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Novartis Research and Development

CFZ533 (Iscalimab)

Clinical Trial Protocol CCFZ533X2207 / NCT04129528

Investigator- and subject-blinded, randomized, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics and efficacy of CFZ533 in pediatric and young adults with new onset type 1 diabetes mellitus (T1DM)

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body Mass Index
BUN	Blood urea nitrogen
BW	Body weight
C-SSRS	Columbia Suicide Severity Rating Scale
CD-ROM	Compact disc – read only memory
CDS	Core Data Sheet (for marketed drugs)
CFR	U.S. Code of Federal Regulations
CK	Creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
CMV	Cytomegalovirus
CO_2	Carbon dioxide
COVID-19	Coronavirus disease 2019
CQA	Clinical Quality Assurance
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CV	Coefficient of variation
DDC	Direct Data Capture
DMC	Data Monitoring Committee
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	Hour
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HSV	Herpes Simplex Virus
ICF	Informed Consent Form

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
Kg	Kilogram
LADA	Latent autoimmune diabetes of the adult
LDH	Lactate dehydrogenase
LFT	Liver function test
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
mAb	Monoclonal Antibody
MABEL	Minimum anticipated biological effect level
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
mL	Milliliter(s)
MMTT	Mixed Meal Tolerance Test
MODY	Maturity-onset diabetes of the young
MRSD	maximum recommended starting dose
NCDS	Novartis Clinical Data Standards
NOVDD	Novartis Data Dictionary
PA	Posteroanterior
PBMC	Peripheral blood mononuclear cell
PC	Personal computer
PCR	Polymerase chain reaction
PCR	Protein-creatinine ratio* as 1 abbreviation is common for 2 meanings these are clarified in text
PD	Pharmacodynamic(s)
PIP	Pediatric investigation plan
PK	Pharmacokinetic(s)
PSD	Premature subject discontinuation
PT	Prothrombin time
RBC	Red blood cell(s)
RDC	Remote Data Capture
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SC	Subcutaneous
sCR	Serum creatinine
SD	Standard deviation
SOM	Site Operations Manual

SUSAR	Suspected Unexpected Serious Adverse Reactions
T1DM	Type 1 Diabetes Mellitus
TBL	Total bilirubin
TD	Study Treatment Discontinuation
Tfh	Follicular helper T cells
TP	Therapeutic protein
ULN	Upper limit of normal
ULQ	Upper limit of quantification
WBC	White blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Cohort	A specific group of subjects fulfilling certain criteria.
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial.
Dosage	Dose of the study treatment given to the subject in a time unit (*e.g.* 100 mg once a day, 75 mg twice a day).
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (*i.e*. prior to starting any of the procedures described in the protocol).
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Hybrid Trial Design	Flexible model incorporating both on-site (traditional site based) and off-site (decentralized) elements within the same study design
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system.
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the subject's home.
Off-site Healthcare Professional (OHP)	A qualified healthcare professional, such as a nurse, who performs certain protocol procedures for the subject in an off-site location such as a subject's home.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease.
Subject	An individual with the condition of interest
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment.
Screen Failure	A subject who is screened but is not treated or randomized.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.

Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy.
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date.
Subject	A trial participant (can be a healthy volunteer or a subject).
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
SUSAR	Serious, Unexpected and Suspected Adverse Reaction.
Telemedicine	Electronic information and telecommunications technologies (both video-based and audio-only) to facilitate the delivery of health care and health related education where subject and health care provider (HCP) are not in the same location.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data.

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Protocol summary

Protocol number	CCFZ533X2207
Full Title	Investigator- and subject-blinded, randomized, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics and efficacy trial of CFZ533 in pediatric and young adult subjects with new onset type 1 diabetes (T1DM).
Brief title	Study of safety and efficacy of CFZ533 in type 1 diabetes pediatric and young adult subjects.
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to enable the development of CFZ533 in new onset T1DM and to inform the design of subsequent confirmatory studies.
Primary Objective(s)	• To evaluate safety and tolerability of CFZ533 in new onset T1DM by assessing adverse events (AEs) and standard safety labs. • To evaluate the treatment effect of CFZ533 on pancreatic beta cell function in new onset T1DM after 52 weeks, by assessing stimulated C-peptide AUC by mixed meal tolerance test (MMTT).
Secondary Objectives	• To evaluate the pharmacokinetics (PK) of CFZ533 in new onset T1DM by measuring free CFZ533 plasma concentrations at baseline, during treatment and follow up period. • To evaluate the treatment effect of CFZ533 on full remission by HbA1c ≤6.5% (48 mmol/mol) and no exogenous insulin use, or partial remission by insulin dose adjusted HbA1c (IDAA1c) ≤9.0 *or* HbA1c < 7.0% (53 mmol/mol) with total daily insulin dose of <0.5 units /kg /day, at week 52 in new onset T1DM. • To evaluate durability of effects after washout of CFZ533 on pancreatic beta cell function by assessing stimulated C-peptide AUC by MMTT at week 72 in subjects with new-onset T1DM.
Study design	CCFZ533X2207 is a Phase 2, non-confirmatory, investigator- and subject-blinded, randomized, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of CFZ533 on preservation of residual pancreatic β-cell function in new onset T1DM in pediatric and young adult subjects. The study is planned for 44 subjects randomized and assuming ~18% dropout rate, 36 subjects for primary efficacy (at 52 weeks) and safety endpoints (at 72 weeks). Eligible subjects will be enrolled and randomized to active or placebo in a 2:1 ratio, stratified by age at first screening visit (≥18 to 21 years, followed by ≥12 to <18 years). The study timeline includes a screening period of approximately 8 weeks, a baseline period of 2 weeks, a treatment period of 52 weeks and a follow-up period following last dose of CFZ533 of 20 weeks. This study will be the first study to evaluate CFZ533 in a pediatric population in any indication. Thus, enrollment will be staggered to evaluate safety and

	tolerability on a rolling basis and enable gradual enrollment of younger age and lower weight groups. The PK profile of CFZ533 will be evaluated throughout the study (Month 3, 6 and 9). Dosage adjustments may be introduced based on emerging PK data. The current assumptions considered allometric scaling based on body weight. The PK assumptions will be confirmed using population PK modelling. Sequential enrollment by age and body weight (BW) categories include: • Cohort 1: age ≥15 to ≤21 years (older adolescents to young adults), body weight ≥40 kg to ≤125 kg. • Cohort 2: age ≥12 to ≤21 years (adolescents to young adults), body weight ≥30 kg to ≤125 kg. Before opening a subsequent cohort, safety and tolerability data from at least 6 subjects in Cohort 1 must be reviewed and deemed safe to proceed by the Sponsor and Lead Investigator.
Population	The study population will be comprised of newly diagnosed T1DM pediatric and young adult subjects. Forty-four subjects between the ages of 12 and 21 (inclusive) will be enrolled and randomized in the study in sequential order as outlined in the study design.
Key Inclusion criteria	• Newly diagnosed auto immune T1DM confirmed by at least one positive auto antibody: glutamic acid decarboxylase (anti-GAD), protein tyrosine phosphatase-like protein (anti-IA-2); zinc transporter 8 (anti-ZnT8); islet cell (cytoplasmic) (anti-ICA). • Peak stimulated C-peptide levels ≥ 0.2 nmol/L (0.6 ng/mL) following standard liquid MMTT within one month prior to randomization. • Study participants are to complete all recommended inactivated (killed) immunizations at least 2 weeks prior and attenuated (live) immunizations at least 8 weeks in accordance with local immunization guidelines and prior to first dose with study drug. • Able to receive the intravenous (IV) loading dose of CFZ533 within 56 days of diagnosis (which may be extended to 100 days in the event a screening assessment needs to be confirmed or for vaccine administration).
Key Exclusion criteria	• Diabetes forms other than autoimmune T1DM such as maturity-onset diabetes of the young (MODY), latent autoimmune diabetes of the adult (LADA), acquired diabetes (secondary to medications or surgery), type 2 diabetes. • Diabetic ketoacidosis within 2 weeks of the baseline MMTT test. • History of polyglandular autoimmune disease, Addison's disease, pernicious anemia, celiac sprue. • History of immunodeficiency disorders, such as HyperIgM syndrome; history of recurrent infections suggestive of immune deficiency disorders. • Major dental work within 8 days prior to CFZ533 intravenous loading dose; febrile illness within 48 hours prior to first dose. • Use of other investigational drugs or use of immunosuppressive agents at the time of enrollment, or within 5 half-lives of enrollment, or until the

	expected pharmacology effect has returned to baseline, whichever is longer; or longer if required by local regulations.
	• Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a subject. Subjects with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA should be excluded
	• Evidence of Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Herpes simplex virus (HSV), or coronavirus SARS-CoV-2 by viral load above laboratory threshold or only positive IgM serology in the absence of positive IgG, suggestive of active or recent infection.
	• Any of the following abnormal laboratory values at screening:
	  • total white blood cell count (WBC) outside the range of 1,500-15,000/mm^3 (1.5-15.0 x 10^9/L).
	  • neutrophil count (<1500/mm^3) (<1.5 X 10^9 / L).
	  • lymphocyte count <500/mm^3 (<0.5 X 10^9 / L).
	  • hemoglobin (Hgb) <8.0 g/dL.
	  • platelets <100,000/mm^3 (<100 x 10^9/L).

Study treatment	Subjects will be assigned to one of the 2 treatment arms in a ratio of 2:1, CFZ533 or matching placebo, stratified by age at first screening visit (≥18 to 21 years and ≥12 to <18 years). For the single intravenous (IV) loading dose, all subjects receive the same dose: CFZ533 30 mg/kg IV on Study Day 1. For the subcutaneous (SC) maintenance regimen, a fixed CFZ533 dose by body weight (BW) category will be administered every week from Day 8 (Week 1) up to Week 51 (last dose). Last dose is administered at CCI and the end of the treatment assessment will be performed at Week 52. • BW category II (≥30 to <50 kg): 195 mg (1 injection of 1.3 mL) SC weekly. • BW category III (≥ 50 kg): 300 mg (1 injection of 2 mL, or 2 injections of 1 mL) SC weekly. **note earlier versions of the protocol included body weight in the 20 to 30 kg range, which would have been in a Body weight Category I. This lower body weight category is no longer included and explains the nomenclature of weight categories II and III only.*
Efficacy assessments	• C-peptide during MMTT.
Pharmacodynamic assessments	• Soluble CD40 (sCD40) concentrations in plasma (target biology and target engagement in whole blood) at baseline, during treatment and follow-up period.
Pharmacokinetic assessments	• CFZ533 concentrations in plasma (at baseline, during treatment and follow up period).
Key safety assessments	• AE and serious adverse events (SAEs). • Vital signs, height and weight. • Physical exam. • Tanner staging (only for subjects aged 12-17 years, inclusive).

	• Hematology. • Chemistry. • Urinalysis. • Thyroid function tests. • Viral load and serology. • Lymphocyte class T cells, B cells, and NK cells (TBNK). • ECG evaluation. • Pregnancy and assessments of fertility.
Other assessments	Commercially Confidential Information
Data analysis	Primary efficacy analysis will be conducted based on all randomized subjects reaching the Week 52 visit or discontinued early. For all analyses, subjects will be analyzed according to the study treatment(s) received. The safety analysis set will include all subjects that received any study treatment. The PK analysis set will include all subjects with at least one available valid CFZ533 concentration measurement, who received any study drug and with no protocol deviations that impact PK data. The PD analysis set will include all subjects with available PD data and without major protocol deviations that affect the PD outcome.
Key words	Type 1 diabetes mellitus (T1DM), pediatric, juvenile

1 Introduction

1.1 Background

Type 1 diabetes is a life-threatening autoimmune disease with no cure.

Insulin replacement is life-saving and treats the symptoms of type 1 diabetes mellitus (T1DM) but does not alter disease progression. Around 132,600 children and adolescents develop T1DM each year worldwide (Cho et al 2018) and prevalence is rising, with an estimated 3% increase per year. The number of children with T1DM in Europe is projected to triple between 2010 and 2050 (Imperatore et al 2012). New onset T1DM can occur at any age but peak incidence occurs between the ages of 5 and 15 years. Life expectancy is reduced by 12 years on average compared to the general population (Secrest et al 2010). Long-term micro and macrovascular complications continue to be burden for T1DM patients, their families, and for society (Secrest et al 2010).

Pediatric compared to adults patients are at increased risk for acute complications of T1DM, diabetic ketoacidosis and severe hypoglycemia (a side effect of insulin); and for death from these complications (Wherrett et al 2015). Pediatric patients are also at higher risk for neurocognitive changes due to chronic hyperglycemia and severe hypoglycemia (Wherrett et al 2015). Transformative therapies are urgently needed to improve clinical outcomes for children with T1DM.

Glycemic control is the most important factor for reducing the long-term microvascular complications in T1DM of retinopathy, nephropathy, and neuropathy as shown in the landmark Diabetes Control and Complications Trial (DCCT) (Diabetes Control and Complications Trial Research Group 1994, Steffes et al 2003). Yet, despite technological and clinical advances in the standard of care of T1DM, the majority of patients and particularly pediatric patients are not meeting glycemic targets. The mean glycated hemoglobin (HbA1c) level in adolescents was 9.0% (75 mmol/mol), well above guideline driven target for youth <7.5% (<58 mmol/mol) and close to levels in the 1980's (Miller et al 2015). T1DM patients with residual β-cell function, as measured by stimulated C-peptide > 0.2 nmol/L, achieve better glycemic control, are protected from severe hypoglycemia with insulin therapy (62% reduction), and have a 79% lower risk for progression of retinopathy and long-term complications (Diabetes Control and Complications Trial Research Group 1994; Steffes et al 2003). Therefore, therapies preserving residual β-cell function have potential to improve glycemic control and avoid serious short and long complications associated with T1DM.

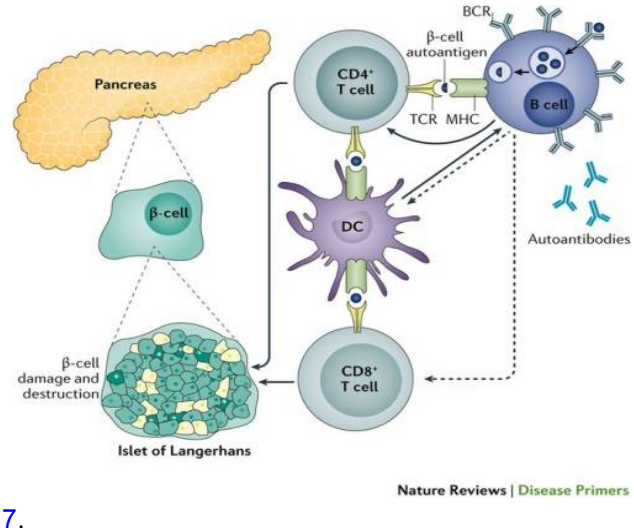
T1DM disease onset and progression over the first year are markedly more aggressive in pediatric versus adult patients. Pediatric patients with new onset T1DM present with lower residual β-cell function at disease onset and a more rapid decline in remaining β-cell function over the first year when compared to adults. At 1 year of T1DM, pediatric patients lose about 50% of residual beta cell function while adults lose about 15% (Greenbaum et al 2012). Pediatric patients with new onset T1DM have more severe insulitis (inflammation of the pancreatic β-cells) with increased infiltration of B lymphocytes, including aggressive CD20+ B lymphocytes in pancreatic islets. Yet pediatric patients with new onset T1DM appear to be more responsive to immune modulatory interventions such as rituximab and teplizumab in randomized control trials (Woittiez and Roep 2015). Collectively, these observations support a

different pathobiology and disease kinetics between adults and pediatrics, such that interventions in one age group may not translate to the other in clinical trials.

Overview of auto-immune mechanisms in type 1 diabetes

T1DM develops when pathogenic autoreactive immune cells invade the pancreatic islets, and damage insulin producing in β-cells (Katsarou et al 2017) (Figure 1-1). Insulitis is a hallmark of aggressive disease and has higher prevalence in pediatric patients (Leete et al 2016). T1DM is generally considered a T lymphocyte-mediated autoimmune disease as islet autoantibodies are currently the best available biomarker for autoimmunity and disease risk, but are not considered pathogenic. These antibodies are produced by autoreactive B cells, in which activation is largely dependent on the function of follicular B helper T cells (also known as follicular helper T cells or Tfh) and thus the role of B lymphocytes in T1DM disease pathogenesis is being increasingly recognized (Bottazzo et al 1983). This is partly due to the efficacy of rituximab, an anti-CD20 antibody that broadly depletes B lymphocytes, in delaying disease progression in patients with new onset T1DM (Pescovitz et al 2014). One course of rituximab reduced circulating Tfh cells in T1DM with disease duration of < 2 years, p< 0.01 (Xu et al 2013), Islet antigen reactive B lymphocytes act as antigen-presenting cells (APC), which prime and activate diabetogenic CD4+ T effector and CD8+ T lymphocytes. Pediatric patients with new onset T1DM or autoantibody-positive at-risk children with impaired glucose tolerance have multiple features indicative of an aggressive auto-immune process including (1) a higher frequency of activated Tfh lymphocytes compared to controls, Tfh being critical activators of autoreactive B lymphocytes; (2) multiple auto-antibody specificities (markers of beta-cell autoimmunity) and elevated IFNγ (marker of inflammation) compared to adults with T1DM; and (3) evidence of insulitis with increased B lymphocyte infiltrates and increased numbers of CD20+ B lymphocytes in the pancreas, all hallmarks of aggressive inflammation (Viisanen et al 2017, Leete et al 2016). Overall these observations implicate an important role of auto-reactive pathogenic B lymphocytes in the pathophysiology of aggressive T1DM.

Figure 1-1 Immune-mediated mechanisms in type 1 diabetes



From Katsarou et al 2017.

Role of the CD40 Pathway in type 1 diabetes

CD40 is a transmembrane glycoprotein in the tumor necrosis factor receptor superfamily expressed by immune and non-immune cells. CD154, the ligand for CD40 (also known as CD40L) is also widely expressed (Peters et al 2009). CD40-CD154 interactions mediate T-dependent B cell responses and is important for priming and activation of CD4+ autoreactive T lymphocytes and CD8+ cytolytic T lymphocyte. Aberrant expression of MHC class II molecules on endocrine tissue may contribute to the initiation of autoimmune disease.

CD40 is upregulated upon antigen presenting cell (APC) activation, and the interaction between CD40+ APCs such as B lymphocytes with naïve T lymphocytes induces the production of CD154 on the surface of these lymphocytes. CD40 signaling may also function at the level of T cell selection in the thymus, and enhance production of pro-inflammatory cytokines which can further influence T cell differentiation into active Th17 cells (Iezzi et al 2009). Thus, CD40 plays a pathogenic role in T1DM, and disrupting CD40-CD154 interactions or activity may be an effective autoimmune therapeutic strategy for this disorder.

