NOVARTIS

Global Drug Development

CFZ533

Investigator's Brochure

Document type:	Investigator's Brochure
Edition number:	Edition 7, replacing Edition 6 dated 13-Dec-2016
Release date:	12-Dec-2017
Safety cut-off date:	15-Nov-2017

IB Template version 3.0, 02-Dec-2016

Confidential

IMPORTANT: This document contains proprietary and confidential information belonging to Novartis. Its contents may not be disclosed or used without the express permission of Novartis.

Clause de confidentialité

IMPORTANT: Ce document contient des informations confidentielles et internes à l'entreprise. Il est la propriété exclusive de Novartis. Son contenu ne pourra être ni divulgué, ni utilisé sans l'autorisation expresse de la société.

Clausola di confidenzialità

IMPORTANTE: Questo documento contiene informazioni confidenziali di esclusiva proprietà della Novartis. Il suo contenuto non deve essere né divulgato né utilizzato senza autorizzazione esplicita della Novartis.

Confidencial

IMPORTANTE: Este documento contiene información confidencial propiedad de Novartis. Su contenido no podrá divulgarse ni utilizarse sin la autorización explícita previa de Novartis.

Vertraulichkeit

WICHTIG: Die in diesem Dokument enthaltenen Informationen sind vertraulich und Eigentum von Novartis. Der Inhalt dieses Dokuments darf ohne ausdrückliche Genehmigung von Novartis nicht weitergegeben oder für andere Zwecke verwendet werden.

Summary of key changes from Edition 6 to Edition 7

Section description	Section No. in current Edition 7	Key changes from last Edition
Title page		IB owner updated to Global Drug Development
Multiple sections		Administrative changes, e.g., to correct typographical and grammatical errors and to improve story flow have been implemented across multiple sections
Overall Risk-Benefit		Section has been revised, mainly to provide update on the overall CFZ533 clinical development in various indications, and to provide the most updated information related to ongoing clinical trials.
Summary	1	Section has been revised to update status of CFZ533 pre-clinical and clinical studies.
Indications being tested or under consideration	2.2	Updated status of CFZ533 clinical development program.
Physical, chemical and pharmaceutical properties	3	This section has been revised to incorporate minor updates, including details regarding the cell line and for the addition of "do not freeze" in the storage condition sub-section 3.2.2.
Non-clinical studies	4	This section has been revised to incorporate updated information, and references to the corresponding sections were added.
Human studies	5.1	This section has been revised to mainly incorporate: (i) final PK/PD data from study CCFZ533X2101 (Section 5.1.1); (ii) the flow was improved for study CCFZ533X1101 (Section 5.1.2); (iii) Interim and preliminary PK/PD data from study CCFZ533X2203 (Section 5.1.3) are provided, the flow was improved (iv) Interim and preliminary PK/PD data from study CCFZ533X2101 Part 1 (Section 5.1.4) are provided (v) Interim and preliminary PK data from study CCFZ533X2204 are provided in Section 5.1.5 (vi) Interim and preliminary PK data from study CCFZ533X2205 are provided in Section 5.1.6 (vii) Sections 5.1.7 to 5.1.13 were updated to provide general statement.

Section description	Section No. in current Edition 7	Key changes from last Edition
Summary of clinical trials	5.2.1	Update of human clinical data per CFZ533 study.
Investigator Notifications	5.2.2	Added two new Investigator Notifications submitted including gastroenteritis and Polyomavirus-associated nephropathy.
Reference Safety Information	6	Infection removed as an adverse drug reaction from RSI table. Injection site pain removed as an adverse drug reaction from RSI table.
Summary of the data and guidance for the Investigator.	7	Minor changes made following completion of CFZ533X2101 and CFZ533X2205 (final data available). Potential human safety concerns section updated: changes in lymphoid structures as potential risk, systemic inflammation and renal dysfunction risks removed.

Overall Risk-Benefit

CD40 signaling has been implicated in the pathology of several immune-mediated conditions including renal allograft transplantation, primary Sjögren's syndrome (pSS), systemic lupus erythematosus (SLE), lupus nephritis, myasthenia gravis and Graves' disease (GD). In these indications with high unmet medical needs, a blocking anti-CD40 antibody may provide therapeutic benefit. We therefore developed CFZ533, a fully human, non-depleting IgG1 anti-CD40 antibody that blocks recombinant CD154 (rCD154)-induced activation of CD40 pathway signaling *in vitro* and *in vivo*. Section 4.1 and Section 4.3 describe in detail the pharmacology and preclinical toxicology of CFZ533, respectively. Findings related to safety, pharmacokinetics and pharmacodynamics of CFZ533 in human are discussed in Section 5.

