X	X		X	X
Concomitant therapies													as required				
Serious adverse events													as required				
Adverse events													as required				
Immunogenicity ³			X						X				X	X	X		X
Comments													as required				
Study completion information																	X
TSH	X	X	X		X		X		X		X		X	X	X	X	X
Total and free T3 & T4	X	X	X		X		X		X		X		X	X	X	X	X
PK (CFZ533) ⁹			X	X	X	X	X	X	X	X	X	X	X	X	X		X
Free & total CD40 on B cells ⁵				X			X		X		X		X	X	X		X
Soluble CD40 ⁵				X			X		X		X		X	X	X		X
Soluble CD154 ⁵				X			X		X		X		X	X	X		X
Exploratory Biomarkers in Serum ⁶		X	X		X		X		X		X		X	X	X	X	X
Corporate Confidential	X	X	X		X		X		X		X		X	X	X	X	X
Corporate Co	X	X	X		X		X		X		X		X	X	X	X	X
Corporate Confidential Information			X ⁸														
Corporate Confidential Information		X ¹³									X						

¹ Visit structure given for internal programming purpose only

² Only those inclusion/exclusion criteria that are specific for baseline visit

³ Immunogenicity: 0-hour sample is taken **pre-dose**

⁴ Corporate Confidential Information

⁵ On days when patient is dosed, sample is taken **pre-dose** (0-hour)

⁶ Corporate Confidential Information

⁷ Corporate Confidential

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⁹ 0-hour sample (or assessment) is taken **pre-dose**, 1-hour sample is taken 1 hour **AFTER** the END of infusion

¹⁰PPD or QuantiFERON TB-gold test

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¹²The baseline visit assessments can be completed on Day 1 (pre-dose) when the first dose (Day 1) is received within 7 days of the screening visit.

¹³These assessments will be completed prior to the study treatment on Day 1 (Visit 101, **pre-dose**) if Day 1 is scheduled within 7 days of the screening visit (Visit 1).

8.1 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If incapable of doing so, in cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Novartis will review the Investigators proposed informed consent form to ensure it complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any further changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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8.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients at Screening (Visit 1). The following will only be assessed at the Screening Visit and not at subsequent visits:

- Demography
- Medical History/Current medical conditions
- Hepatitis and HIV Screen
- Alcohol Test and Drug Screen

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses rather than symptoms will be recorded.

Investigators have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Pharmacodynamics

Pharmacodynamic assessments are specified below. The details for sample collection and assay methods will be specified in the Study Operations Manual (SOM). Samples will be collected and assessments will be performed at the timepoint(s) defined in the [Assessment schedule](#).

In order to better characterize the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

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8.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the [Assessment Schedule](#) detailing when each assessment is to be performed.

8.4.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, as well as avascular and neurological examination. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded in the eCRF. Significant findings that are present prior to informed consent are included in the Relevant Medical History eCRF. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event eCRF.

8.4.2 Vital signs

Vital signs include body temperature, blood pressure (BP) and pulse measurements. After the patient has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using a validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

To ensure accurate measurement of heart rate or blood pressure, the Investigator may obtain a total of up to three consecutive assessments, with the patient seated quietly for approximately five minutes preceding each repeat assessment.

8.4.3 Height and weight

- Height (cm)
- Body weight (kg)
- Body mass index (BMI) will be calculated (Body weight (kg) / [Height (m)]²)

8.4.4 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g., neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count will be measured.

Clinical chemistry

Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, total protein, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, amylase, lipase, CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Urinalysis

A midstream urine sample (approximately 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative “dipstick” evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood sample will be sent for microscopic analysis of WBC, RBC and casts.

Coagulation panel

Prothrombin time (PT) and active partial thromboplastin time (aPTT) will be assessed. Additional parameters such as International Normalized Ratio (INR) may be estimated at the discretion of the Investigator.

8.4.5 Electrocardiogram (ECG)

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12-lead ECGs are collected. The original ECGs, appropriately signed, should be collected and archived at the study site.

Each ECG tracing should be labeled with study number, patient initials, patient number, date and time, be appropriately signed and dated to confirm review, and filed in the study site source documents.

For any ECGs with patient safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant abnormalities should be recorded on the relevant section of the medical history/current medical conditions/AE eCRF page as appropriate.

The eCRF will contain:

- Date and time of ECG
- Heart rate
- PR interval
- RR
- QT uncorrected
- QTcF
- QRS duration

8.4.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy tests during the study. Serum pregnancy tests will be performed at screening; at all other times urine pregnancy tests may be used. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms). A positive urine pregnancy test requires immediate interruption of study drug until serum β -hCG is performed and found to be negative.

8.4.7 Other safety evaluations

8.4.7.1 PPD skin test or QuantiFeron test

A purified protein derivative (PPD) skin test will be performed and read at screening in order to evaluate the infection with tuberculosis (TB). The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD injected intradermally into usually the volar surface of the forearm. The site is cleansed and the PPD extract is then injected into the most superficial dermal layer of the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48-72 hours to develop, the patient must return to the investigators' site within that time for a proper evaluation of the test site. This will determine whether the patients have had a significant reaction to the PPD test. A reaction is

measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥ 5 mm is interpreted as positive result.