Non-clinical data strongly support a role for the CD40-CD154 costimulatory pathway in defective tolerance in autoreactive T lymphocytes, development of insulitis and diabetes (Price et al 2014). The non-obese diabetic (NOD) mouse, a model of spontaneous autoimmune diabetes, shows functional tertiary lymphoid structures with ectopic germinal centers (GC) in early pancreatic lesions during progression from peri- to intrainsulitis (Astorri et al 2010). Data in the NOD mouse supports a causative and functional role of the CD40-CD154 pathway in disease pathogenesis including:

- CD40-CD154 is necessary for the initiation of insulitis and diabetes in the NOD mouse (Balasa et al 1997).
- NOD mice deficient for CD154 (CD154-KO/NOD) do not develop insulitis or diabetes (Eshima et al 2003).
- CD 40+CD4+T lymphocytes from the NOD are highly pathogenic and readily transfer progressive insulitis and diabetes (Wagner 2017).
- Blockade of CD40 at different stages of disease delayed disease progression, prevent hyperglycemia and reverse new-onset diabetes (Vaitaitis et al 2014, Vaitaitis et al 2017).
- Blockade of CD154 restores dendritic cell-mediated induction of tolerance in autoreactive CD4+ T lymphocytes (Price et al 2014).
- In the RIP-CD154 transgenic model, β cell-specific expression of CD154 mediates immune activation, insulitis, and diabetes on a non-diabetes-prone background (Haase and Markholst 2007).
- Transient blockade of BAFF, a B lymphocyte survival and maturation factor provides protection against early and late stage T1DM in NOD mice by enriching in B lymphocytes that suppress T cell proliferation (Wang et al 2017).

In summary, non-clinical data provides compelling evidence that multiple CD40+ immune cell types contribute to insulitis and pathogenesis of T1DM.

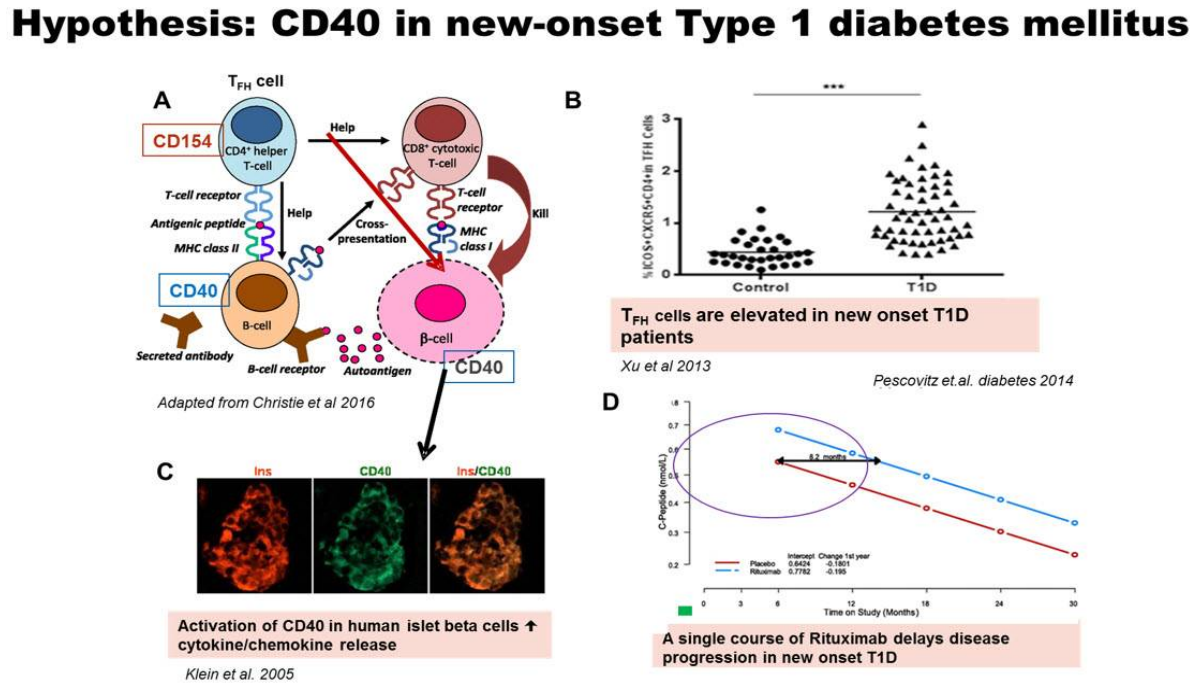
Clinical data in patients with T1DM also support a role for the CD40-CD154 costimulatory pathway disease pathogenesis (Figure 1-2). Pediatric patients with new onset T1DM have 2-fold

elevated levels of soluble CD40 (sCD40) (Chatzigeorgiou et al 2010b). T1DM patients with disease duration from diagnosis between 1 and 6 months exhibit the highest levels of sCD40. Elevated levels of sCD40 levels in pediatric patients with new onset T1DM are positively associated with HbA1c, hyperglycemia, and inflammatory markers, CRP, IL-6 and MMP-9 (Chatzigeorgiou et al 2010b, Chatzigeorgiou et al 2010a). Although there are no data for sCD40 in adults with T1DM, for those with disease duration over 1 year and with no complications, circulating CD154 concentrations are increased compared to age- and sex-matched healthy controls (Devaraj et al 2006). Together these observations point to a role for the CD40-CD154 pathway in T1DM in general and in pediatric new onset T1DM that could respond to an intervention with an anti-CD40 monoclonal antibody like CFZ533.

Mechanistically, CD40-CD154 interactions may contribute to autoimmune T1DM by the priming of autoreactive T cells via activated diabetogenic B lymphocytes in target tissue, *e.g.* pancreas and pancreatic lymph nodes. Human pancreatic β-cells express functional CD40 receptors that release inflammatory cytokines and chemokines upon activation with CD154, which could contribute to insulitis in new onset T1DM (Klein et al 2005).

Collectively these data indicate a complex role for the CD40-CD154 pathway and pathogenic B-T lymphocyte interactions in the pathogenesis of T1DM, justifying the evaluation with CD40 blockade with CFZ533, an anti-CD40 antibody, in new-onset T1DM patients. It is therefore hypothesized that blockade of CD40-CD154 activation with CFZ533 in patients with new-onset T1DM could halt the immune-mediated β-cell destruction and the insulitis leading to preservation of residual β-cell function.

Figure 1-2 Putative role of the CD40-CD154 co-stimulatory pathway in type 1 diabetes



A Schematic diagram of the complex role of CD40-CD154 in various aspects of T1DM pathophysiology (Adapted from Christie 2016). B, Circulating follicular T helper cells are significantly elevated in patients with recent onset T1DM (duration < 2 years) (Xu et al 2013). C, CD40 is expressed in human pancreatic β-cells (Klein et al 2005). D, A single treatment course of rituximab (green bar) in patients with new onset T1DM delays disease progression (Pescovitz et al 2014).

CFZ533 (iscalimab) - a CD40 blocking antibody for type 1 diabetes

CFZ533 (iscalimab) is a fully human, immunoglobulin G1 (IgG1) anti-CD40 antibody that blocks recombinant(r) CD154-induced CD40 signaling and which does not cause depletion of CD40 expressing cell types (*i.e.* Fc-silent).

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The CFZ533 clinical development program consists of completed studies in both healthy volunteers (HVs) and patients. CFZ533 is in clinical development for autoimmune diseases (AID). Additional information can be found in the Investigator's Brochure (IB).

1.2 Purpose

The purpose of this study is to enable the development of CFZ533 in new onset T1DM and to provide clinical data for the design of subsequent confirmatory studies.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate effects of CFZ533 on pancreatic beta cell function in subjects with new-onset T1DM.	• Stimulated C-peptide AUC by mixed meal tolerance test (MMTT) after 52 weeks of treatment.
• To evaluate the safety and tolerability of CFZ533 in subjects with new onset T1DM.	• Adverse events, safety labs.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the pharmacokinetics (PK) of CFZ533 in subjects with new onset T1DM.	• CFZ533 plasma concentrations at baseline, during treatment (Cmax, Tmax after IV administration, and Ctroughs after SC administration) and follow-up period.
• To evaluate durability of effects after washout of CFZ533 on pancreatic beta cell function in subjects with new-onset T1DM.	• Stimulated C-peptide AUC by MMTT at 20 weeks from last dose.
• To evaluate the treatment effect of CFZ533 on remission or partial remission in subjects with new onset T1DM.	• Not requiring exogenous insulin therapy with HbA1c <6.5% (remission) or Insulin dose adjusted HbA1c (IDAA1c ≤9.0) *or* HbA1c < 7.0% (53 mmol/mol) and total daily insulin dose <0.5 units per kg per day at 52 weeks (partial remission).

3 Study design

CCFZ533X2207 is a Phase 2, non-confirmatory, investigator- and subject-blinded, randomized, placebo-controlled study to evaluate the safety, tolerability, PK, and efficacy of CFZ533 compared to placebo on preservation of residual pancreatic β-cell function in new onset T1DM pediatric and young adult subjects.

Newly diagnosed T1DM patients are identified based on American Diabetes Association diagnostic criteria and National Institute for Health and Care Excellence (NICE) (Johnston 2004), and the presence of at least one diabetes-related autoantibody as specified in Section 5. Enrollment in the trial should occur no less than two weeks and within 56 days (8 weeks) from the time of diagnosis and first study drug administration, however this 56 day interval may be extended to 100 days in the event a screening assessment needs to be confirmed or vaccination is required prior to initiation of the study drug (see Sections on Risks Section 4.5 and Screening procedures Section 8.1). Enrollment will be based on both screening and baseline results. The screening and baseline visit(s) may be conducted over 1 or more than one visit depending on the subject's body weight and World Health Organization (Howie 2011) and European Medicines Agency (EMA) recommendations for trial related phlebotomy limits (see Site Operations Manual - SOM for more details).

Forty-four subjects aged 12-21 years with weight between 30 to ≤125 kg, will be enrolled. Two sequential study cohorts (based on age at first screening visit) are planned.

Cohorts are based on descending order of age and weight groups (Figure 3-1).

Sequential enrollment by age and body weight (BW) categories include:

- Cohort 1: age ≥15 to ≤21 years (older adolescents to young adults), body weight ≥40 kg to ≤125 kg.
- Cohort 2: age ≥12 to ≤21 years (adolescents to young adults), body weight ≥30 kg to ≤125 kg.

The screening and baseline periods continue until the first dose of CFZ533 or placebo is administered. Screening and baseline assessments may be conducted over one, two, or more visits but must provide adequate time for subjects and their guardians to consider the risks and benefits and trial burden, adhere to safe phlebotomy limits based on subject weight, and have sufficient time for laboratory reporting of all inclusion/exclusion criteria and safety measures prior to administration of the study drug.

After a screening and baseline period Commercially Confidential Information

subjects eligible for a cohort open for enrollment will be randomized to receive either CFZ533 or placebo (2:1 ratio, stratified by age at first screening visit ≥18 to 21 years and ≥12 to <18 years) for one year, in addition to background standard of care with intensive insulin therapy, Commercially Confidential Information . In case of screening being extended, some screening procedures may need to be repeated, please refer to Site Operations Manual (SOM) for more information.

The treatment includes an initial loading dose of CFZ533 (administered at a dose of 30 mg/kg via a peripheral intravenous (IV) line CCI on Day 1; all subjects receive the same dose in mg/kg) or matching placebo. All subjects will be observed for at least one hour following IV infusion to monitor for any untoward infusion-related adverse reaction. All subsequent doses of CFZ533 (or matching placebo), from Day 8 CCI are administered on a weekly basis by subcutaneous (SC) injections at a dose which is based on body weight (details in Section 4.2). The last dose of the study drug is administered CCI , and the end of the treatment assessment will be performed at Week 52.

A standardized liquid MMTT to assess β-cell function using C-peptide will be performed at baseline, Week 12, 24, 36, 52, and 72 (end of study), during the course of the study, as described in Section 8.2.1. The following diabetes-related endpoints will also be monitored during the study: HbA1c, Commercially Confidential Information

and diabetic ketoacidosis and hypoglycemic events. A study diary must be provided to subjects to report daily dose of insulin administration and glucose values Commercially Confidential Information , whenever possible and for a period of at least approximately 3-10 days. At the baseline visit (prior to first dose), CCI

and instructed to start collecting data

3 to 10 days before the administration of first dose of study drug, with data collection intervals at:

- screening or baseline (prior to first dose),
- after receiving first dose of study drug,
- every 3 months (Weeks 12, 24, 36, and 52 or early drug discontinuation) during the first year of treatment,
- and Week 72 during follow-up, or early termination.
- Any subject enrolled in the study under an earlier version of the protocol which had longer follow up and who is beyond Week 72 when Clinical Study Protocol Amendment 6 is approved, will have an end of study visit at the next scheduled visit.

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Glycemic measures and insulin dosage may be obtained from device records (*i.e.* meter and Commercially Confidential Information glucose and insulin pump downloads for insulin dosing) if available. Date and time of study drug dosing will also be captured in a study diary.

Safety assessments will include height, weight, vital signs, physical examination, ECGs, standard clinical laboratory evaluations of hematology, blood chemistry, urinalysis, viral load and serology, adverse events and serious adverse events. Additional safety assessments for children and adolescents include: Tanner stage, growth velocity, and serial bone ages. Blood samples will also be taken for inflammatory CCI biomarkers at various time points during the study, as indicated in the Assessment Schedule, Table 8-1.

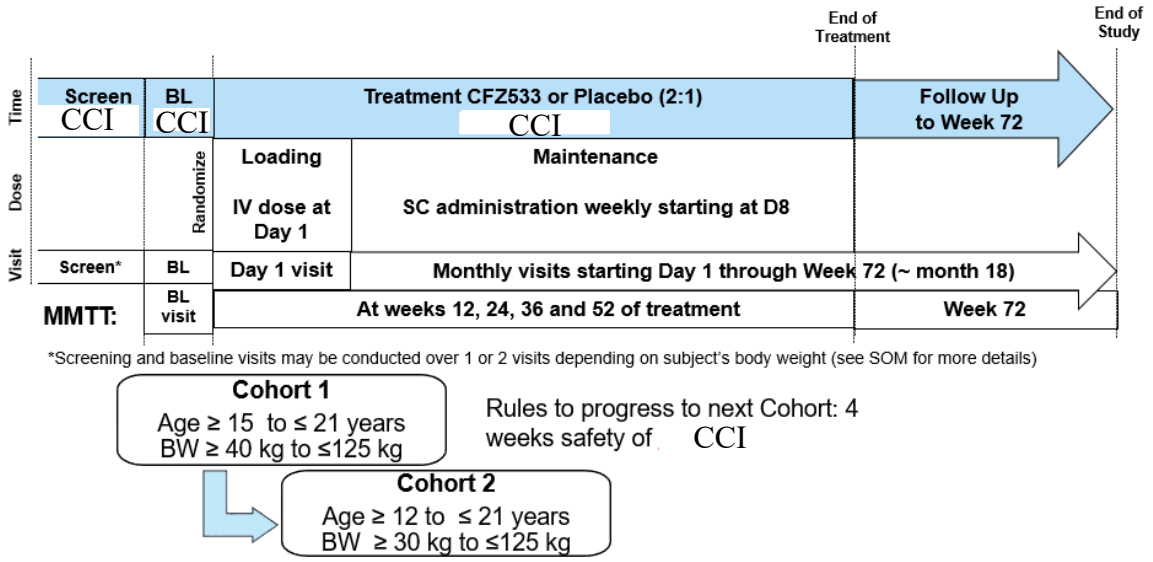
Subjects must be instructed to use their own insulin as this is part of standard of care and not part of the study. Insulin management including dose adjustments will be made by the subject's care provider according to local guidelines and individualized glycemic targets.

Minimum safety monitoring for each subject will be performed at least CCI post-last dose of CFZ533 or placebo, a time when pharmacodynamic response is anticipated to have returned to the subject's baseline. However, subjects will be followed until week 72, 20 weeks post dose, to assess safety and effects on pancreatic β-cell function after stopping the investigational drug.

Reviews of safety and pharmacokinetic (PK) data will be jointly completed by the Sponsor (limited unblinding) and Lead Investigator (blinded) (see Section 6.5 and Section 12.7). The safety evaluation will include all SAEs and AEs, laboratory evaluations, and ECGs. Cohort expansion will be based on the following:

- To open Cohort 2: At least CCI (aged 15 to ≤21 years) of Cohort 1 treated with CFZ533 or placebo CCI along with the safety data for all subjects enrolled up to that point, must be reviewed and deemed satisfactory jointly by the sponsor and Lead Investigator. Assessment of CCI subjects in this cohort, as opposed to CCI in other cohorts, is because existing safety data is more robust for subjects in this age and weight range population.

Figure 3-1 Study Design



3.1 Off-site procedures

A hybrid trial design is planned for this study incorporating a flexible model of both on-site and off-site (remote from clinic, also known as remote or decentralized) visits. The off-site procedures will be utilized in certain countries and sites as determined by Novartis based on national and local regulations. Subjects have the option of participating in one or more off-site visits, based on national and local regulations, investigator discretion, and subject preference. Specific clinical trial procedures that may be performed at an off-site location are defined in Section 8.

One or more of the following elements may be implemented to support off-site visits where allowed by national and local regulations:

- Telemedicine.
- Off-site healthcare professionals (OHP).
- Direct-to-patient shipment of study supplies.
- Direct-to-patient shipment of study treatment (refer to Section 6).
- Electronic Source (eSource) Direct Data Capture (DDC) (refer to Section 3.1.4).

3.1.1 Responsibility of Investigators

Procedures that are performed off-site remain under the oversight of the investigator, who retains accountability for the conduct of all safety and efficacy assessments delegated to an OHP. This includes ensuring the following (including, but not limited to):

- Identification, management and reporting of adverse events and serious adverse events (AEs and SAEs) are performed in accordance with the protocol and applicable regulations.
- Thorough review and approval of the qualifications and experience of the OHP, including an interview where requested, prior to delegating responsibilities to the assigned OHP.

- Source data collected off-site are reviewed and evaluated in a timely manner.
- The investigator or delegate is available to be contacted by the off-site healthcare professionals if any issues or concerns are noted during an off-site visit.
- Where relevant, the Investigator or delegate will be present via telemedicine for a portion of the off-site visit to support the physical examination.

3.1.2 Responsibility of off-site healthcare professional (OHPs)

The OHPs must have the required qualifications, training, and experience to conduct off-site assessments. The OHP are responsible to conduct delegated assessments and collect relevant data at off-site visits in accordance with the clinical trial protocol, International Conference for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and national and local regulations and guidelines.