Potential risks for CFZ533 have been identified based on preclinical and clinical results available to date, as well as from data available for other compounds of the same class. These currently include infusion and injection related reactions, infections, therapeutic failure of vaccination during CFZ533 treatment, changes in lymphoid structure, loss of efficacy or allergic/immune-mediated inflammatory reactions due to anti-CFZ533 antibodies, thrombophilia and lymphoproliferative disorders.

Potential benefits of CD40 blockade (including CFZ533) in patients are based on evidence suggesting that pharmacological inhibition of CD40-CD154 interactions reduced autoimmune disease pathology in various pre-clinical and clinical studies, blocked T cell-dependent immune responses, and prolonged allograft survival in non-human primates (NHPs).

To date approximately 286 subjects receiving either CFZ533 (n=approximately 198) or control drug (n=87, 69 on placebo or 18 on standard of care treatment) have been enrolled in the CFZ533 clinical development program.

In the First-in-human Phase 1 clinical study (Section 5.2.1.1), single doses of intravenous (IV) or subcutaneous (SC) CFZ533 up to 30 mg/kg (inclusive) were evaluated and showed a favorable safety and tolerability profile in healthy volunteers and in rheumatoid arthritis (RA) patients. A Chinese HV cohort receiving a single dose of 3 mg/kg IV was also included in this first-in-human (FIH) study. CFZ533 at 3 mg/kg was generally safe and well tolerated in Chinese subjects, no differences are observed between the Chinese and non-Chinese subjects receiving the same dose. Similarly, in a Phase 1 study of Japanese healthy volunteers, single IV (0.3, 1 and 3 mg/kg), and SC (3 mg/kg) doses of CFZ533 were safe and well-tolerated (Section 5.2.1.2). Furthermore, interim data from a Phase 2a study (Section 5.2.1.4), where clinically active primary Sjögren`s syndrome (pSS) patients have received multiple doses (8 doses over 21 weeks) of 3 mg/kg SC or 10 mg/kg IV CFZ533 or placebo suggest a favorable safety and tolerability profile in both dose cohorts. Preliminary efficacy data from this study also suggest that multiple doses of 10 mg/kg IV CFZ533 may have therapeutic benefit in pSS patients.

Studies in renal transplantation (CFZ533X2201) and Myasthenia Gravis (CFZ533X2204) are still ongoing; interim data from both studies suggest that CFZ533 is well tolerated, with favorable safety and support further development of the CFZ533 in transplantation and Myasthenia Gravis.

The study in patients with Graves` disease (CFZ533X2205) is completed. Based on the events reported (Section 5.2.2 and Section 6) as well as review and recommendations by the Data Monitoring Committees (for the renal transplantation and myasthenia studies), no major new safety signals have emerged.

Overall, the risk-benefit remains unchanged since Edition 6 of the Investigator's Brochure and is considered favorable to support investigation of CFZ533 in renal transplant patients and patients with autoimmune diseases such as primary Sjögren`s syndrome, Graves`s disease, systemic lupus erythematosus, lupus nephritis, Type 1 Diabetes and myasthenia gravis.

Table of contents

List of tables

List of figures

List of abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
APC	antigen presenting cells
aPTT	activated partial thromboplastin time
BPAR	biopsy proven acute rejection rates
ca	circa (from Latin, meaning 'around, about')
CDC	complement dependent cytotoxicity
CHO	Chinese hamster ovary
CK	creatine kinase
CNI	calcineurin inhibitor
CRP	C-reactive protein
CsA	cyclosporine
ELISA	enzyme-linked immunosorbent assay
EOS	eosinophils
ESSDAI	EULAR Sjögren Syndrome Disease Activity Index
EULAR	European League Against Rheumatism
Fab	antigen binding fragment of an antibody
Fc	crystalizeable fragment of an antibody
FIH	first-in-human
GC	germinal center
GD	Graves' disease
GVHD	graft versus host disease
HEV	high endothelial venules
HIGM	hyper IgM syndrome
HUVEC	human umbilical vein endothelial cell
Ig	immunoglobulin
IHC	immunohistochemistry

IV	intravenous
KLH	keyhole limpet hemocyanin
LCV	Lymphocryptovirus
LN	lymph node
LYM	lymphocyte
MFI	mean fluorescence intensity
mg	milligram(s)
mL	milliliter(s)
MMF	mycophenolate mofetil
NHP	non-human primate
NOAEL	no observed adverse effect level
OPD	ortho-phenylenediamine
PALS	periarteriolar lymphatic sheath
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PML	post-transplant lymphoma
p.o.	oral
pSS	primary Sjögren's syndrome
PT	prothrombin time
QoL	quality of life
RA	rheumatoid arthritis
RBC	red blood cell(s)
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SLE	systemic lupus erythematosus
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
Tac	tacrolimus
TDAR	T-cell–dependent antibody response
TK	toxicokinetic(s)