Based on the study site's normal practice, QuantiFeron test may replace PPD skin test at screening. A positive QuantiFeron test at screening will exclude the patients from the participation in the study.

T-SPOT or other types ELISPOT assays based on interferon-gamma release may also be used for tuberculosis diagnosis as per local practice.

Results will be available as source data and will not be recorded within the eCRF.

8.4.7.2 Infections

All occurrences of infections must be carefully monitored by the investigator. Significant findings, which meet the definition of infection, must be recorded in the Adverse Event eCRF.

8.4.8 Immunogenicity

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8.5 Pharmacokinetics

PK samples will be collected at the timepoints defined in the [Assessment schedule](#).

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8.6 Other assessments

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9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with the underlying disease(s). Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for liver related events are included in [Section 9.3](#).

Adverse events must be recorded on the Adverse Events CRF for patients that pass screening and enter into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. The severity grade is as follows based on CTC-AE grading:
 - 1 mild: usually transient in nature and generally not interfering with normal activities
 - 2 moderate: sufficiently discomforting to interfere with normal activities
 - 3 severe: prevents normal activities
 - 4 life threatening

CTC-AE grade 5 (death) is not used, but is collected in other CRFs (e.g. Study Completion, Death/Survival).

2. its relationship to the investigational treatment (no/yes), or other study treatment (non-investigational) (no/yes), or both or indistinguishable,
3. its duration (start and end time/dates) or if the event is ongoing, an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE). See [Section 9.2.1](#) for the definition of SAE.
5. action taken regarding study treatment

All adverse events should be treated appropriately. Action may include one or more of the following:

- no action taken (i.e. further observation only)
- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged

6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis in a timely manner (see [Section 9.2.2](#)).

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (Graves' disease)
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are 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 dependency or abuse.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per [Section 9.2.2](#).

9.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until the study completion, must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after the completion of the study should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

SAEs (initial and follow-up) that are recorded electronically in the Electronic Data Capture system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first. Study site personnel must also inform the Clinical Trial Leader.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to the investigational treatment, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

9.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter

- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to [Table 9-1](#) and [Table 9-2](#) for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in [Table 9-2](#).

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug (refer to [Section 7.1](#), if appropriate)
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF, including the liver event overview CRF pages.

Table 9-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers	<ul style="list-style-type: none"> • $3 \times \text{ULN} < \text{ALT} / \text{AST} \leq 5 \times \text{ULN}$ • $1.5 \times \text{ULN} < \text{TBL} \leq 2 \times \text{ULN}$
Liver events	<ul style="list-style-type: none"> • $\text{ALT or AST} > 5 \times \text{ULN}$ • $\text{ALP} > 2 \times \text{ULN}$ (in the absence of known bone pathology) • $\text{TBL} > 2 \times \text{ULN}$ (in the absence of known Gilbert syndrome) • $\text{ALT or AST} > 3 \times \text{ULN}$ and $\text{INR} > 1.5$ • Potential Hy's Law cases (defined as $\text{ALT or AST} > 3 \times \text{ULN}$ and $\text{TBL} > 2 \times \text{ULN}$ [mainly conjugated fraction] without notable increase in ALP to $> 2 \times \text{ULN}$) • Any clinical event of jaundice (or equivalent term) • $\text{ALT or AST} > 3 \times \text{ULN}$ accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity *

Table 9-2 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case ^a	<ul style="list-style-type: none"> • Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	<ul style="list-style-type: none"> • Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	<ul style="list-style-type: none"> • Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	<ul style="list-style-type: none"> • Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for <i>more than 2 weeks</i>, discontinue the study drug • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms ^b	<ul style="list-style-type: none"> • Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> • Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient 	<p>Investigator discretion</p> <p>Monitor LFT within 1 to 4 weeks</p>
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	<ul style="list-style-type: none"> • Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF 	<p>Investigator discretion</p> <p>Monitor LFT within 1 to 4 weeks or at next visit</p>

Criteria	Actions required	Follow-up monitoring
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	<ul style="list-style-type: none"> Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient 	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	<ul style="list-style-type: none"> Discontinue the study drug immediately Hospitalize the patient Establish causality Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	<ul style="list-style-type: none"> Consider study drug interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver CRF 	Investigator discretion

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

^aElevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

^b(General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

^cResolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

9.4 Renal safety monitoring

Renal events are defined as one of the following:

- confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
- new onset (≥1+) proteinuria, hematuria or glucosuria; or as a
- doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

The following two categories of abnormalities/adverse events have to be considered during the course of the study:

- Serum creatinine triggers that will require follow up and repeat assessments of the abnormal laboratory parameter
- Urine dipstick triggers that will require follow up and repeat assessments of the abnormal laboratory parameter