The OHP will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use OHP that are not provided by Novartis this must be agreed with Novartis before use.

Any issues or safety concerns identified by the OHP will be promptly communicated to the investigator or delegate according to a pre-defined communication plan.

3.1.3 Telemedicine

The sponsor has qualified and contracted a third-party vendor to provide telemedicine platform technology for this study. The selected platform is a validated system complying with relevant ICH E6 GCP guidelines. Trial subjects can interact with site personnel using online communication tools built into the platform, enabling the following capabilities:

- Secure videoconferencing which allows the subject, OHP, and site personnel to be connected.
- eSource Direct Data Capture (DDC) (see Section 3.1.4).

3.1.4 Data flow

Investigators will have continuous, near real time access to all subject records in the eSource Direct Data Capture (DDC) platform, with the ability to add, edit, review and sign forms within subject records.

The OHPs will enter data at off-site visits into electronic source documentation forms contained in an eSource DDC platform, which has been validated for use in clinical research. Where paper source documentation exists, images of documentation will be uploaded electronically into the same platform as certified copies, and the original documentation will then be sent to the trial site for review and retention.

Data contained in the platform are available to site and sponsor staff based on role-based access and permissions, and will be stored in a robust and secure cloud-based back-end environment. Only sponsor staff who are responsible for field monitoring activities will have access to the source data, which may include some personally identifiable information, consistent with the access that is provided to a field monitor in a traditional on-site clinical trial model.

Relevant data in the eSource DDC platform may be manually transcribed by site staff into the study electronic data capture (EDC) system. Alternatively, the platform allows for configuration that enables data to be automatically exported into the study EDC system.

Certified copies of data in the eSource DDC platform will be provided to investigator and/or site personnel, and promptly and regularly uploaded into the subject's medical records, according to local guidelines.

The platform maintains a secure, GCP-compliant audit trail and uses measures such as encryption and access controls to ensure that data privacy and security is maintained. Additional details will be contained in a separate Off-Site Study Operational Manual.

4 Rationale

4.1 Rationale for study design

The study employs staggered inclusion of subject cohorts by age and body weight in order to facilitate enrollment of younger subjects in a gradual manner based on emerging safety and tolerability in previous cohorts.

Cohorts are designed according to a descending age range (for the lower age limit). Lower age cut-offs per cohort are selected based on International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Topic E11 2001 approximate stages of development: Age 15-21 years late adolescent to young adult; and age 12 to <18 years adolescent. Body weight thresholds are based on anticipated weight boundaries for age (CDC 2001), noting that permitted weight ranges may impact age of each cohort.

The first cohort will be used to evaluate safety as lower age and weight subjects are exposed in the second cohort. CCI of exposure per age and body-weight cohort will be required before a decision to open the next cohort can be made. CCI considered long enough to observe any potential acute/immediate effects (infusion site reactions, allergic reactions, delayed type hypersensitivity reactions, etc.) and mid-term effects. Effects which may occur at a later point will be monitored throughout the study at any point in time and for all cohorts.

Dosing by body weight categories for the subcutaneous doses (lower body weight receive a lower fixed dose) is justified to provide similar exposures throughout the body weight range (see Section 4.2).

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Age: Age range of 12 to 21 years. Cohorts advance from Cohort 1 of young adult to late adolescents (ages ≥15 to ≤21 years) to Cohort 2, comprised of young adult through adolescents (ages ≥12 to ≤21 years). The age range enables enrollment of young adult and adolescent subjects in whom new onset T1DM frequently occurs.

The upper age limit of 21 years is selected because the severity of T1DM at diagnosis and T1DM progression in new onset T1DM up to this age are reported to be similar to that of adolescents (Hao et al 2016).

The lower age limit of 12 years is selected because the disease is more aggressive in children and adolescents, and they may be more likely to respond to treatment (Greenbaum et al 2012, Woittiez and Roep 2015). In addition, 12 years of age provides ample time for immune system development and maturation, and vaccinations, which both occur generally by the approximate age of 6 years:

- The immune system is considered fully competent by age 6 years for T lymphocyte subsets (for *e.g.* CD4+, CD8+) and B lymphocyte subsets (for *e.g.* absolute counts, percentages of naive, isotype switched, and non-isotype switched memory B cells (Shearer et al 2003, Simon et al 2015, Huck et al 2009). Immunoglobulin levels, especially IgM and IgG plateau by age 6-8 years (Thomas 2012).
- Childhood immunization schedules are largely completed by age 6 years for primary and major booster immunizations consistent with maturation of the immune system.

Investigator- and subject- blind design: avoids bias in treatment allocation, causality assessment, and reporting of adverse events. Limited unblinding of the lead investigator (*e.g.* at safety reviews) could improve the accuracy of safety-related decisions. Novartis will have limited unblinding so as to enable rapid, accurate and effective safety evaluation, and because this trial is non-confirmatory.

Placebo control: CFZ533 treatment and placebo will be administered on top of standard of care. First, placebo control is justified as there is no available active comparator for disease modification in T1DM. Second, placebo control provides a comparison group for safety/tolerability and pharmacodynamic endpoints. Concomitant medication and devices to treat the underlying disease diabetes (*e.g.* insulin, pen or pump) will be allowed in the active and placebo groups. Placebo comparator is required to understand the rate of progression of the underlying disease in the study cohort meeting specific inclusion/exclusion criteria and to distinguish treatment-related adverse events from underlying disease or study procedures.

Parallel two arm design: Allows for valid treatment group comparison between active and placebo. As new onset disease is required, sequential trial designs would be ineffective.

Randomization: Decreases the chance of an imbalance in subject characteristics (for example age, BMI, or duration of T1DM) between treatment groups, as there may be differences in pancreatic β-cell function at presentation of T1DM, rate of decline of residual β-cell function early after diagnosis, and severity of autoimmunity at different ages.

Treatment allocation 2:1 (2 active, 1 placebo) enables evaluation of safety of CFZ533 (first-in-pediatrics) and assessment of the risk-benefit of CFZ533 in pediatric subjects with new onset T1DM, optimizing exposure to obtain safety data for CFZ533 and minimizing exposure to placebo with attendant study burden.

Treatment duration: One year of treatment is required to be able to differentiate potential drug effect on reduction in β-cell function (slowing of the decline) from the natural disease progression, over a clinically relevant duration of time (Ehlers 2016).

Follow-up duration: Subjects will be followed CCI from the last dose of study drug to ensure health during drug pharmacokinetic and pharmacodynamic elimination. Follow-up observation CCI from the last dose of study drug permits assessment of the elimination of CFZ533 down to plasma levels that are expected to have no pharmacodynamic (PD) effects in tissues, and safety monitoring. Up to 20 weeks of follow-up is planned (with last dose of CFZ533 or placebo administered CCI), which permits monitoring of durability of effect on the primary endpoint of β-cell preservation, approximately 20 weeks post treatment.

4.1.1 Rationale for choice of background therapy

Subjects with T1DM require insulin therapy to avoid the life-threatening complication of diabetic ketoacidosis. Multiple insulin preparations are available with differing half-lives and dosing schedules may vary to cover daily basal and meal-related insulin requirements. Insulin may be administered by multiple daily injection or continuous subcutaneous insulin infusion via insulin pump. Therapeutic approaches to achieve individualized glycemic targets will be permitted with adjustment in order to achieve to local, provider, and subject goals. CFZ533 or placebo will be administered in the setting of good medical care.

4.2 Rationale for dose/regimen and duration of treatment

Overview of dose rationale: The CFZ533 dosing approach is in line with the allometric scaling assumptions and is predicted to ensure consistency of exposure and consequently comparable immunosuppression in a broad population of treated pediatric T1DM patients independent of body weight. Allometric scaling, based on a power law relationship between body weight and pharmacokinetic parameters, is widely used to predict pharmacokinetics of monoclonal antibodies; the emerging CFZ533 pharmacokinetic data from adult populations are in line with these allometric assumptions and body weight appears to be a good predictor of plasma pharmacokinetics of CFZ533.

The dosing regimen in this trial includes an initial intravenous loading dose to fully saturate the CD40 binding sites followed by a body weight adjusted subcutaneous maintenance dose CCI . The recommended body weight-adjustments aim to provide consistent plasma exposures for all treated young adult and pediatric subjects in this study (Figure 4-1).

While the maintenance subcutaneous doses are adjusted based on three predefined body weight categories, the initial intravenous loading dose (mg) is individualized based on the body weight of the individual subject. All subjects in the study will receive the weight based intravenous loading dose of 30 mg/kg. For example, the total intravenous loading dose for a hypothetical 70 kg subject will be 2100 mg (30 mg/kg x 70 kg) while a lighter subject with body weight of 30 kg will receive a lower total intravenous loading dose of 900 mg (30 mg/kg x 30 kg).

Dose rationale: The dosing rationale for CFZ533 in new onset T1DM subjects is based on exposure, safety and tolerability data from trials with CFZ533 in:

- Kidney transplant (kidney Tx; Study CCFZ533X2201-Part 2),
- Primary Sjögren's Syndrome (pSS; Study CCFZ533X2203),
- Graves' disease (GD; Study CCFZ533X2205),

- Myasthenia gravis (MG; Study CCFZ533X2204),
- Rheumatoid arthritis (RA) subjects (first in human Study CCFZ533X2101),

and based on efficacy data in kidney transplant, Primary Sjögren's Syndrome, and Graves' disease.

The CFZ533 dosing regimen includes,

- A body weight-adjusted intravenous (IV) loading dose of 30 mg/kg on Day 1 for all subjects in the trial, followed by
- A weight-tiered fixed subcutaneous (SC) dose administered weekly from Day 8 (Week 1) to CCI (last dose), which is based on the following body weight categories,
  - Body weight Category II* (≥30 to <50 kg): 195 mg (1 injection of 1.3 mL),
  - Body weight Category III* (≥ 50 kg to ≤125 kg): 300 mg (1 injection of 2 mL or 2 injections of 1 mL).
    *note earlier versions of the protocol included body weight in the 20 to 30 kg range, which would have been in a Body weight Category I. This lower body weight category is no longer included and explains the nomenclature of weight categories II and III only.

The CFZ533 IV loading dose will be administered at the Investigator site.

The CFZ533 SC weekly dose (195 or 300 mg) will be defined based on the body weight of the subject recorded every 3 months at site visits on Day 1, Day 85/Week 12, Day 169/Week 24, Day 253/Week 36 and Day 337/Week 48 to account for body weight gain or loss during the treatment period. Last dose is administered CCI and the end of the treatment assessment will be performed at Week 52. CFZ533 Weekly SC doses may be administered at home or at Investigator site. Every effort should be made to respect the weekly schedule and the protocol specified visits. Compensatory doses must be administered at the discretion of the Investigator, on-site only, and not at an off-site visit. See Section 6.1 for instructions when a dose of the investigational drug is delayed or missed, and when a dose is considered compensatory.

Body weight Categories (II, and III) differ from Cohort age based anticipated weights, but are designed to maintain comparable exposure across the weight ranges anticipated in the trial.

Rationale for the intravenous (IV) loading dose on Day 1

The CFZ533 30 mg/kg IV loading dose on Day 1 is predicted:

- To rapidly saturate CD40 receptors in target tissues (*i.e.* pancreatic lymph nodes) and minimize the CD40-mediated elimination of CFZ533 in conditions early after diagnosis where the aggressiveness of the disease (including insulitis, B- and T-lymphocytes infiltration in pancreatic islets, active ectopic germinal centers) is greatest and likely to be associated with high tissue CD40 expression,
- To rapidly block the aggressive autoimmune destruction of residual β-cells, insulitis and local infiltration of pathogenic auto reactive B lymphocytes.

CD40 expression in new onset T1DM patients

Patients with autoimmune diseases (including T1DM) generally present with increased CD40 expression in target tissues and elevated serum/plasma soluble CD40 (sCD40; shed receptors) levels.

In T1DM patients, data on tissue CD40 levels, distribution and turnover in the pancreas and pancreatic lymph nodes are not available. As well, the quantitative relationship between plasma sCD40 and tissue CD40 levels is unknown. Nevertheless, elevated plasma sCD40 levels are assumed to reflect elevated expression of CD40 in target tissues.

In Chatzigeorgiou et al (2010a),

- Pediatric T1DM patients had significantly higher plasma sCD40 levels (93 pg/mL) compared to healthy controls (66 pg/mL), which were associated with elevated plasma interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9) and CRP levels.
- Urine sCD40 levels were also elevated in T1DM compared to healthy controls: 335 pg/mL and 150 pg/mL, respectively, suggesting that the elevated plasma levels of sCD40 in these patients reflect increased CD40 production rather than diminished kidney excretion.
- Upregulation of cellular CD40 (peripheral blood mononuclear cells) was also observed and was positively correlated with plasma sCD40, IL-6, CRP as well as hemoglobin A1c (HbA1c).
- Plasma and peripheral blood mononuclear cell (PBMC) CD40 levels appear to be elevated in pediatric patients with T1DM, and positively correlate with inflammation.

In Chatzigeorgiou et al (2010b), plasma CD40 concentrations were also significantly higher in diabetic patients than in healthy controls (about 110 pg/mL vs. 55 pg/mL) and correlated positively with HbA1c. Moreover, for patients with disease duration < 1 month, 1-6 months, or > 6 months, plasma CD40 was about 75, 190 and 88 pg/mL, respectively.

Achieving saturating and efficacious conditions in pancreatic islets at start of treatment (dosing to be within 56 days of diagnosis which may extend to within 100 days of diagnosis in the event a screening assessment needs to be confirmed or vaccination administered) through an IV loading dose is critical for an effective immune intervention to preserve residual β-cell function.

Saturation of CD40 receptors in inflamed tissues

The CFZ533 30 mg/kg IV loading dose is further justified considering that CFZ533 is subject to CD40-mediated drug disposition (or target mediated drug disposition - TMDD; a process in which a significant proportion of the drug (relative to dose) is bound to CD40 receptors and affects CFZ533 clearance).

The extent of TMDD is dictated by the level of CD40 receptors in tissues and the level of saturation of these receptors. Elevated CD40 expression may be associated with a high elimination rate of CFZ533 and loss of target engagement in target tissues if CD40 is not fully saturated.

The loading regimen is expected to provide full CD40-CD154 pathway blockade at start of treatment.

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Failure to saturate CD40 receptors in conditions where CD40 expression in tissues is significantly enhanced can translate in clinical efficacy failure.

This was demonstrated with a competitor anti-CD40 antibody ASKP1240 (bleselumab; Goldwater et al 2013).

Bleselumab was investigated in kidney transplant (Tx) subjects (Phase 2 trial; Harland et al 2017) and in transplanted monkeys (Ma et al 2014).

In the Phase 2 trial with bleselumab, most of the rejections in the calcineurin inhibitor-free arm occurred before Day 60. Commercially Confidential Information

CFZ533 exposures after the 30 mg/kg IV loading dose

The CFZ533 30 mg/kg IV loading dose is expected to reach exposures (including a median Cmax of about 826 µg/mL) which correspond to doses and regimens which have been used in Rheumatoid arthritis (RA) and kidney transplant patients.

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Rationale for the subcutaneous (SC) maintenance regimen

As opposed to the body weight (BW)-adjusted approach for the IV loading dose, the weekly SC maintenance regimen which starts on Day 8/Week 1 up to the last dose on CCI , is based on a fixed SC dose selected according to the following two body weight categories,

- Body weight Category II (30 to <50 kg): 195 mg SC weekly.
- Body weight Category III (≥ 50 kg to ≤125 kg): 300 mg SC weekly.

Assuming a fixed dosing strategy, body weight categories were created to maintain similar exposure levels for all subjects across the body weight range in this study. This is justified based on the anticipated effect of body weight on the clearance of CFZ533. If the same fixed dose would have been applied across the body weight range in this study, lower body weight subjects would have been overexposed. This is typical for a monoclonal antibody like CFZ533 and consistent with allometric principles where a fixed dose strategy is used (Wang et al 2009, Wang and Prueksaritanont 2010).

Two body weight categories are proposed (30 to < 50 kg and ≥ 50 kg to ≤125 kg). This is justified to ensure similar between subject variability within each category and based on similar fold-exposure differences between each boundary within a body weight category CCI

The selected body-weight adjusted maintenance CFZ533 doses of 195 and 300 mg SC weekly for the two body weight categories of pediatric T1DM patients, are expected to provide steady-state exposures comparable with the CFZ533 maintenance doses of 600 mg SC every other week in adults. Maintenance doses of CFZ533 up to 600 mg SC every other week are being evaluated across multiple indications as potential future dosing regimens, which may provide the optimal risk-benefit in adult patients treated with CFZ533. This maintenance dosing regimen is being used specifically in the ongoing dose-range finding studies in adult Sjögren's Syndrome (CCFZ533B2201) and *de-novo* kidney transplant patients (CCFZ533A2201) and to date, has not been associated with any major safety concerns. To date, approximately 50 *de-novo* kidney transplant patients have been continuously treated at least one year with CFZ533 600 mg SC every other week.

Weekly as opposed to every other week dosing is being used in this pediatric trial for reduced variability in drug levels, and allows for the reduction of injection volumes, which may increase the comfort of administration and treatment compliance in youth.

In body-weight Category III (≥50 kg body weight) CFZ533 300 mg SC weekly will lead to the predicted typical steady-state trough CFZ533 plasma concentration (Ctrough, ss) CCI Commercially Confidential Information . Similar CFZ533 plasma steady state (ss) Ctrough values are predicted for Category II (body weight 30 to < 50 kg) with CFZ533 195 mg SC weekly.

Predicted CFZ533 plasma Ctrough, ss values in T1DM were already evaluated in ongoing or completed clinical studies with CFZ533 in Primary Sjögren's Syndrome, kidney transplant, Graves' disease and Myasthenia gravis patients, where they were overall safe and well tolerated. Predicted CFZ533 plasma Ctrough, ss values for T1DM patients/subjects in body weight Category III (similar Ctrough,ss are predicted for Category II) are compared to observed trough

concentrations for CFZ533 in previous clinical trials

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Previous experience with the 300 mg weekly SC regimen

The CFZ5533 300 mg weekly SC regimen for T1DM patients with body weight ≥ 50 kg (Category III) has recently been evaluated in Primary Sjögren's Syndrome patients from Study CCFZ533X2203-Cohort 3 (N=25; after an IV loading dose or after a SC loading regimen).

The predicted steady state median CFZ533 trough concentration CCI for T1DM patients/subjects in Category III is:

- similar to the mean trough level observed in Primary Sjögren's Syndrome subjects in Study CCFZ533X2203-Cohort 2 Commercially Confidential Information and

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Similar steady state trough plasma concentrations of CFZ533 are predicted for Category II (195 mg SC weekly) and III (300 mg SC weekly).

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Efficacy

Predicted plasma CFZ533 exposures in T1DM patients/subjects are within observed exposures demonstrated to be efficacious in Primary Sjögren's Syndrome and kidney transplant subjects.

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4.2.1 Rationale for treatment duration and subsequent follow up without continued treatment

Type 1 diabetes is characterized by progressive loss of pancreatic β-cell function. No acceleration in loss is anticipated after discontinuing CFZ533. It is possible that there may be prolonged protection from loss in β-cell function for some time after stopping CFZ533. Whether prolonged protection may occur is being evaluated during the post-treatment follow up period of the trial.

The treatment period with CFZ533 in this study is one year. This is the amount of time generally considered to be the minimum interval necessary to demonstrate a clear preservation of pancreatic β-cell function in the active treatment group compared to the placebo assigned group (Ehlers 2016). Subjects will be followed for an additional 20 weeks post treatment period (up to week 72) to establish the durability of the effect off-treatment. This will potentially inform recommendations for duration of CFZ533 use in clinical care following drug approval.

No treatment beyond 12 months is anticipated at this time. If the drug is effective, then it is important to understand the durability of response to inform future clinical use (*i.e.* to address for what duration of time should the drug be prescribed and when should treatment be discontinued). This important information will be obtained in this study, when both efficacy and safety of prolonged exposure is uncertain.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Placebo is used as control since there are no approved therapies for disease modification in T1DM.

4.3.1 Rationale for diabetes-specific endpoints

C-peptide is a direct measure of beta cell function and sustained C-peptide values reflect preservation of function. In diabetes, preservation of beta cell function is disease modifying. The primary trial endpoint of stimulated C-peptide (area under the curve following MMTT) is aligned with both US and EU regulatory guidance for the determination of the preservation of

beta cell function, recognizing that Health Authorities will require additional clinically meaningful co-primary or secondary endpoints at the time of registration.

Secondary CCI endpoints in this study will help establish the clinical value of preservation of pancreatic beta cell function. These additional measures include:

- Diabetes remission or partial remission including not requiring exogenous insulin therapy with HbA1c <6.5% (remission) or insulin dose adjusted HbA1c (IDAA1c ≤9.0) or HbA1c < 7.0% (53 mmol/mol) and total daily insulin dose <0.5 units per kg per day at 52 weeks (partial remission),
- HbA1c,
- Episodes of severe hypoglycemia,
- Episodes of diabetic ketoacidosis,
- Fasting glucose, 2 hour glucose after mixed meal tolerance test,

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4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

Type 1 diabetes is characterized by progressive loss of pancreatic β-cell function. No acceleration in loss is anticipated after discontinuing CFZ533. It is possible that there may be prolonged protection from loss in β-cell function after stopping CFZ533. Whether prolonged protection may occur is being evaluated during the post-treatment follow up period of the trial.

It is hoped that treatment with CFZ533 will provide a new therapeutic approach to treat or prevent T1DM. There is no established benefit to individual study participants although it is possible that individuals with T1DM participating in the trial who receive CFZ533 will benefit from preserved β-cell function.

Overall, CFZ533 has been safe and well tolerated in clinical trials to date. The available data in subjects in the CFZ533 development program Commercially Confidential Information as reported in the Investigator Brochure Edition 12,

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Clinical safety risks with CFZ533 include:
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- **Class (biologic)-related risks:** hypersensitivity reactions, anaphylactic reactions and immunogenicity.
- **Pediatric-specific safety considerations:** immaturity of the immune system, growth, puberty, blood volume.
- **Study related risks:** venipuncture, injection site reactions.

The safety profile of CFZ533 should be viewed separately for transplant and autoimmune (non-transplant) indications. Kidney transplant is a more severe and complex indication due in part to background immune suppressive therapy per standard of care. Adverse events leading to discontinuation are reported in the transplant trials and not in autoimmune diseases (AID) trials.
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Key differences include that the subjects in the CCFZ533X2207 trial:

1. will not be receiving concomitant immunosuppressive therapy,
2. will be excluded for leukopenia/lymphopenia,
3. will be screened for CMV viral status at study entry, and
4. will be monitored at weeks 16, 32 and 48 for seroconversion (with additional monitoring added in the Protocol V02 amendment).

Potential infection risk

CD40 is important for the development of protective immune responses against a broad range of external pathogens, bacterial, viral, fungal and parasitic in origin. Blockade of CD40 with CFZ533 may impair the immune response to new pathogens but should not affect the preexisting humoral immunity which is expected to provide adequate protection from infections to known pathogens. Once CFZ533 concentrations fall below levels associated with full receptor occupancy, the drug undergoes target mediated drug clearance and the immune system recovers.

There are specific infection risk challenges in the pediatric population (Allen 2016). The potentially immunocompromised child may be at a greater risk of acquiring specific infections compared to their adult counterparts. Several reasons may contribute to this increased infection risk. Multiple infections are more prevalent in younger age groups, such as respiratory viral diseases including respiratory syncytial virus illness (Hall et al 2009), such that infection risk is related to their age group regardless of immune competence. Children have increased likelihood of primary infections as they are still developing their immune repertoire. For example, adult organ transplant recipients are more likely to be partially immune to some

infections, such as CMV and EBV, whereas their pediatric counterparts are not. Primary infections typically are associated with more severe illnesses because of no preexisting host immunity.

Compared with adults, young children are less likely to have received their full series of vaccines and generally tend to be at a greater risk of vaccine-preventable diseases after the onset of immunosuppression. For this reason this study will not enroll children under the age of 6 years, where most primary vaccine series have been administered.

The immune system is mature by age 6 years (Thomas 2012), and immunosuppression is not anticipated to be different across age groups included in this study.

Infections are reported separately for non-transplant studies (healthy volunteers, Rheumatoid arthritis subjects, autoimmune diseases (AID) indications), and for the kidney transplant study where background immune suppressive therapy is universally present as standard of care therapy.

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T1DM patients are not immunosuppressed and the data generated to date in healthy volunteers, and in patients with no or minimal immunosuppression, such as Primary Sjögren's Syndrome are likely to be more relevant: such data also do not suggest an increased infection risk. However, as data are limited, no definitive conclusions can be made and infection remains an important risk for CFZ533 and will be mitigated in the proposed trial.

In autoimmune diseases under investigation, to date, CCI

which can be seen in hyperimmunoglobulin M syndrome, a rare disorder of CD154 (CD40 ligand (CD40L)) deficiency characterized by defective class-switch recombination (CSR), resulting in normal or increased levels of serum IgM associated with deficiency of immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin E (IgE) and poor antibody function.

Potential risk associated with SARS-CoV-2 (COVID-19)

Novartis is committed to supporting the safety and well-being of our study participants, investigators, and site staff. All local regulations and site requirements must be applied in the countries that are affected by the COVID-19 pandemic. Having T1DM does not make patients more susceptible to contracting COVID-19, but the disease may be more severe in patients with diabetes than in those without (CDC 2020). This is largely driven by obesity and type 2 diabetes and there is no current evidence that younger individuals with type 1 diabetes are at increased risk for more severe disease (CDC 2020).

SARS-CoV-2 Vaccination

Study subjects are not specifically mandated to receive COVID-19 vaccination prior to study entry. However, subjects must complete all locally recommended immunizations, including COVID-19 vaccinations where applicable, prior to first dose with study drug and in accordance with local immunization guidelines. Killed/inactive vaccines must be administered at least 2 weeks prior to first dose with study drug. Currently, there are no live, attenuated COVID-19 vaccinations available, but this may be subject to change if new vaccine types are developed. Investigators must be sure to check locally approved vaccine types. Immunization with a live, attenuated vaccine must be completed at least 8 weeks prior to the first dose. Administration of live, attenuated vaccines during treatment is prohibited and should be avoided while receiving CFZ533 (iscalimab) and for at least CCI thereafter.

Vaccination during treatment with CFZ533 (iscalimab) prior to clearance of CFZ533 (iscalimab) from the body is anticipated to result in an insufficient immune response (*i.e.* non-protective antibody titers). Reduced or absent immunization effectiveness may be expected for both live (attenuated) and killed (inactivated) vaccines.

SARS-CoV-2 Testing

Subjects will be tested for SARS-CoV-2, the virus causing COVID-19 disease prior to receiving the study drug. Those with active viral load or evidence of recent infection based on serologic testing (IgM positive, IgG negative) will not be dosed. Retesting is permitted for viral clearance and seroconversion for subjects who have remained asymptomatic or whose symptoms have resolved. It is important for investigators to follow local guidelines for reporting of positive cases. It is also important to recognize that subjects who were not previously infected can be exposed and develop COVID-19 despite previously normal testing. Repeat testing or consult with infectious disease specialist may be warranted. Subjects must be advised to continue social and personal hygiene to reduce infection risk according to local guidance, and to report any signs and symptoms of infection to the Site Investigator immediately. As the COVID-19

situation evolves, investigators must use their best judgement to minimize risk to subjects during the conduct of the study.

Impaired vaccination effectiveness and related-infection risk

Overview: The ability to mount primary and secondary T-cell-dependent antibody responses (TDAR) is expected to be affected by CFZ533. However, the memory B-cell repertoire should remain intact and protective. Antibody concentrations in the blood and existing immune memory are not impacted by CFZ533 in non-clinical and *in vivo* studies. Pre-formed immunity to pathogens and vaccines (circulating antibody titers and plasma cells) is not expected to be affected by exposure to CFZ533. Finally, the effect of CFZ533 on the immune system is reversible; once CFZ533 is cleared, the capability to generate humoral immune responses is restored.

Blockade of CD40 receptors by CFZ533 impairs T-lymphocyte dependent antibody responses (TDAR) to vaccines. CFZ533 plasma concentrations above CCI were associated in non-human primates with complete suppression of germinal center development, and prevented recall antibody responses after Keyhole Limpet Hemocyanin (KLH) vaccinations. Upon elimination of CFZ533 a normal memory antibody response could be mounted in all animals (more details in the Investigator Brochure). In healthy volunteers a single dose of 3 mg/kg (IV or SC) of CFZ533 transiently suppressed anti-KLH responses to the first KLH immunization at CFZ533 concentrations corresponding to full receptor occupancy (RO) in whole blood (RO; ≥90%) for about 3-4 weeks. Anti-KLH primary responses were detected in all subjects as CFZ533 concentration and accompanying receptor occupancy declined. All subjects were able to mount recall responses to a second KLH immunization (administered after loss of RO; details in the IB).

CFZ533 is non-depleting of cells that express CD40, including memory B lymphocytes, which supports rapid functional recovery of immune responses as the compound is being cleared. CFZ533 is not expected to affect plasma cells as they are not believed to express functional CD40 receptors.

The ability to mount a T lymphocyte-dependent primary and memory immune response to vaccines and pathogens is expected to be impaired in subjects with plasma CFZ533 concentrations CCI . The risk to subjects of vaccination ineffectiveness while exposed to CFZ533 is mitigated by eligibility requirements of up-to-date immunizations (per local guidelines) and confirmation of protective serology prior to initial dosing with CFZ533. Mitigation plans for the infection risks to subjects during exposure to CFZ533 was covered previously. Once CFZ533 is cleared, subjects are expected to mount normal primary and secondary immune responses to vaccines and pathogens as CD40 receptor blockade is released.

Pre-formed immunity to pathogens and vaccines (circulating antibody titers and plasma cells) is not expected to be affected by exposure to CFZ533. Plasma cells are long lived and confer long-lasting immune protection to subjects, for example at least 10 years for tetanus toxoid and potentially even longer for measles. Thus, subjects with pre-formed immunity are expected to retain protection against pathogens during exposure to CFZ533.

There is always a risk of infection with new pathogens that have not been previously encountered and for pathogens against which there are no available or commonly used vaccines

in the first world countries where this study will be conducted. Such examples include cholera and typhoid fever for which vaccines are not standard in these countries. Subjects enrolled in the study must be advised against traveling to areas with endemic diseases that they are not vaccinated against, particularly because preventive travel vaccines will not work during exposure to CFZ533. Immunization with live attenuated vaccines is prohibited for eight weeks prior to first dose administration of study drug (Rubin et al 2014) until CCI following the last dose.

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Potential risk of thrombotic events

The risk of thrombotic events with CFZ533 is considered minimal.

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renders an association between CFZ533 and the thrombotic events highly unlikely (Andrassy et al 2004). Finally, thrombosis rates for CFZ533 should be considered versus the rate seen with standard of care in renal transplant trials.

Overall, while anti-CD154 antibodies are clearly associated with a high risk for thrombophilia, both preclinical and clinical data from an extensive Phase 2 clinical program across healthy subjects and patients across different indications have not indicated an associated risk with CFZ533.

Lymphoproliferative risk

A hypothetical risk for lymphoproliferative disorders for some subjects under strong immunosuppression cannot be excluded for CFZ533. Commercially Confidential Information

Additional safety considerations for CFZ533 in a pediatric population

Immune system maturation in pediatrics: The immune system, adaptive and innate, is deemed functionally competent at 6 years of age, and comparable to that of adults. Thus, this study enrolls pediatric subjects anticipated to have a mature immune system.

CD40 and bone growth: There is no indication of an effect of the CD40-CD154 pathway on linear bone growth. Commercially Confidential Information

CD40 and puberty: There is no known role or involvement of the CD40 pathway in puberty.

In general, the risk in this trial will be managed and minimized by appropriate eligibility criteria, specific dose selection criteria and stopping rules.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, stopping rules, and periodic safety reviews by the clinical team, the PI and in addition by an independent DMC. This is a first in pediatric study and information on safety of CFZ533 in this age group is not yet available indicating the potential for unknown risks.

Females of child bearing potential (*e.g.* menstruating) must be informed that taking the study treatment 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 requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Male contraception is not required based on the low distribution of IgG monoclonal antibodies into the semen and low exposure to the female partner and potential fetus (Moffat et al 2014; Morris et al 2014).

Potential risks and benefits related to off-site visits

Subjects are not anticipated to be exposed to greater risks when participating in off-site assessments. OHPs will perform assessments according to the same processes and instructions defined in the protocol and study manuals for on-site visits wherever possible, thus data integrity is also expected to be comparable to on-site assessments. Safety management in an off-site setting will adhere to the same quality standards as for the traditional on-site model, and remains under the responsibility of the Investigator (refer to Section 3.1.1). Furthermore, all subject data is treated with the strictest confidence to align with the requirements of local guidelines (*i.e*. General Data Protection Regulation and Health Insurance Portability and Accountability Act). Off-site procedures minimize burden on subjects and parent/caregiver, and offer them increased flexibility to participate in the study from a convenient off-site location (as described in Section 3 and defined in Section 8). This has the potential to broaden access to clinical trials for both subjects and parent/caregiver and the investigators. The hybrid approach will allow subjects to maintain contact with the Investigator, both face-to-face during on-site clinic visits, and through the telemedicine platform during off-site visits.

The scope of off-site procedures was determined based on a thorough operational feasibility review of the assessment schedule to assure comparability with on-site assessments, together with consideration of patient safety and investigator feedback. Off-site procedures will only be conducted where approved by the Health Authority and Ethic Committee.

4.5.1 Blood sample volume

Recognizing the pediatric population under study, and following recommended by the World Health Organization (Howie 2011) and European Medical Agency (EMA) for trial related blood volume in pediatric populations, total blood volume per single time point is less than 1% of a subject's total blood volume at a single time point, and the total blood volume will not exceed 3% of a subject's total blood volume and in a 4 week period. In Cohorts 1 and 2 subjects have body weight ≥30 kg, and total blood volume will not exceed EMA recommendations for trial related blood volume (see Appendix 4). Commercially Confidential Information

In addition, screening visit may be organized over two separate visits to adhere to safe phlebotomy limits. Likewise for larger subjects, screening and baseline visits may be combined.

Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule.

A summary blood log is provided in the Site Operations Manual . Instructions for all sample collection, processing, storage and shipment information is also available in the Site Operations Manual and central laboratory manual.

See the Section 8.4.6 on the potential use of residual samples.

4.6 Rationale for Public Health Emergency mitigation procedures

In addition to the planned off-site procedures, in the event of a Public Health emergency as declared by Local or Regional authorities *i.e.*, pandemic, epidemic or natural disaster, additional mitigation procedures to ensure subject safety and trial integrity may be implemented. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (*e.g.* telephone assisted consult) or additional visits by OHPs to the subject's home, can replace on-site study visits (in addition to the already planned off-site visits), for the duration of the disruption until it is safe for the subject to visit the site again.

Notification of the Public Health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. Subject selection is to be established by checking through all inclusion/exclusion criteria at screening and again prior to dosing as appropriate. A relevant record (*e.g.* checklist) must be stored with the source documentation at the study site. Deviation from any entry criterion excludes a subject from enrollment into the study.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent, and if needed assent from the child on the trial, must be obtained before any assessment is performed.
2. Males and females aged between 12 and 21 years (inclusive, and enrolled in stages) at screening.
3. Body weight range from 30 to 125 kg (inclusive).
4. Evidence of one or more type 1 diabetes autoantibody(ies) against: glutamic acid decarboxylase (anti-GAD), protein tyrosine, phosphatase-like protein (anti-IA-2); zinc transporter 8 (anti-ZnT8); islet cell (cytoplasmic) (anti-ICA) at screening or baseline in the central laboratory OR historical clinical record of one or more of the T1DM diabetes autoantibodies. As part of the historical record insulin autoantibodies (IAA) may have been used as part of the autoantibody panel but the blood sample must have been obtained prior to or within one week of starting exogenous insulin treatment.
5. Able to receive first dose of study drug within 56 days of diagnosis of T1DM (which may be extended to within 100 days of diagnosis in the event a screening assessment needs to be confirmed or vaccine administered).