Table 9-3 Specific renal alert criteria and actions

Renal Event	Actions
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Serum creatinine increase \geq 50 % compared to baseline	Follow up within 24-48h if possible Consider drug interruption Consider patient hospitalization /specialized treatment
Albumin- or Protein-creatinine ratio increase \geq 2-fold	Confirm value after 24-48h Perform urine microscopy
Albumin-creatinine ratio (ACR) \geq 30 mg/g or \geq 3 mg/mmol; New dipstick proteinuria \geq 1+ Protein-creatinine ratio (PCR) \geq 150 mg/g or >15 mg/mmol	Consider drug interruption / discontinuation
New dipstick glucosuria \geq 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
Document contributing factors: co-medication, other co-morbid conditions, and additional diagnostic procedures performed in the CRF	
<u>Monitor patient regularly (frequency at investigator's discretion) until one of the following:</u> Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) Event stabilization: sCr level with $\pm 10\%$ variability over last 6 months or protein-creatinine ratio stabilization at a new level with $\pm 50\%$ variability over last 6 months.	

9.5 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments. Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on an SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

All SAEs relating to suicidal behavior should be reviewed by the Safety Management Team or Early Project Teams.

9.6 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

CRO working on behalf of Novartis review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to CRO working on behalf of Novartis who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

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10.3 Data Monitoring Committee

Not required.

10.4 Adjudication Committee

Not required.

11 Data analysis

11.1 Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment(s) received.

The safety analysis set will include all patients that received any study drug.

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11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by patient. Summary statistics will be provided.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by patient.

11.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration (rescue medication) and concomitant therapies will be listed by patient.

11.4 Analysis of the primary variable(s)

The primary aim of this study is to assess the effects of CFZ533 on thyroid function, focusing on TSH levels, total T3 and free T4 in GD after 12 weeks of treatment.

11.4.1 Variable(s)

The effects of CFZ533 on thyroid function will be primarily assessed by the proportion of patients whose TSH levels normalize (above 0.35 mU/L) after 12 weeks of treatment. They will also be assessed by the difference in mean total T3 and free T4 between baseline and after 12 weeks of treatment.

11.4.2 Statistical model, hypothesis, and method of analysis

One of the main efficacy criteria for this study is to show that the proportion of patients with normalization of TSH (above 0.35 mU/L) after 12 weeks of treatment with CFZ533 is statistically greater than 5%, according to a 1-sided exact test for proportions with a 10% type I error. This will be achieved if we observe at least 3/12 responders since in that case the lower bound of an 80% confidence interval for the proportion of responders will be about 10%. The other efficacy criteria are that there is a significant reduction in average total T3 and free T4 after 12 weeks of treatment, according to a 1-sided paired t-test with 10% type I error for each of these two endpoints.

11.4.3 Handling of missing values/censoring/discontinuations

Patients who discontinue after the 4 week efficacy assessment for any reason will be considered non-responders in the primary analysis (unless their last recorded TSH value was after 8 weeks of treatment and was above the lower limit of the normal range, 0.35 mU/L). Patients who discontinue before 4 weeks of treatment for any reason will be replaced and not counted for the calculation of responders. For total T3 and free T4, the last recorded value will be used for the change from baseline, provided it was obtained after at least 8 weeks of treatment.

11.4.4 Supportive analyses

In case more than 2 discontinuations occur in this study, additional methods may be used to assess sensitivity of the results to different imputation techniques to deal with the missing data.

11.5 Analysis of secondary and exploratory variables

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11.5.2 Safety

Vital signs

All vital signs data will be listed by patient, visit and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by visit.

ECG evaluations

All ECG data will be listed by patient and visit/time, and abnormalities will be flagged. Summary statistics will be provided by visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by patient and visit, and if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by visit.

Adverse events

All information obtained on adverse events will be displayed by patient.

The number and percentage of patients with adverse events will be tabulated by body system and preferred term. A patient with multiple adverse events within a body system is only counted once towards the total of this body system.

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11.5.3 Pharmacokinetics

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11.5.4 Pharmacokinetic / pharmacodynamic interactions

Not Applicable.

11.5.5 Other assessments

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11.6 Sample size calculation

The proposed sample size for this study is 12 patients (to complete the study). Assuming CFZ533 is associated with 38% normalization of the TSH levels after 12 weeks of treatment (which is consistent with the response rate seen with Rituximab in 26 weeks in one small, open-label study ([Heemstra et al 2008](#)), there is around 89% power to detect a proportion of TSH responders significantly higher than 5% (this would be achieved with at least 3/12 responders), with a type I error of 10%. Additionally, this sample size provides 98% power to detect normalization of the total T3 (and free T4, respectively) below the upper limit of the normal range (2.79 nmol/L and 22.7 pmol/L, respectively). The assumed baseline levels are 7.2 nmol/L for total T3 and 58.55 pmol/L for free T4, which are the average values reported in GD patients in [Andrade et al \(2001\)](#). The assumed standard deviation for the change from baseline are 4.24 nmol/L and 34.58 pmol/L respectively.

11.7 Power for analysis of key secondary variables

Not applicable

11.8 Interim analyses

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12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g. advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

13.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the CTL should be informed and (serious) adverse event reporting requirements ([Section 9](#)) followed as appropriate.

14 References

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