6. Peak stimulated C-peptide levels ≥0.2 nmol/L (0.6 ng/mL) following standard liquid mixed meal tolerance test (MMTT), to be conducted when the subject is metabolically stable, at least 2 weeks from diagnosis and within 56 days prior to randomization (or within 100 days of diagnosis in the event a screening assessment needs to be confirmed or vaccine is required).
7. Study participants are to complete all recommended immunizations with live, attenuated vaccine at least eight weeks prior and killed, inactivated vaccine at least two weeks prior to first dose with study drug and in accordance with local immunization guidelines. In the event a subject has not had all vaccinations recommended according to local guidance, the screening period may be extended beyond 56 days to allow these vaccinations to be administered, but first dose of study drug must be administered within 100 days of diagnosis of T1DM (see Sections on Risks Section 4.5 and Screening procedures Section 8.1).
8. Must be willing to comply with the standard of care for diabetes management.
9. A negative pregnancy test at screening is required for all sexually mature female subjects prior to participation in the study.
10. Subject and/or guardian must be able to communicate well with the investigator, to understand and comply with the requirements of the study.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Diabetes forms other than auto immune type 1 such as maturity-onset diabetes of the young (MODY), latent autoimmune diabetes of the adult (LADA), acquired diabetes (secondary to medications or surgery), type 2 diabetes by judgement of the investigator.
2. Diabetic ketoacidosis within 2 weeks of the baseline MMTT test.
3. Polyglandular auto immune disease, Addison's disease, pernicious anemia, celiac sprue. Note: Investigators are not mandated to test for Celiac disease (also known as Sprue). Subjects suspected of having Celiac disease should be tested for the presence of disease, as part of good medical care, as treatment would differ. Treated, stable Hashimoto's thyroiditis is not exclusionary.
4. Any of the following abnormal laboratory values at screening:
   - total white blood cell count (WBC) outside the range of 1,500-15,000/mm^3 (1.5-15.0 x 10^9/L)
   - neutrophil count (<1500/mm3) (<1.5 X 10^9 / L)
   - lymphocyte count <500/mm3 (<0.5 X 10^9 / L)
   - hemoglobin (Hgb) <8.0 g/dL
   - platelets <100,000/mm^3 (<100 x 10^9/L)
5. History of immunodeficiency disorders, such as HyperIgM syndrome; history of recurrent infections suggestive of immunodeficiency disorders.
6. History of or active coagulation disorder with increased thromboembolic risk; a PTT and PT/ INR below lower limit of normal prior to inclusion.

7. Tuberculosis infection assessed by positive QuantiFERON TB-Gold test (QFT) at screening. Subjects with a positive QFT test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then anti tuberculosis treatment must have been initiated and maintained according to local country guidelines.
8. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, at screening, excludes a subject. Subjects with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA should be excluded.
9. Positive human immune virus HIV test (ELISA and Western Blot) at screening.
10. Evidence of EBV, CMV, HSV, and/or SARS-CoV-2 infection by viral load above laboratory upper limit of normal or only positive IgM serology in the absence of positive IgG at screening. Rescreening is permitted in persistently asymptomatic or post-symptomatic subjects, but study drug must be able to be administered within 100 days of diagnosis of T1DM and viral load must be negative and IgG titers positive.
11. Major dental work (*e.g.* tooth extractions or dental surgery with access to dental pulp) within 8 days of first dose; febrile illness within 48 hrs of first dose.
12. Use of other investigational drugs or use of immunosuppressive agents at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.
13. History of multiple and recurring allergies or allergy to the investigational compound/compound class being used in this study. Multiple and recurring allergies refer to known allergies to the investigational compound, to immunoglobulin based therapies, or to multiple drug classes. Dust mites, hay fever, and similar environmental allergies are not exclusionary.
14. History of severe hypersensitivity reaction or anaphylaxis to biological agents, *e.g.* human monoclonal antibody.
15. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within 5 years of screening, regardless of whether there is evidence of local recurrence or metastases.
16. Active serious psychiatric disorders (diagnosed or treated by a psychiatrist), such as eating disorders and psychosis or history thereof.
17. Any complicating medical issues or clinically abnormal laboratory results that may cause an increased safety risk to the subject as judged by the investigator.
18. Ongoing, and up to 2 weeks prior to screening, use of medications that may affect glucose control (e.g, systemic steroids, thiazides, beta blockers). A short course of oral steroids < 10 days if medically required is permissible with sponsor notification.
19. History of drug abuse, nicotine or harmful alcohol use within 12 months prior to first dose, or evidence (as determined by the investigators) of such abuse at screening. For example, harmful alcohol use in adults is defined as five or more drinks per day for 5 or more days in the past 30 days. Harmful alcohol use by adolescents (age 13-18 years) is to be determined by the investigator, based on local culture and laws. Harmful cannabinoid use is difficult to

define universally and the determination of abuse will be made by the Investigator based on local culture and law.

20. Taking medications prohibited by the protocol (see Section 6.2.2 (Prohibited treatment) or Table 6-2 Prohibited medication).
21. Pregnant or nursing (lactating) 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.
22. Women of child-bearing potential, defined as all women, who are sexually active, physiologically capable of becoming pregnant (*e.g.* menstruating), unless they are using highly effective methods of contraception during dosing and for 14 weeks (Section 4.2) after stopping the investigational drug. Highly effective contraception methods include:
    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (*e.g.* calendar, ovulation, symptothermal, post-ovulation 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 prior to first dose. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization in the sexual partner of female study participant (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - Use of oral (estrogen and progesterone), 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 be stable on the same pill for a minimum of 3 months prior to first dose.

If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

- Refer to Section 8.3.4 (Pregnancy).

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

6 Treatment

6.1 Study treatment

Dosing of the study drug, CFZ533 (iscalimab) or placebo, will be based on body weight (details in Section 4.2).

Study drug dosage will be adjusted based on bodyweight recorded at Day 1 and then every 3 months during site visits (Section 4.2) to account for body weight gain or loss during the treatment period.

The first dose of study drug will be administered in clinic intravenously (IV) on study Day 1 and two subcutaneous (SC) dose will be administered under observation at a scheduled visit on Commercially Confidential Information Thereafter, weekly subcutaneous (SC) doses may be administered at home or at Investigator site (see Assessment Schedule Table 8-1).

Every effort should be made to respect the weekly dosing schedule regardless of whether dosing is planned in clinic, off-site, or at home by subject or guardian in order to maintain target plasma CFZ533 exposure levels, and ensure complete CD40-CD154 pathway blockade in target tissues, and permit assessment of drug safety and potential efficacy. A ± 3 days window may be applied to the study drug SC administrations (regardless of whether dosing is planned in clinic, off-site, or at home by subject or guardian). In all cases the original visit and dosing schedule should be maintained, so that the visits and doses must continue to be administered as per the original schedule, and the administration schedule should not be recalculated from the time of the last dosing. For example, if the subject's usual dosing day is Wednesday, but a visit is planned for Friday, the dose would be administered at the time of the Friday visit (on-site or off-site), but the next dose administration would continue on the following Wednesdays as originally planned.

One delayed dose or missed dose: Every effort should be made to administer the study drug dose within the ± 3 days intended window. However, in case of exceptional medical or operational need, or unintentional omission (*i.e.* forgotten dose) study drug administration may be delayed by a maximum of 6 days before it is considered a missed dose (*i.e.* if subject's dosing day is Wednesday the late dose may be administered up to and including Tuesday, but a dose is considered missed on the day the next scheduled dose is due).

Compensatory dosing: Administration of a compensatory dose aims to minimize the impact of missed doses. In case of a missed in-home CFZ533 or placebo SC administration (CCI), the subject should contact the Investigator to plan the administration of a compensatory SC dose at the Investigator site. In case of one missed dose, an additional compensatory SC dose, same as the SC maintenance dose used for the individual subject may be administered at Investigator site together with the scheduled SC dose administration (*i.e.* two doses administered simultaneously, the compensatory dose and the next scheduled dose). In this case, an individual subject in body weight Category III may receive a cumulative dose up to 600 mg SC per occasion (up to two x 300 mg SC). The compensatory dose will enable the subject to rapidly re-establish the steady-state exposures and consequently reduce the overall variability associated with the missed dose. Since the compensatory dose may be administered only in case of a previously missed dose it is not expected to be associated with risk of over-exposure and exposures will not exceed the steady-state exposure expected with

the full compliance to the recommended treatment regimen. Additionally, administration of two x 2 mL 300 mg SC injections at one occasion is routinely used in ongoing trials with CFZ533 in adult populations and up to date it does not appear to be associated with lower tolerability or an increased risk of hypersensitivity reactions.

Compensatory doses can be administered only at the Investigator site and cannot be administered during an off-site or in-home SC administration by the OHP or the subject/guardian. If the subject cannot present to the site within the week of the missed dose, the site should contact Novartis for further guidance on consideration of a missed dose or administration of a later compensatory dose.

Delayed or missed consecutive dosing: In case of an exceptional medical or operational need, or in case a second consecutive dose administration has been delayed or missed, the investigator must contact the Sponsor immediately to discuss if the subject can remain on treatment or be permanently discontinued from randomized study treatment and managed as per local practice. Two consecutive doses can be missed no more than once within CCI

Missing CCI will drop systemic drug levels below concentrations which can be expected to provide clinical efficacy. Subjects who have missed CCI will need to discontinue treatment permanently.

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual.

6.1.1 Investigational and control drugs

Table 6-1 Overview of study medication (CFZ533/Placebo)

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Packaging	Sponsor (global)
CFZ533 150 mg/mL	Concentrate/solution for injection and for Infusion;	Intravenous and subcutaneous	Double blind subject packs; Type I glass vials	Novartis
CFZ533 matching Placebo 0 mg/mL	Concentrate/solution for injection and for Infusion;	Intravenous and subcutaneous	Double blind subject packs; Type I glass vials	Novartis

6.1.2 Additional study treatments

There are no additional study treatments to CFZ533 or placebo. All subjects should continue on background intensive insulin therapy per standard of care to optimize glycemic control (see Section 4.1.1).

6.1.3 Treatment arms/group

Two parallel treatment arms CFZ533 or matching placebo receiving one IV loading dose of study drug on Day 1, followed by CCI SC maintenance doses CCI (see dose section in Section 4.2).

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Insulin therapy, contraceptive measures as described in exclusion criterion number 22, per standard of care is allowed.

All medications administered after a subject is enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies.

Each concomitant medication must be individually assessed against all exclusion criteria and all prohibited medications. If in doubt the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact the Novartis medical monitor to determine if the subject should continue participation in the study.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed during the prohibited period stated in Table 6-2.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Immune suppressive therapy	Screening until CCI after last dose of study drug	Discontinue dosing with study drug
Attenuated "live" vaccine	Eight weeks prior to first dose administration of study drug until CCI after last dose of study drug	Discontinue dosing with study drug, monitor closely for signs and symptoms of infection, initiate anti-infective therapy per standard of care
Killed, inactivated vaccine	At least two weeks prior to first dose with study drug	Delay first dose of study drug, however first administration must be within 100 days of diagnosis of T1DM
Oral corticosteroids except for < 10 day treatment *e.g.* asthma exacerbation*	Screening until CCI after last dose of study drug	Adjust background insulin dose to correct hyperglycemia
*Topical or inhaled corticosteroids may be permitted, for example for treatment of mild stable asthma, when doses are not anticipated to have systemic effects of adrenal suppression		

6.2.3 Rescue medication

There is no specific rescue medication for CFZ533.

Infections should be treated promptly with anti-infective therapies and symptomatic treatment as per standard of care. Refer to Protocol Section 10.2.1 for guidance on viral safety monitoring.

In addition, depending on clinical severity of an infection and response to anti-infective treatment, stopping of CFZ533 treatment should be considered by the Investigator.

Plasmapheresis may be used as needed in case of severe infection not responding to standard of care anti-infective therapy, should the need arise to clear CFZ533 quickly.

Anaphylactic and hypersensitivity reactions should be treated per standard of care.

Glucagon may be used as needed per T1DM standard of care for the treatment of hypoglycemia.

6.2.4 Restriction for study subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

6.2.4.1 Dietary restrictions and smoking

Subjects should comply with a diabetic diet per standard of care.

On visits where the mixed meal tolerance test (MMTT) is scheduled, subjects should comply with an overnight fast for 8-10 hours and until the MMTT is completed. A standard mixed meal will be provided by the site and subjects must consume the entire contents of this meal. No food other than the mixed meal should be given for the duration of the test. Water intake is allowed.

Smoking should be discouraged and is not permitted during MMTT.

6.2.4.2 Other restrictions

Subjects should be advised against travelling to an area of the world with endemic disease, (*e.g.*, tuberculosis, dengue, Chagas disease, etc.) for which they have not been vaccinated or no vaccine exists due to potential effects of CFZ533 to limit immune response to new infectious pathogens. Notably, subjects treated with CFZ533 can mount recall immune responses after the drug has been eliminated.

Subjects need to be informed that vaccinations under treatment with CFZ533 most likely will not mount an adequate immune response and therefore will not be protective. This information is also contained in the informed consent form.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see ‘Subject numbering’ section in the Site Operations Manual.

6.3.2 Treatment assignment, randomization

Subject's eligibility is assessed at the Screening and baseline visits. If no change in status occurs subjects will be randomized at the Day 1 visit, and treatment will be assigned via the IRT system used for randomization of eligible subjects and for distribution and assignment of the study medication. Eligible subjects will be assigned to a treatment arm (see Site Operations Manual for details).

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff.

A randomization list will be produced by the IRT provider using a validated system that automates the assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the Site Operations Manual (SOM) regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is a subject and investigator-blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below. The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

Site staff (including study investigator and study nurse), will be blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.6.3).

Drug product will be supplied as double-blind subject kits and treatment allocation will be determined by IRT system.

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study: Unblinded sample analysts for PK, PD (sCD40) and IG.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

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All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Subjects, investigator staff, persons performing the assessments, and CTT will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with a few exceptions, eg: PK analyst.
(2) The identity of the treatments will be concealed by the use of the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance and odor.

The randomization codes associated with subjects from whom PK samples are analyzed will be disclosed to PK analysts who will keep PK results confidential until data base lock. Unblinding will occur in the case of subject emergencies and at the conclusion of the study. CCI

Drug product will be supplied in double blinded kits, so no unblinded site personnel is required for this study. Study staff or site pharmacist will receive a medication code after entering eligible subject into IRT system. Sample data may be provided to the independent committee/analysis team, under unblinded conditions.

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Table 6-3 Blinding Levels

Role	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Cohort progression
Subjects	B	B	UI	B
Site staff (including OHP)	B	B	UI	B
Unblinded site staff *e.g.* pharmacy staff	Not applicable			
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff *e.g.* for drug re-supply, PK bioanalyst, biomarker analyst	B	UI	UI	UI
Statistician/statistical programmer	B	B	UI	UI
Independent committees (*e.g.* DMC, internal stats analysis team) CCI	B	B	UI	UI
Sponsor Trial team	B	B	UI	UI
All other sponsor staff not identified above (project team, management & decision boards, support functions)	B	B	UI	B

B Remains Blinded

UI Allowed to be unblinded on individual subject level

CCI

6.5 Dose escalation and dose modification

Data to be reviewed for moving between Cohorts include all adverse events, and safety laboratory values.

The sponsor (limited unblinding) and lead investigator (blinded) will perform a joint review of safety data to assess the nature of adverse events, laboratory abnormalities, and decide upon study continuation with the next subject cohort.

To open enrollment into Cohort 2, Commercially Confidential Information treatment must be reviewed for safety and tolerability and assessed as satisfactory to proceed to the next cohort. Commercially Confidential Information

6.6 Additional treatment guidance

6.6.1 Treatment compliance

After the intravenous loading dose at Day 1 (administered at the Investigator site), two subcutaneous (SC) doses will be administered under observation at a scheduled visit on CCI in order to provide instruction on correct study drug administration to the subject/caregiver. The subsequent subcutaneous doses of the study drug (Commercially Confidential Information) may be administered at home or at Investigator site, or when applicable during the off-site visit by the OHP. Last dose is administered at CCI and the end of the treatment assessment will be performed at Week 52.

The investigator must promote compliance by instructing the subject/guardian (or trained designee) to take the study treatment exactly as prescribed and by stating that compliance (weekly dose schedule) is necessary for the subject's safety and the validity of the study. The subject/guardian must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using vial counts and information provided by the subject/guardian. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Recommended treatment of adverse events

This is a first in indication trial in type 1 diabetes and a first in pediatrics trial for CFZ533. Infections should be treated promptly with anti-infective therapies and palliative treatment as per standard of care. Refer to Risk/Benefit section (Section 4.5) in this document and in the Investigator Brochure.

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

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time. A subject can continue to be monitored in the study after an emergency break but cannot continue dosing with study drug.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under the investigational and control drugs section (Section 6.1.1).

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a two-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

CFZ533 will be administered to the subject via the following route of administration: IV for the loading dose on Day 1, and subcutaneous injections for the weekly maintenance regimen (CCI). The IV loading dose will be done at the site on Day 1, and the first and the second subcutaneous (SC) dose will be administered under observation at a scheduled visit on CCI . Thereafter, weekly subcutaneous (SC) doses may be administered at home or at Investigator site, or when applicable during the off-site visit by the OHP. SC maintenance doses may be administered at home, by subject or caregiver after training, if the subject or caregiver feels comfortable administering SC injections. See the Site Operations Manual and Pharmacy Manual for further details.

Where delivery of investigational medicinal product (IMP) directly to a subject's secure off-site location (*e.g.* home) is permitted by national and local governing regulations, then dispatch of study medication from the site to the subject may be performed under the accountability of the Investigator. The provisioning of supply will be for a maximum of CCI doses to last till the next follow-up visit. In this case, regular contacts (approximately every 4 weeks or more frequently if needed) will occur between the site and the subject for instructional purposes, safety monitoring, and discussion of the subject's health status until the subject's next visit to the study site.

The treatment for off-site administration will be handled and shipped in line with the pharmacy manual and required procedures for shipping.

Off-site treatment administration compliance will be assessed by the OHP and information provided to the Investigator and/or study personnel.

7 Informed consent procedures

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

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent/assent document.

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

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

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent/assent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent/assent and then must be discussed with the subject.

Women of child-bearing potential must be informed that taking the study treatment 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 requirements.

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A copy of the approved version of all consent/assent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Subjects receiving CFZ533 therapy who will be travelling to an area of the world with endemic disease, *e.g.*, tuberculosis, dengue, Chagas disease, etc. for which they have not been vaccinated or no vaccine exists should be informed of a potential increased infection risks. Of note, subjects treated with CFZ533 can mount recall immune responses after the drug has been eliminated.

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience. Refer to the Site Operations Manual for a complete list of ICFs included in this study.

The study includes the option for the subject to have certain study procedures performed off-site by an OHP instead of at the study site, for which a signature on a separate consent form is required if the subject agrees. It is required as part of this protocol that the Investigator presents this option to the subject, when permitted by national and local governing regulations and deemed appropriate by the Investigator. The process for obtaining consent should be exactly the same as described above for the main informed consent.

8 Visit schedule and assessments

Assessment schedule lists all of the assessments and indicates with an "X" the visits when assessments are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue study dosing should be encouraged to continue in study, off drug. Those who prematurely fully withdraw consent or discontinue the study for any reason should be scheduled for the end of treatment visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Specification and timing of each assessment are detailed in the protocol.

Table 8-1 Assessment Schedule

Period	Screening[1]		Treatment															
Visit Name	**Screening**	**Baseline**	**Day 1[2]**	**Wk 1**	**Wk 2[3]**	**Wk 4[3]**	**Wk 8[3]**	**Wk 12**	**Wk 16[3]**	**Wk 20[3]**	**Wk 24**	**Wk 28[3]**	**Wk 32[3]**	**Wk 36**	**Wk 40[3]**	**Wk 44[3]**	**Wk 48[3]**	**Wk 52 or EOT[20]**
Days	**-56 to -14**	**-14 to -1**	**1**	**8 ±3**	**15 ±3**	**29 ±3**	**57 ±3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**197 ±3**	**225 ±3**	**253 ±3**	**281 ±3**	**309 ±3**	**337 ±3**	**365 ±3**
Informed consent	X																	
Commercially Confidential Information																		
Demography	X																	
Inclusion / Exclusion criteria	X	X	X															
Medical history/current medical conditions	X	X																
Alcohol Test, Drug Screen, and Cotinine Test	X																	
Insulin dose and other Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration (iv/sc) AT SITE			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vaccine administration	S																	
Study diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Commercially Confidential Information																		
Physical Examination [4]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Tanner staging (subjects 12-17 only) [21]	X																	X

Period	Screening[1]		Treatment															
Visit Name	**Screening**	**Baseline**	**Day 1[2]**	**Wk 1**	**Wk 2[3]**	**Wk 4[3]**	**Wk 8[3]**	**Wk 12**	**Wk 16[3]**	**Wk 20[3]**	**Wk 24**	**Wk 28[3]**	**Wk 32[3]**	**Wk 36**	**Wk 40[3]**	**Wk 44[3]**	**Wk 48[3]**	**Wk 52 or EOT[20]**
Days	**-56 to -14**	**-14 to -1**	**1**	**8 ±3**	**15 ±3**	**29 ±3**	**57 ±3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**197 ±3**	**225 ±3**	**253 ±3**	**281 ±3**	**309 ±3**	**337 ±3**	**365 ±3**
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Height	X	X						X			X			X				X
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X							X				X						X
Bone age[5]	X																	X
MMTT Glucose and C-peptide[6]		X						X			X			X				X
Commercially Confidential Information																		
Urinalysis[7]	X		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation parameters		X																
Hematology	X		X			X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1C	X		X			X		X			X			X				X
Clinical Chemistry	X		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy[8]	S	S	S			S	S	S	S	S	S	s	S	S	S	S	S	S
Thyroid function tests	X									X							X	
HLA		X																
Diabetes Autoantibodies	X								X			X			X			
Serology for vaccines[9]	X																	

Period	Screening[1]		Treatment															
Visit Name	**Screening**	**Baseline**	**Day 1[2]**	**Wk 1**	**Wk 2[3]**	**Wk 4[3]**	**Wk 8[3]**	**Wk 12**	**Wk 16[3]**	**Wk 20[3]**	**Wk 24**	**Wk 28[3]**	**Wk 32[3]**	**Wk 36**	**Wk 40[3]**	**Wk 44[3]**	**Wk 48[3]**	**Wk 52 or EOT[20]**
Days	**-56 to -14**	**-14 to -1**	**1**	**8 ±3**	**15 ±3**	**29 ±3**	**57 ±3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**197 ±3**	**225 ±3**	**253 ±3**	**281 ±3**	**309 ±3**	**337 ±3**	**365 ±3**
Viral load/serology for CMV, EBV[10]	X					X	X	X	X	X	X	X	X	X	X	X	X	
Viral Load HSV	X																	
Viral serology for HSV	X								X				X				X	
Viral load for SARS-CoV-2 [11]	X																	
Serology for SARS-CoV-2 [11]	X							X			X			X			X	
Hepatitis and HIV screen	X																	
Tuberculosis test	X																	
Immunoglobulin CCI	X					X			X			X			X		X	
Commercially Confidential Information																		
PK blood collection[13]			X[14]			X	X	X	X	X	X	X	X	X	X	X	X	X

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Period	Screening[1]		Treatment															
Visit Name	**Screening**	**Baseline**	**Day 1[2]**	**Wk 1**	**Wk 2[3]**	**Wk 4[3]**	**Wk 8[3]**	**Wk 12**	**Wk 16[3]**	**Wk 20[3]**	**Wk 24**	**Wk 28[3]**	**Wk 32[3]**	**Wk 36**	**Wk 40[3]**	**Wk 44[3]**	**Wk 48[3]**	**Wk 52 or EOT[20]**
Days	**-56 to -14**	**-14 to -1**	**1**	**8 ±3**	**15 ±3**	**29 ±3**	**57 ±3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**197 ±3**	**225 ±3**	**253 ±3**	**281 ±3**	**309 ±3**	**337 ±3**	**365 ±3**

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Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study completion information																		

Period	Follow-up Period				
Visit Name	**Wk 56[3]**	**Wk 60[3]**	**Wk 64[3]**	**Wk 68[3]**	**Wk 72 End of Study**
Days	**393 ±7**	**421 ±7**	**449 ±7**	**477 ±7**	**505 ±7**
Informed consent					
Genetic consent					
Demography					
Inclusion / Exclusion criteria					
Medical history/current medical conditions					
Alcohol Test, Drug Screen, and Cotinine Test					
Concomitant medications	X	X	X	X	X
Study Drug Administration (iv/sc) AT SITE					
Vaccine administration					
Study diary	X	X	X	X	X
Commercially Confidential Information					
Physical Examination[4]	S	S	S	S	S
Tanner staging (subjects 12-17 only)					
Vital Signs	X	X	X	X	X
Body Height					
Body Weight	X	X	X	X	X
Electrocardiogram (ECG)					X
Bone age[5]					
MMTT Glucose and C-peptide[6]					X
Commercially Confidential Information					
Urinalysis[7]	X	X			X
Coagulation parameters					
Hematology	X	X	X		X
HbA1C		X			X
Clinical Chemistry	X	X			X

Period	Follow-up Period				
Visit Name	**Wk 56[3]**	**Wk 60[3]**	**Wk 64[3]**	**Wk 68[3]**	**Wk 72 End of Study**
Days	**393 ±7**	**421 ±7**	**449 ±7**	**477 ±7**	**505 ±7**
Pregnancy[8]	S	S	S	S	
Thyroid function tests					
HLA					
Diabetes Autoantibodies	X			X	
Serology for vaccines[9]					
Viral Load/serology for EBV, HSV, CMV[10]			X		
Hepatitis and HIV screen					
Tuberculosis test					
Immunoglobulin CCI		X			X

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PK blood collection[13]	X	X	X	X	X

Commercially Confidential Information

Adverse Events	X	X	X	X	X
Study completion information					X

“S” denotes source data only.

[1] The screening and baseline evaluations continue until the first dose of study drug is administered. Investigators should note that the turnaround time for screening and baseline laboratory assessments range from 4 to 21 business days and visits should be planned to ensure reporting of inclusionary and safety labs. Turnaround times of laboratory measures are provided in the SOM under section 1.2. Study months equal 28 days or 4 weeks. Screening and Baseline evaluations may be done over one or more visits. World Health Organization and European Medicine Agency recommendations for trial related blood volume will not be exceeded. All inclusion/exclusion assessments must be resolved and reviewed prior to CFZ533 administration.
[2] First dose of CFZ533 is to be administered as early as possible following diagnosis of T1DM and within a 56 day interval from the time of diagnosis, however the interval from diagnosis to first study drug administration may be extended to 100 days in the event a screening assessment needs to be confirmed or vaccination is required.
[3] This visit may be performed in clinic or scheduled as an off-site visit at an off-site location as allowed by local laws and regulations
[4]Abbreviated Physical exam can be done after day 1 visit. Exam of the thyroid must be included in all physical exams.
[5] Bone age assessments will be performed on all subjects aged 12-17 at screening. Assessments at subsequent visits will only be performed if bone age is < 17 years
[6] Glucose and C-peptide will be done in serum, at the time of MMTT, 6 timepoints.
[7] Including the assessment of creatinine, and C-peptide concentration in urine.
[8] Urine pregnancy tests will be used at all visits indicated, for subjects of child-bearing age (at the discretion of the investigator). Serum testing can be done for confirmation at the discretion of the investigator.
[9] Vaccination records will be required at screening. If documentation is not available for any reason, serology for missing vaccine's documentation will be performed prior to inclusion.

[10]Viral load and/or serology can be assessed at additional times at the discretion of the investigator. For subjects with evidence of an active CMV infection based on viral load measurement, increase the frequency of serial polymerase chain reaction (PCR) to detect CMV DNA and clinical monitoring for early signs of CMV end organ disease, to at least weekly frequency until resolution of the viral infection.
[11]SARS-CoV-2 is the virus associated with COVID-19 virology is performed by nasopharyngeal swab and serology is run at baseline and saved for later analysis during treatment. This sample may be used for additional infectious testing, if warranted.
[12] Commercially Confidential Information
[13] Unless otherwise stated, blood samples are taken pre-dose (within 1 hour before dosing) on dosing visits at site
[14] Two blood samples are taken: (i) at pre-dose (within 1 hour before dosing) and (ii) at about 90 minutes AFTER the start of the IV infusion (duration of the infusion is about 30 minutes).
[15]
Commercially Confidential Information
[16]
[17]
[18]
[19]

[20] Subjects that discontinue treatment or stop both treatment and study early are to complete subsequent end of treatment visit as soon as possible, if they are willing to do so.

[21] Tanner staging assessments will not be performed at subsequent visits after the subject has reached Tanner stage 5 (fully mature).

8.1 Screening

Rescreening is allowed once, after subject has failed screening. Rescreening must be done to permit initial dosing within 100 days of diagnosis to meet inclusion criterion. The earliest dosing possible is preferred to protect remaining pancreatic beta cell function. Subjects deemed eligible for rescreening will be re-consented and a new subject ID will be assigned.

Information on re-screening is outlined in the Site Operations Manual. However, rescreening must be discussed and agreed with the sponsor on case by case basis.

8.1.1 Eligibility screening

Following registering in the IRT for screening, subject eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Subjects who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the screening phase disposition page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see Section 10.1.3 for reporting details). If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

8.2 Subject demographics/other baseline characteristics

- **Subject Demographics:** Subject demographic and baseline characteristic data to be collected on all subjects include: date of birth, sex, race, predominant ethnicity.
- **Relevant Medical History/Current Medical Conditions:** A diagnosis of T1DM will be confirmed by the presence of at least one diabetes-related autoantibody. A MMTT will also be conducted at baseline to confirm a stimulated C-peptide level $\geq$0.2 nmol/L. Where possible, diagnoses and not symptoms will be recorded. Family history of T1DM will also be included (grandparents, or parents, or siblings, or relatives diagnosed with T1DM). Other relevant medical history and current medical conditions will be recorded on the in the eCRF until the start of the study drug. Any event or change in the subject's condition or health status occurring prior to the initial study drug administration will be reported in the Relevant medical history/Current medical conditions section of the eCRF.
- **Diabetes autoantibodies:** Blood samples will be collected to measure the following markers of immune destruction of beta-cells: autoantibodies to glutamic acid decarboxylase (anti-GAD65), autoantibodies to protein tyrosine phosphatase-like protein (anti-IA-2), autoantibodies to islet cell (cytoplasmic) (ICA), autoantibodies to zinc transporter 8 (anti-ZnT8). The presence of one or more of the T1DM diabetes autoantibodies from the historical clinical record may also be used for inclusion. As part of the historical record insulin autoantibodies (IAA) may have been used as part of the autoantibody panel, but the

blood sample must have been obtained prior to or within one week of starting exogenous insulin treatment for this to be used for eligibility.

- **HLA profiling:** A blood sample will be collected for HLA profiling in order to characterize the subject population. Specifically to T1DM disease, linkage for class II genes encoding HLA-DR and HLA-DQ genes, and high resolution genotyping for DRB1, DQA1 and DQB1 will be carried out. Sample handling and shipping instructions will be provided in the Laboratory Manual.
- **Hepatitis screen, HIV screen:** All subjects will be screened for Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies. Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, *e.g.*, Western blot. If required, appropriate counseling will be made available by the Investigator in the event of a positive finding. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator. Results will be available as source data and will not be recorded within the eCRF.
- **Screening for SARS-CoV-2:** All subjects will be screened for the coronavirus SARS-CoV-2, the virus causing the COVID-19 disease. Nasopharyngeal swab and blood samples will be taken at screening to assess viral load and serology (IgM and IgG), respectively for recent or past exposure. Rescreening for SARS-CoV-2 is permitted in persistently asymptomatic or post-symptomatic subjects, but first dose of study drug must be able to be administered within 100 days of diagnosis of T1DM and viral load must be negative and IgG titer positive. Serum will be stored for subsequent analysis. Subjects who have clinical signs and laboratory evidence of active infection with SARS-CoV-2 will not receive first dose of study drug until resolution of the active infection. When vaccination becomes available per local and National guidance, study subjects are to complete all recommended immunizations prior to first dose with study drug and in accordance with local immunization guidelines (See Section 5.1, Inclusion Criteria). This includes emergency authorization vaccine use. During the time of emergency use authorization of SARS-CoV-2 vaccine eligible subjects who have not received vaccination per local guidance or who have negative titers, may be encouraged to receive or be re-vaccinated during screening. However, as with all vaccines (Section 6.2.2), study drug must not be administered within eight weeks of live (attenuated) vaccine or within two weeks of inactivated vaccine (Rubin et al 2014). The screening window may be extended to permit these vaccinations if required, but the goal is to start the study drug as soon after diagnosis of T1DM as possible and the first dose of study drug must be administered within 100 days of diagnosis of T1DM. Notification of state and federal authorities, as required by law, of positive SARS-CoV-2 testing will be the responsibility of the Investigator.
- **Tuberculosis test:** Subjects will be tested for tuberculosis at screening using the Quantiferon Gold™ blood test.
- **Screening for CMV, EBV, and HSV:** Subjects will be monitored for infection with CMV, EBV, and HSV during the study. Blood samples will be taken at screening to assess viral load and serology (IgM and IgG) for recent or past exposure. During treatment and follow up, blood samples will be collected for viral load and/or serology to monitor for new exposure or viral reactivation. Samples at additional times may be assessed if clinically indicated. Subjects who have clinical signs and laboratory evidence of active infection with

CMV, EBV or HSV will not receive additional study drug administrations until resolution of the active infection. Subjects who have not received vaccination per local guidance or who have negative titers, may receive or be re-vaccinated during screening. Study drug must not be administered within eight weeks of live (attenuated) vaccine or within two weeks of inactivated vaccine (Rubin et al 2014). The screening window may be extended to permit these vaccinations if required, but the goal is to start the study drug as soon after diagnosis of T1DM as possible and the first dose of study drug must be administered within 100 days of diagnosis of T1DM.

- **Alcohol test, Nicotine and Drug screen:** Subjects will be tested for substances of abuse (*e.g.*, alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine and opiates). Age range is applied according to exclusion criterion number 18. Results will be available as Source data and will not be recorded within the case report form (CRF).
- **Study diary**: A study diary must be provided to subjects to report insulin dose administration, Commercially Confidential Information , and hypoglycemic events. Glycemic measures and insulin dosage may be obtained from device records (*i.e.* meter CCI downloads of glucose and insulin pump downloads for insulin dosing) if available. The study diary can be provided at screening or baseline, but data capture will start at baseline to ensure values prior to first dose.
  At every visit, subjects will report their daily dose of insulin administration for the three full days prior to the visit, along with daily glucose values CCI

Date and time of study drug dosing will also be captured in study diary.

Glycemic measures and insulin dosage may be obtained from device records (*i.e.* meter CCI downloads of glucose and insulin pump downloads for insulin dosing) if available. Glycemic measures, insulin dosage and hypoglycemic events will be entered in CRFs as per CRF Completion Guidance documents.

Date and time of study drug dosing will also be captured in a study diary.

- **Efficacy and pharmacodynamic assessments**

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a vein. Local anesthetic, such as Emla® cream or similar, is permitted if approved by local and National Health Authorities.

Details of sample processing, handling, storage and shipment will be described in a separate laboratory manual.

Samples will be given a unique sample number (as listed in the Blood Log in Site Operations Manual - SOM). The actual sample collection date and time will be entered on the appropriate CRF. The detailed methods and analysis will be described in Bioanalytical Data Reports.

Measures are described in the next sections.

8.2.1 Mixed Meal Tolerance Test (MMTT) for glucose and stimulated C-peptide

The mixed meal tolerance test (MMTT) has appropriate sensitivity to detect residual insulin secretion and beta cell function. In the MMTT, following an 8-10 hour overnight fast, a weight-based liquid meal provided as 6 mL/kg (maximum 360 mL) of mixed meal (Ensure Plus, Abbott , see Site Operations Manual), ingested over 5 min with timed blood samples for glucose and C-peptide determination obtained 10 min prior to ingestion ($t = -10$), at baseline ($t = 0$), and at 15, 30, 60, 90, and 120 min after consumption of the liquid meal (Leighton et al 2017). The time collections for post load samples are based on the start time of the mixed meal.

Blood sample collection will allow measurement of area under the curve ($AUC_{0\text{-}2\ hr}$) and peak C-peptide values. MMTT will be collected at baseline, at Weeks 12, 24, 36 and 52 on treatment, and at Week 72 (End of study) visit. The primary efficacy endpoint is the treatment effect on stimulated C-peptide $AUC_{0\text{-}2\ hrs}$ by mixed meal tolerance test (MMTT) at Week 52 (12 months). Detailed instructions for subjects regarding fasting requirements are summarized in Site Operations Manual.

Proportion of subjects with detectable C-peptide, rate of decline from baseline C peptide; time to undetectable C peptide will be assessed. A timed urine for C-peptide:creatinine ratio will also be assessed as a measure of beta cell function.

8.2.2 Insulin requirements and glycemic control

A key secondary analysis will be to assess partial remission following CFZ533 compared to placebo.

HbA_{1c} is measured as indicated in the Assessment Schedule (Table 8-1).

Total daily dose of insulin is reported as total daily units of insulin (adding short and long acting preparations) adjusted per body weight (unit/Kg/24 h). This information will be recorded at the site for at least 3 days and up to 7 days prior to each visit, as available (See Site Operations Manual). The average of total daily units of insulin per day (at each visit) will be calculated.

The Insulin Dose Adjusted HbA1c (IDAA1c) is a validated measure to determine beta cell reserve in subjects with T1DM. IDAA1c values ≤9.0 correspond to a predicted stimulated C-peptide >300 pmol/L. The formula for IDAA1c is defined as follows: HbA1c (%) + [4× insulin dose (units/kg/24 h)] (Andersen et al 2014). If HbA1c is stated in mmol/mol, it can be converted to percent by the following formula: HbA1c % = (HbA1c mmol/mol × 0.0915) + 2.15).

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8.2.4 Appropriateness of efficacy assessments

- The mixed-meal tolerance test (MMTT) is a standardized, reproducible measure of beta cell function with C-peptide measures to evaluate endogenous residual beta cell function in T1DM in the setting of exogenously administered insulin (Leighton et al 2017).
- HbA1c is the standard clinical measure of average glycemia. National Glycohemoglobin Standardization Program (NGSP) methodology will be used.

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8.3 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to the AE section (see Section 10.1.1).

Table 8-2 Safety assessments

Assessment	Specification
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, extremities, vascular, and neurological. Tanner staging will include examination of external genitalia, breast and pubic hair. A short physical exam will include the examination of general appearance, vital signs (blood pressure [SBP and DBP] and pulse), thyroid, skin for injection sites. A short physical exam will be at all visits starting from screening visit except where a complete physical examination is required. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.
Vital signs	Vital signs include temperature, BP and pulse measurements. For all visits: After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured once using an automated validated device and with an appropriately sized cuff including for pediatric use. A single repeat measurement for systolic and diastolic BP can be performed as needed to verify the first measurement and as per the PI's judgment.
Height and weight	Height in centimeters (cm and to the nearest 0.1 cm, without shoes and with the use of a calibrated equipment for subjects < age 18 years) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing and without shoes) will be measured.

The methods, assessment, specification, and recording for each assessment will be detailed in the Study Operation Manual.

8.3.1 Hypoglycemic events

The American Diabetes Association (ADA) has proposed a definition of hypoglycemia as an event accompanied by a measured plasma glucose concentration ≤3.9 mmol/L (70 mg/dL) based on the observed threshold for glucose counter-regulation activation in a non-diabetic population with a lower threshold of 3.9 mmol/L (70 mg/dL) as the definition of clinically relevant glucose levels (Workgroup on Hypoglycemia, American Diabetes Association 2005; Seaquist et al 2013).

While standardized reporting of hypoglycemia is desirable, it has been argued that defining hypoglycemia at a glucose level ≤3.9 mmol/L (70 mg/dL) may lead to considerable overestimation of the frequency of clinically relevant hypoglycemia. In a study report with a large cohort of patients it was shown that a threshold level of 3.1 mmol/L (56 mg/dL) would provide a more accurate estimate of the frequency (Swinnen et al 2009) Continuous glucose monitor (Dexcom) alert and alarm thresholds are set at 54 mg/dL (3.0 mmol/L) and so this proposed cut-off value will be used in the current study to define hypoglycemia events.

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions.

Hypoglycemic data will be classified as defined in Table 8-3. Glycemic thresholds above and below 54 mg/dL (3.0 mmol/L) indicate different degrees of urgency for clinical action: Hypoglycemia with glucose 54 to 69 mg/dL (3.0 to 3.9 mmol/L, often referred to as Level 1 hypoglycemia), is an alert threshold, independent of any acute symptoms, and healthcare professionals and people with diabetes should monitor time spent in this range of hypoglycemia. Hypoglycemia with a glucose level of below 54 mg/dL (3.0 mmol/L, often referred to as Level 2 hypoglycemia), with or without symptoms, is considered clinically significant in that it may trigger counterregulatory responses, cause cognitive impairment leading to severe hypoglycemia, and therefore requires immediate attention.

While hypoglycemic adverse events will follow the classification in Table 8-3, adverse events other than hypoglycemia will follow standard grading mild, moderate, or severe (Section 10.1.1) grading system.

Hypoglycemia events will be recorded in the study diary which will be reviewed and discussed with the subject at each visit. Hypoglycemia may also be assessed via CCI data review performed by the investigator, but asymptomatic events do not need to be entered as adverse events when additional treatments are not required. CCI

The investigator will record these events according to the table below under actions taken:

Table 8-3 Recording and classification of hypoglycemia as reported in the Study Diary

Severity	Symptoms	Plasma Glucose[1]	Action Taken	Classification[2]
Subject able to initiate self-treatment if necessary	Symptoms suggestive of hypoglycemia	≥ 3.0 mmol/L (54 mg/dL)	Complete the Adverse Event and-Hypoglycemia forms of the eCRF	Pseudo or possible symptomatic hypoglycemia (other causes of symptoms reasonably excluded)
	Symptoms suggestive of hypoglycemia	≤ 3.0 mmol/L (54 mg/dL)	Complete the Adverse Event and-Hypoglycemia forms of the eCRF	Documented Symptomatic Hypoglycemia
	Symptoms suggestive of hypoglycemia	Not taken	Complete the Adverse Event and-Hypoglycemia forms in the eCRF	Probable Hypoglycemia
	Asymptomatic	≤ 3.0 mmol/L (54 mg/dL)	Enter on Hypoglycemia form unless detected on CGM[3] (*i.e.* enter if detected by fingerstick) Confirm glucose value(s) in the study diary, unless detected on CGM.	Asymptomatic Hypoglycemia

Severity	Symptoms	Plasma Glucose[1]	Action Taken	Classification[2]
Subject is unable to initiate self-treatment and requires third party assistance or hospitalization	Symptoms suggestive of hypoglycemia	< 3.0 mmol/L (54 mg/dL)	Enter symptom(s) and glucose value(s) in the Adverse Event and Hypoglycemia forms of the eCRF.	Severe Hypoglycemia
	Symptoms suggestive of hypoglycemia	Not taken	Enter symptom(s) in the Adverse Event and Hypoglycemia forms of the eCRF	Suspected Severe Hypoglycemia

1. A plasma glucose level of 3.0 mmol/L (54 mg/dL) corresponds to a whole blood glucose (glucometer data) of about 2.7 mmol/L (49 mg/dL), noting plasma glucose values are about 11% higher than those of whole blood when the hematocrit is normal.

2. The classification of adverse events as hypoglycemic events should be adjudicated by the clinical Investigator.

3. Low glucose values that are asymptomatic Commercially Confidential Information do not need to be entered into the Hypoglycemia form. If the subject is not using CGM and the low glucose value is detected by alternate means (*i.e*. fingerstick or serum/plasma) then the asymptomatic hypoglycemic event should be captured on the Hypoglycemia form.

8.3.2 Laboratory evaluations

In the case where a laboratory range is not specified by the protocol, but is outside the reference range for the center or study central laboratory assays at screening, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once (for the purpose of inclusion) and in any case, prior to enrollment/randomization, to rule out laboratory error.

In all cases, the Investigator must document in the source documents, the clinical considerations (*i.e*., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study. 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.

For off-site visits (described in Section 3.1), samples will be collected, processed and shipped from the off-site location to the Central Laboratory for analysis in line with instructions contained in the study laboratory manual.

8.3.2.1 Clinical Chemistry, including coagulation parameters

Sodium, potassium, creatinine, BUN/urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, bicarbonate/HCO_3, LDH, GGT, AST, ALT, CK, glucose, total cholesterol, HDL-C, LDL-C, triglycerides, Prothrombin Time (PT)/ International Normalized Ratio (INR), activated partial thromboplastin time (aPTT).

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

HbA1c and CCI will be collected during the trial as per the Assessment Schedule (Table 8-1).

8.3.2.2 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured.

8.3.2.3 Urinalysis

A midstream urine sample (approx. 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, leukocytes, creatinine, and blood, microalbumin. If the dipstick result is positive for protein leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

8.3.2.4 Endocrinology

Thyroid function tests: TSH and total T4.

8.3.2.5 Viral Monitoring

CMV and EBV viral load and serology (IgM and IgG) will be obtained at screening and monthly following dosing during the treatment period. SARS-CoV-19 viral load and serology (IgM and IgG) will be obtained at screening. Serum will be banked for subsequent evaluation as needed, for clinical assessment or when testing sensitivity/specificity are better understood. This banked specimen may be analyzed for additional infectious agents if warranted.

HSV viral load and serology (IgM and IgG) will be obtained at screening and serology will be assessed at week 16, 32 and 48 following dosing. This will provide surveillance for new exposure, seroconversion, and potential reactivation of viral infections.

8.3.2.6 Tanner staging (subjects 12 to 17 years only)

For subjects aged between 12 and 17 at visits as indicated in the Assessment Schedule, pubertal assessment will be carried out using the Tanner scale. While the details of the assessment will remain with the source document, the outcome of the evaluation (scale values 1 through 5) will be recorded in the eCRFs. Subjects who have reached sexual maturity, Tanner stage 5, do not need to have continued assessments.

8.3.3 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the eCRF. Each ECG tracing should be labeled with the

- study number
- subject/ initials
- subject/ number
- date and kept in the source documents at the study site.

Only clinically significant abnormalities should be reported on this page. Clinically significant abnormalities should also be recorded on the relevant medical history/Current medical conditions eCRF page. Clinically significant findings must be discussed with the sponsor. Original ECG tracings, appropriately signed, will be archived at study site. The CRF will contain:

- date and time of ECG
- heart rate
- PR interval
- QT and QTcF interval
- RR interval
- QRS duration

8.3.4 Pregnancy

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric subjects who are menarchal or who become menarchal during the study. Urine pregnancy test will be performed for all females of child-bearing potential according to the schedule in Table 8-1. Serum pregnancy tests can be performed for positive urine tests and at the discretion of the site investigator. All menarchal girls and their guardian/caregiver should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study.

Pediatric subjects: In case of puberty and sexual activity, adolescents and when appropriate children will be informed about the need for preventing any pregnancy, testing for pregnancy and the management of the test results, including whether they will be shared with the guardian/caregiver. They should be counseled in a sensitive manner about abstinence (which should be promoted) and other forms of birth control. Their need, request and rights for privacy during the counseling process should be respected. Building a trusting relationship is important. These discussions with the subject and her guardian/caregiver are therefore best performed by investigators familiar with the pediatric subject and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the subject and her guardian/caregiver. The privacy of the subject should be considered in accordance with the local law and ethics. Additional pregnancy tests may be performed at the

investigator's discretion during the study. Subjects becoming pregnant must be discontinued from study drug. However, a subject may choose to remain in the study should she become pregnant, and be followed according to the protocol-defined study visits.

Pharmacokinetic (PK) and pharmacodynamic (PD) studies show CFZ533 is cleared from the body and immune responses have normalized CCI post dose, and women are advised not to become pregnant until the PK/PD responses are eliminated. However, in the case that a subject becomes pregnant at any time during the trial, 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 to inform on fetal and early growth and developmental health. After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery or the pregnancy has ended in the absence of a live birth.

8.3.5 Appropriateness of safety measurements

The majority of safety assessments in this study are standard for this type of study (*i.e.*, AE monitoring, standard laboratory safety assessments, vital signs, ECGs and physical examinations).

Additional specific clinical laboratory assessments are included to exclude any active infection before treating the subject with study drug, which based on the pharmacology of CFZ533 could potentially put the subject at risk.

8.4 Additional assessments

Additional assessments are described below.

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9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject, the investigator, or the Sponsor.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Informed consent/assent is withdrawn
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section (see Section 6.2.2)
- Any situation in which study participation might result in a safety risk to the subject
- Following emergency unblinding

Subjects may voluntarily discontinue the study for any reason at any time.

Missing CCI will drop systemic drug levels below concentrations which can be expected to provide clinical efficacy. Subjects should therefore not miss more than 2 subsequent doses of study drug in CCI . Similarly, 2 consecutive doses cannot be missed more than once within a CCI period as this would also drop systemic levels below concentrations which can be expected to provide clinical efficacy. Subjects who have missed 3 or more doses in CCI or have missed 2 consecutive doses more than once within CCI will need to discontinue treatment permanently. The site should contact Novartis for further guidance if multiple compensatory doses are required.

Site Investigators should discontinue or temporarily suspend study treatment for any given subject if, on balance, they believe that continuation would be detrimental to the subject's well-being. Site Investigators should contact Novartis prior to resuming study drug that was discontinued or temporarily suspended for safety reasons. The DMC may be involved in the decision to resume dosing.

Study treatment must be discontinued and medical treatment must be started per standard of care where needed at the site Investigator's discretion under the following circumstances:

- Infusion reactions/anaphylaxis reactions to CFZ533.
- Recurrent systemic or severe infections. Recurrent local candidiasis, *e.g.* genital that is responsive to topical standard of care treatment and is deemed related to inadequate glycemic control is exempt.
- Severe infections. Resumption of dosing may be considered once the course of anti-infective therapy is completed and the infection is documented as cleared, so long as 3 or more doses have not been missed. For COVID-19, clearance of infection in order to resume treatment during the study requires resolution of symptoms and absence of infectious virus / viral replication from a respiratory specimen.
- Neutropenia with an absolute neutrophil count (ANC) < 0.5 x10(9)/L until resolution defined as an ANC > 1x10(9)/L on 2 separate occasions.
- Severe and symptomatic hypogammaglobulinemia, *e.g.* IgG levels lower than 400 mg/dL necessitating replacement therapy with gamma globulins.

Resumption of dosing for subjects in whom study treatment was temporarily suspended must be decided based on the site Investigator's judgement, in consultation with the Sponsor and the DMC on a case-by case basis.

If permanent discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects 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/assent (see Section 9.1.2 withdraw of informed consent section). Where possible, they should return for the assessments indicated in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (*e.g.* telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section (see Section 9.1.3). This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- Adverse Events/Serious Adverse Events

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.1.1 Replacement policy

Subjects who were randomized, but not dosed may be replaced.

9.1.2 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a subject:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (*e.g.* in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (*e.g.* to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the investigator should make a reasonable effort (*e.g.* telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the subject has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.If the subject agrees, a final evaluation at the time of the subject's withdrawal of consent/exercise data privacy rights should be made as detailed in the assessment table (Table 8-1).

Further details on withdrawal of consent or the exercise of subjects' data privacy rights are included in the corresponding informed consent form.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, *e.g.* dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 Study stopping rules

The Sponsor, the DMC and Lead Investigator will continually review and *ad hoc* as needed, adverse events and laboratory findings throughout the study, including the number and/or severity of adverse events, cumulative cases of clinically significant adverse events, severe adverse events, clinically significant laboratory changes, except those that are reasonably suspected to be due to extraneous causes.

As a result of the safety review, study recruitment or the study (a part/ or cohort of the study) may be placed on hold pending further safety analysis if Novartis, the DMC, and Lead Investigator, considers that the cumulative number and/or severity of AEs or other clinically significant changes are deemed unsafe to continue recruitment or dosing. Novartis and the Lead Investigator must jointly evaluate the relationship between an adverse event and CFZ533, and decide whether to resume enrollment, or to stop one cohort, all dosing, or to terminate the study prematurely.

Study recruitment will be stopped, pending a full safety review, if any of the following criteria are met:

- At least 2 of the 6 (for Cohort 1) or 3 of the 10 (for Cohort 2) subjects in the same cohort experience a CFZ533-related AE (CTCAE grade 3 or higher) in the first month of treatment.
- Three (3) or more subjects with recurrent and severe systemic infections (CTCAE grade 3) per cohort in the first month of treatment, or more than 50% of all treated subjects at any point in time.
- One (1) or more subjects with a severe allergic reaction (CTCAE grade 3 or higher) to study drug in the first five (5) treated subjects or an incidence of > 20 % thereafter.
- One (1) or more subjects with cytokine release syndrome.
- The sponsor unilaterally requests it.
- The DMC recommends it.

If one of the above stopping rules is met, the Competent Authorities and Institutional Review Board/Independent Ethics Committee (IRB/IEC) will be informed of the temporary halt of study via a Substantial Amendment in accord with local regulations. The study may resume following the safety review, if the Sponsor and DMC, and Lead Investigator agree it is safe to proceed and after approval to restart the study is obtained from the Competent Authorities and IRB/IECs.

Cohort stopping rules are described in the above study stopping criteria list.

Individual stopping rules are listed in the Section 9.1.1.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk assessment of participating to subjects enrolled in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons.

- Decision based on recommendations from applicable board(s) after review of safety and efficacy data.
- Discontinuation of study drug development.

In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion 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.

All randomized and/or treated subjects will be followed up for an additional 20 weeks period. During the 20 week follow up period, safety monitoring will continue as described in the assessments table, Table 8-1.

All randomized and/or treated subjects who do not continue study visits after receiving treatment should have a safety follow-up call conducted a minimum of CCI after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 and the Site Operations Manual. Documentation of attempts to contact the subject should be recorded in the source documentation.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (*e.g.*, 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 investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

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

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them. Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Definitions of hypoglycemia are provided in Section 8.3.1 and Table 8-3. All other adverse events reported in the CRF should be accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade
   - mild: usually transient in nature and generally not interfering with normal activities.
   - moderate: sufficiently discomforting to interfere with normal activities.
   - severe: prevents normal activities.
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (*i.e.* progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject.
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. action taken regarding with study treatment.
   - All adverse events must be treated appropriately. Treatment may include one or more of the following:
     - Dose not changed
     - Drug interrupted/withdrawn
6. its outcome,
   a. not recovered/not resolved;
   b. recovered/resolved;
   c. recovering/resolving,
   d. recovered/resolved with sequelae;
   e. fatal; or unknown.

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued until end of study visit.

Information about adverse drug reactions for the investigational drug can be found in the IB.

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

Follow the instructions found in the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

10.1.2 Serious adverse events

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:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject 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 it were more severe (please refer to the ICH-E2D Guidelines).

- 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
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - 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
- is medically significant, *e.g.* defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above
- Hypoglycemia which requires the assistance of another person to treat must be reported as an SAE.

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 subject or might require intervention to prevent one of the other outcomes listed above. Such events should be

considered as “medically significant”. 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 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.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 Serious Adverse Event (SAE) reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Randomized subject's SAEs will be collected between time subject signs ICF until subject has discontinued or stopped study participation, or until CCI after last treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, and under no circumstances later than within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS 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 study 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.

Adverse events and serious adverse events (AE and SAE) will continue to be collected after the CCI post dosing interval, but will generally not be attributed to CFZ533 as pharmacodynamics effects of the drug are anticipated to be back to baseline. These events may help elucidate potential benefits of preserved pancreatic beta-cell function.

10.1.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent 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.

After consent for pregnancy monitoring, the pregnancy reporting will occur up to one year after the estimated date of delivery.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the CFZ533 treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

The study drug must be discontinued, though the subject may choose to remain in the study, if she wishes to do so. If the subject chooses to remain in the study, all assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments. Pregnancy must be recorded on a Drug Exposure in 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 the SAE Report Form.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator’s awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE (see Section 10.1.1) and SAE definition (see Section 10.1.2) and reporting requirements (see Section 10.1.3), please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Viral safety monitoring

Subjects are anticipated to retain immune memory for antigens to which they were previously exposed, but not mount a humoral immune response and memory for neo-antigens. Combined immunotherapy is expected to increase the risk for infection. Thus no additional immunosuppressive agents are permitted in this study.

See Section 16.3 for general guidance information on CMV and EBV.

At screening, identify and exclude subjects with evidence of active CMV, EBV, HSV 1 and 2, or SARS-CoV-2 infection based on baseline viral load (determined via polymerase chain reaction (PCR)) or positive IgM serology in the absence of positive IgG.

At screening, identify subjects at risk for CMV, EBV, HSV, or SARS-CoV-2 primary infection or reactivation based on baseline IgG serology (negative or positive IgG serology, respectively). Rescreening for SARS-CoV-2 is permitted in persistently asymptomatic or post-symptomatic subjects, but study drug must be able to be administered within 100 days of diagnosis of T1DM and viral load must be negative and IgG titers positive.

During the study identify subjects with CMV or EBV reactivation or primary infections with serial PCR to detect virus DNA in addition to serology at least at monthly intervals, or when the clinical presentation suggests possible CMV or EBV infection. During the study monitor for HSV seroconversion quarterly (weeks 16, 32, and 48).

During the study, for subjects with evidence of an active CMV infection based on viral load measurement, increase the frequency of serial PCR to detect CMV DNA and clinical monitoring for early signs of CMV end organ disease, to at least weekly frequency until resolution of the viral infection. Consider consultation with an infectious disease expert.

During the study, for subjects with confirmed or probable cytomegalovirus disease, consider stopping study drug and consider initiating appropriate anti-cytomegalovirus therapy (or other anti-viral therapy as appropriate) in consultation with an infectious disease expert.

For subjects with potential infectious symptoms during the trial, but without laboratory confirmation of CMV or EBV infection, consider age- and country-appropriate infectious exposure risks for alternative infectious etiologies, consider direct isolation of pathogens,

virology, and/or serology, and initiating appropriate targeted anti-viral or anti-bacterial therapies as indicated in consult with an infectious disease expert. Additional viral infection should be considered and viral load/ titer assessed as serology/ immunoglobulin response may be diminished.

For subjects with potential infectious COVID-19 symptoms during the trial repeat virology (PCR) to detect SARS-CoV-2 RNA, serologic evaluation, and clinical monitoring for early signs of end organ disease and initiating appropriate targeted anti-viral or anti-bacterial therapies as indicated in consult with an infectious disease expert may be warranted.

10.2.2 Liver safety monitoring

To ensure subject 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 (irrespective of whether classified/reported as AE/SAE):

- 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 Section 16.1 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Section 16.1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Section 16.1. Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unplanned local laboratory CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Section 9.1.1 Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator’s discretion: serology tests, imaging and pathology assessments, hepatologist’s consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

- Recent European Association for the Study of the Liver (EASL) guidelines support consideration of liver biopsy for patients with hepatotoxicity grade ≥3 to assess the pattern of damage and severity of the liver injury (Andrade et al 2019). Site investigators may consider consult with hepatologist and liver biopsy in cases with hepatotoxicity grade ≥3.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

Refer to the Site Operations Manual for additional details.

10.2.3 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- 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).

Every renal laboratory trigger or renal event as defined in Table 16-3 should be followed up by the investigator or designated personnel at the trial site as summarized in Section 16.2.

Refer to the Site Operations Manual for additional details.

10.2.4 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

11 Data Collection and Database management

11.1 Data collection

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

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

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

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior 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.

Randomization codes and data about all study treatment(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or delegated Contract Research Organization (CRO) representative will review the protocol and data capture requirements (*i.e.* eSource DDE or eCRFs) 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 field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject 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 subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary 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 subjects will be disclosed.

12 Data analysis and statistical methods

Primary safety and efficacy analysis will be conducted based on all randomized subjects having completed treatment, either having reached the Week 52 visit or discontinued early. All participants should be followed for at least CCI following last dose administered to assess safety during drug wash-out.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

For all analyses, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study treatment.

The PK analysis set will include all subjects with at least one available valid (*i.e.* not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

12.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be summarized by treatment group and subject. Summary statistics will be provided by treatment group. Additional summary statistics may be generated by treatment group and age group.

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

12.3 Treatments

Data for study drug administration and concomitant therapies will be listed by treatment group (CFZ533 or placebo) and subject.

12.4 Analysis of the primary endpoint(s)

The primary objectives of this study are (1) to evaluate the safety and tolerability of CFZ533 in subjects with new onset T1DM and (2) to evaluate the effects of CFZ533 on pancreatic β-cell function in subjects with new onset T1DM.

12.4.1 Definition of primary endpoint(s)

All safety data, including laboratory measurements, vital signs, adverse events, and ECGs are considered primary endpoints for the first primary objective.

Stimulated C-peptide AUC by mixed meal tolerance test (MMTT) after 52 weeks, normalized by the duration of measurements, is the primary endpoint for the second primary objective. This endpoint is derived from the blood samples taken for C-peptide determination over the course of 2 hours. The AUC will be logarithmically transformed prior to analysis.

12.4.2 Statistical model, hypothesis, and method of analysis

Safety

- Vital signs

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

- ECG evaluations

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

- Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time.

- Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

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

The number and percentage of subjects with adverse events by maximum severity of adverse events will be tabulated by body system and preferred term with a breakdown by treatment.

The number and percentage of subjects with adverse events classified as related to study drug will be tabulated by body system and preferred term with a breakdown by treatment.

Stimulated C-peptide AUC

Stimulated C-peptide AUC by the standard MMTT, normalized by the duration of measurements, will be analyzed with a mixed model repeated measures analysis and the primary objective will be examined with the results of this analysis at the 52 week time point. The natural log of the AUC will be the dependent variable in this analysis. Independent variables will include age, treatment, visit, and the treatment by visit interaction. The natural log of the baseline AUC will be used as a covariate and subject will be used as a random effect. Least square geometric mean and geometric mean ratio to baseline of each treatment, the ratio of CFZ533 to placebo, the 80% confidence interval of the ratio, and the one-sided p-value of treatment benefit will be presented for each time point.

12.4.3 Handling of missing values/censoring/discontinuations

Safety and efficacy data at key time points will not be imputed for the primary analysis. Data from subjects who discontinue study treatment will be excluded, from the date of study drug discontinuation from the primary efficacy analysis. The primary analysis based on mixed model repeated measurements for Stimulated C-peptide AUC measurements at various visits is valid under the assumption that the missing data are missing at random (MAR).

12.4.4 Sensitivity and supportive analyses

Sensitivity analyses may be considered if a substantial proportion of subjects (*e.g.* more than 15%) discontinue from study treatment. Multiple imputation models may be used to assess the robustness of the missing at random assumption of the primary analysis.

Additional analyses including all subjects regardless of their adherence to treatment will be performed. Further details of these analyses will be specified in the SAP.

Subgroup analyses of primary safety and efficacy data may be conducted by age group, race, gender, and the weight group.

12.5 Analysis of secondary endpoints

The secondary objectives of this study are (1) to evaluate the pharmacokinetics of CFZ533 in subjects with new onset T1D, (2) to evaluate the treatment effect of CFZ533 on full or partial remission, and (3) to evaluate durability effects of CFZ533 over time on pancreatic beta cell function.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Data for the secondary variables (*i.e.* total daily dose of insulin, insulin-dose adjusted HbA1c) will be descriptively summarized for each treatment group and each time point (where applicable).

Full remission will be defined by HbA1c ≤6.5% (48 mmol/mol) and no exogenous insulin use, at 52 weeks (1 year). Two validated criteria will be used to assess partial remission including proportion of subjects with (1) Insulin Dose Adjusted HbA1c (IDAA1c) ≤ 9.0 (Mortensen et al 2009) and (2) HbA1c < 7.0% (53 mmol/mol) and total daily insulin dose <0.5 units per kg per day (Couper and Donaghue 2009). Stimulated C-peptide AUC by MMTT at Week 72 will be analyzed in the same manner as the primary objective. The baseline*visit interaction term may also be considered for this model due to the follow-up.

The proportion of subjects with detectable C-peptide, rate of decline from baseline C-peptide, and time to undetectable C-peptide will be descriptively summarized with estimates and confidence intervals for each treatment group and each time point (where applicable).

12.5.2 Pharmacokinetics

Blood samples for CFZ533 concentrations in plasma will be collected from all subjects (to protect blinding), at selected time points as defined in the Assessment Schedule (Table 8-1). Analysis will be performed in samples collected from CFZ533-treated subjects only.

CFZ533 plasma concentration data will be listed by subject, and visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point, CCI . Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Commercially Confidential Information
The following PK parameters will be determined: Ctrough, Ctrough,ss (steady state) and Cmax, Tmax (after IV loading only) will be directly derived from the bioanalytical data in tables and listings. Additional PK parameters may be determined if data permit.

Pharmacokinetic parameters will be listed by subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

Parameters like clearance, volume of distribution, or half-life will not be derived using non-compartmental analysis (NCA). The pharmacokinetics of CFZ533 is non-linear and characterized by target-mediated disposition where CD40 binding by CFZ533 is leading to CFZ533 elimination (this includes receptor-mediated endocytosis by the membrane bound CD40, and subsequent metabolism of the CFZ533-CD40 complexes). The NCA approach is

not appropriate due to violations of the assumptions that the disposition of the drug is linear, and that the elimination is from sites that are in rapid equilibrium with blood.

12.5.3 Biomarkers

See Section 12.6.1.

12.5.4 PK/PD relationships

The relationship between PK, PD, efficacy or biomarker endpoints may be explored graphically.

Modeling of PK data using a population approach may be performed as appropriate and will be reported if necessary in a separate, standalone modeling and simulation report.

Commercially Confidential Information

12.7 Interim analyses

Commercially Confidential Information

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size calculation is based on the primary endpoint of stimulated C-peptide AUC by the standard MMTT.

In Greenbaum (2012) the average baseline stimulated C-peptide AUC by MMTT is approximately 0.7 pmol*hr/mL. They show a linear decline in untreated subjects resulting in an average AUC of 0.4 pmol*hr/mL at one year. It is assumed that a clinically significant prevention of decline would occur if the rate of decline was one half (50%) of that of untreated subjects. Thus, a clinically relative improvement due to treatment would occur if the AUC at 1-year was 37.5% larger for treatment than placebo (0.55/0.4 = 1.375). Starting with 44 subjects and accounting for ~18% dropout rate, a total of 36 subjects randomized in a 2:1 ratio (stratified by age at first screening visit: ≥18 to 21 years, ≥12 to <18 years) between CFZ533 and placebo provides 55% power to detect an improvement over placebo using a one-sided alpha=0.1 test when the true ratio of treatment to placebo is 1.375 (Note: if the rate of decline in treatment vs placebo is instead 75% less, corresponding to a ratio of 1.56, the power is 75%). This calculation assumes a coefficient of variation of 70% for the AUC; the standard deviation of log (AUC) was derived from the relationship between the CV and variance parameter for the lognormal distribution. This assumption was the result of the observed CV% of 5 TrialNet studies in T1DM subjects (Bundy et al 2016).

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed 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 CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must 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, subject recruitment procedures (*e.g.*, advertisements) and any other written information to be provided to subjects. 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.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last subject last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (*e.g.* Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

14 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 subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an 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 and health authorities, where required, it cannot be implemented.

14.1 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 required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*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
TBL: total bilirubin; ULN: upper limit of normal

Recent European Association for the Study of the Liver (EASL) guidelines support consideration of liver biopsy for patients with hepatotoxicity grade ≥3 to assess the pattern of damage and severity of the liver injury (Andrade et al 2019). Site investigators may consider consult with hepatologist and liver biopsy in cases with hepatotoxicity grade ≥3.

Table 16-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment 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	• Discontinue the study treatment 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	• Discontinue the study treatment 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	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, 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]	• Discontinue the study treatment 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 (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks

Criteria	Actions required	Follow-up monitoring
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• 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 (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the subject • 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*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated 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
[c]Resolution 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.

Recent European Association for the Study of the Liver (EASL) guidelines support consideration of liver biopsy for patients with hepatotoxicity grade ≥3 to assess the pattern of damage and severity of the liver injury (Andrade 2019). Site investigators may consider consult with hepatologist and liver biopsy in cases with hepatotoxicity grade ≥3.

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

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

16.3 Appendix 3: General Guidance on Select Virus - Cytomegalovirus, Epstein-Barr virus, and coronavirus SARS-CoV-2

There are specific infection risk challenges in the pediatric population (Allen 2016). The potentially immunocompromised child may be at a greater risk of acquiring specific infections compared to their adult counterparts, as multiple infections are more prevalent in younger age groups, such as respiratory viral diseases including respiratory syncytial virus illness (Hall et al 2009), such that infection risk is related to their age group regardless of immune competence; and children have increased likelihood of primary infections as they are still developing their immune repertoire and may lack preexisting host immunity. Thus children may experience more severe illnesses and poorer outcomes compared to adults, and consulting with local experts for diagnosing and managing infections in the potentially immunosuppressed patient may be warranted (Drgona et al 2018; Dropulic and Lederman 2016).

16.3.1 Cytomegalovirus

Positive serology for cytomegalovirus is approximately 30% at the age of 6 years and approximately 60% by young adulthood in a western country (Lanzieri et al 2015; Zuhair et al 2019), an approximate doubling of the rates of seropositivity for cytomegalovirus from new exposure over the enrollment age range of this trial.

Acquired cytomegalovirus infection in healthy children and adolescents is most often asymptomatic. However, approximately 10 percent of acquired cytomegalovirus infections produce symptoms. Cytomegalovirus can cause a mononucleosis–like syndrome; the most common manifestations are fever, fatigue, pharyngitis, adenopathy (especially cervical adenopathy), and hepatitis. Headache, abdominal pain with diarrhea, arthralgias, and rash also may occur. Laboratory abnormalities include lymphocytosis or lymphopenia with thrombocytopenia and elevated transaminases. The heterophile antibody titers or monospot tests will be negative.

Unusual manifestations or complications of acquired cytomegalovirus infections in healthy individuals include rare reports of pneumonitis, myopericarditis, hemolytic anemia, viral hemophagocytic syndrome, granulomatous hepatitis, Guillain-Barré syndrome, and meningoencephalitis (American Academy of Pediatrics 2015; Demmler-Harrison 2018).

Cytomegalovirus disease is defined according to published criteria (Ljungman et al 2017) as described below.

a. ACTIVE CYTOMEGALOVIRUS infection is defined as a detectable cytomegalovirus viral load in the absence of signs or symptoms attributable to cytomegalovirus. Active cytomegalovirus infection can be the result of cytomegalovirus reactivation or primary cytomegalovirus infection.
b. PROVEN DISEASE: For pneumonia, central nervous system (CNS) disease, gastrointestinal disease, hepatitis, nephritis, cystitis, myocarditis, pancreatitis, and disease in other organs, definite tissue-invasive disease requires the correct clinical syndrome combined with the detection of cytomegalovirus in tissue samples (or in bronchoalveolar lavage fluid for pneumonia) by virus isolation, immunohistochemical analysis, *in situ*

hybridization, or conventional histologic features. Detection of cytomegalovirus by PCR alone is not sufficient.

- Cytomegalovirus viral syndrome requires fever (oral temperature >38°C) for two or more days within a 4-day period, neutropenia or thrombocytopenia, and the detection of cytomegalovirus in the blood by culture or the detection of antigen, DNA, or RNA. Human herpes virus -6 (HHV-6) infection needs to be excluded.
- For central nervous system (CNS) disease, detection of cytomegalovirus in cerebrospinal fluid (CSF) samples by culture or PCR is sufficient.
- For retinitis, typical cytomegalovirus lesions must be confirmed by an ophthalmologist; detection of cytomegalovirus is not required.

c. PROBABLE DISEASE requires the correct clinical syndrome but the detection of cytomegalovirus cannot be confirmed as outlined above.

16.3.2 Epstein-Barr virus

Epstein-Barr virus (EBV) is a widely disseminated herpesvirus spread by close contact between susceptible persons and asymptomatic EBV shedders. Most primary EBV infections are asymptomatic or subclinical (Demmler-Harrison 2018).

EBV is the primary agent of infectious mononucleosis. Infectious mononucleosis usually begins with malaise, headache, and low-grade fever before onset of more specific signs of the infection, such as pharyngitis and cervical lymph node enlargement. Patients usually have a peripheral blood lymphocytosis, with atypical lymphocytes. Splenic rupture is a rare but potentially life-threatening complication of infectious mononucleosis and may be the first symptom that brings the patient to medical attention.

Antiviral therapy, such as acyclovir, may reduce EBV transmission, but may not impact latent infection. EBV has been associated with the development of B cell lymphoma, T cell lymphoma, Hodgkin lymphoma, and nasopharyngeal carcinoma.

16.3.3 SARS-CoV-2 virus of COVID-19 disease

SARS-CoV-2 is a member of the coronavirus family which is responsible for the COVID-19 disease. Having T1DM does not make patients more susceptible to contracting COVID-19. Although patients with diabetes have higher morbidity from COVID-19 in general, this epidemiologic finding is largely driven from the substantial contribution of data from patients with type 2 diabetes mellitus (T2DM). There is no evidence to date this is the case for pediatric T1DM (https://www.cdc.gov/mmwr, 6th April, 2020). Testing for SARS-CoV-2 virology and serology is performed prior to the first dose of study drug. Serum specimens are banked for testing at later times, and not assayed immediately given current uncertainties on sensitivity and specificity.

Subjects should be reminded to follow local appropriate hygienic preventive guidance to avoid contracting COVID-19. In subjects who are suspected to have COVID-19 additional testing may be warranted during the trial including virology (PCR) to detect SARS-CoV-2 RNA, serologic evaluation, and clinical monitoring for early signs of end organ disease. Appropriate targeted anti-viral or anti-bacterial therapies should be initiated as indicated in consult with an infectious disease expert.

If CFZ533/placebo administration is withheld for COVID-19, clearance of COVID19 infection in order to resume treatment during the study includes resolution of symptoms and absence of infectious virus / viral replication from a respiratory specimen.

16.4 Appendix 4: European Medical Agency Guidance for Trial Related Blood Loss

European Medicines Agency (EMA) recommendations for trial related blood volume (including any losses in the maneuver) in pediatric populations are that no more than 3% of total blood volume should be taken during a four week period and not more than 1% of total blood volume at a single time-point. At a total blood volume estimated at 80 to 90 mL per kilogram (kg) body weight, this equates to 2.4 mL to 2.7 mL blood per kg body weight during a four week period, or 0.8 mL to 0.9 mL blood per kg at any one time.

These recommended volumes must not be exceeded for any patient. Please use the information below to ensure that the recommended volumes are adhered to:

Table 16-4 Total blood volume, 1 percent and 3 percent of total blood volume by weight assuming 85mL per kg total blood volume:

Weight (Kg)	Total Blood Volume (mL)	1% Blood Volume (mL)*	3% Blood Volume (mL)*
5	425	4	12
10	850	8	24
15	1275	12	36
20	1700	17	51
25	2125	21	63
30	2550	25	75
35	2975	29	87
40	3400	34	102
45	3825	38	114
50	4250	42	126
55	4675	46	138
60	5100	51	103
65	5525	55	165
70	5950	59	177
75	6375	63	186
80	6800	68	204