TMD	Target mediated disposition
TRAFs	TNF receptor-associated factors
TRIG	triglyceride
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPRO	protein in urine
TTx	tetanus toxoid

1 Summary

CD40 is a transmembrane glycoprotein constitutively expressed on B cells and other antigen presenting cells (APCs) including monocytes, macrophages, and dendritic cells (DCs), as well as by platelets, and inflamed parenchyma. Binding of CD40 by its ligand CD154 results in cell-type specific activation outcomes, including DC maturation, monocyte survival and cytokine secretion by many cell types including renal epithelial cells (van Kooten and Banchereau 2000). In addition, CD40 pathway stimulation is required for many aspects of humoral immunity including germinal center (GC) formation, memory B cell development, immunoglobulin (Ig) isotype switching, and affinity maturation.

Pharmacological inhibition of CD40-CD154 interactions using anti-CD40 or anti-CD154 antibodies reduced autoimmune disease pathology in numerous pre-clinical and clinical studies, and prolonged allograft survival in non-human primates (NHPs) (Aoyagi et al 2009; Oura et al 2010; Watanabe et al 2010). However, the clinical utility of monoclonal antibodies targeting CD154 has been hampered by the occurrence of thromboembolic complications (Kawai et al 2000). An alternative approach therefore, would be to employ an anti-CD40 antibody.

CFZ533 is a fully human, non-depleting IgG1 (N297A) anti-CD40 antibody that blocks rCD154-induced CD40 signaling without depleting CD40 expressing cell types by antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC). CFZ533 binds human and NHP (but not rodent) CD40 with a Kd value of approximately 0.3 nM. It blocks CD40 pathway activation via direct competition with CD154 for binding to CD40, resulting in inhibition of proliferation and other effector functions without depleting CD40 expressing cells. CFZ533 also has minimal stimulatory activity as demonstrated by an inability to induce human peripheral blood mononuclear cell (PBMC) proliferation or significant upregulation of activation molecules on B cells in human whole blood.

In preclinical transplant studies, CFZ533 prolonged NHP renal allograft survival as monotherapy. CFZ533 also completely suppressed primary and secondary antibody responses to immunization with T cell-dependent antigens. Efficacy in these preclinical models was achieved in the absence of significant peripheral B cell depletion. Importantly, after clearance of CFZ533, subjects were able to mount normal primary and recall humoral immune responses. CFZ533 also suppressed T cell-dependent antibody responses in healthy human subjects at serum concentrations in excess of 20 µg/ml.

Toxicology studies with CFZ533 did not reveal any significant organ toxicities, including no evidence of thromboembolic events. In a 5-week cynomolgus monkey study using CFZ533 intravenously at 100 mg/kg/wk, no toxicity findings were observed. In a 13-week GLP rhesus monkey study, where doses of 10, 50 and 150 mg/kg CFZ533 were administered weekly, increased lymphoid cellularity was noted in 5 out of 22 animals and considered to be due to ongoing infection, an observation consistent with the pharmacology of CFZ533. In addition, inflammatory lesions were noted in the kidneys and lungs of 2 mid-dose (50 mg/kg/wk) animals as well as eyes and trachea in 1 of the 2 mid-dose animals. The weight of evidence, including confirmation of opportunistic pathogens, suggests that these findings are likely secondary to CFZ533-mediated immunosuppression and of an infectious origin. In view of these inflammatory findings in the context of an infectious background at 50 mg/kg, the no

observed adverse effect level (NOAEL) for the 13-week toxicity study was set at 10 mg/kg. In a 26-week chronic toxicity study in cynomolgus monkeys no adverse CFZ533-related findings were discovered. Based on these data, the NOAEL was established at 150 mg/kg (26-week).

To date approximately 286 subjects receiving either CFZ533 (n=approximately 198) or control drug (n=87, 69 on placebo or 18 on standard of care treatment) have been enrolled in the CFZ533 clinical development program. The FIH study (CCFZ533X2101) evaluated:

- a single ascending dose study from 0.03 mg/kg to 3.0 mg/kg in healthy subjects;
- a single subcutaneous (SC) of 3.0 mg/kg in healthy subjects;
- a single dose of 3 mg/kg IV in healthy Chinese subjects
- placebo in 56 healthy subjects
- an IV dose of 10 mg/kg or placebo in 12 RA patients (6 per group)
- an IV dose of 30 mg/kg in RA patients
- placebo in 8 RA patients (4 per group)

All doses up to 30 mg/kg are generally safe and well tolerated, and there was no evidence of cytokine release or CFZ533 related serious adverse events (SAEs). Any reported adverse event (AE) suspected to be related to CFZ533 by the investigator were mild to moderate in severity, transient and did not result in subject discontinuation. The overall rate of infections following single doses of CFZ533 across all cohorts in healthy subjects and RA patients in the Phase 1 program was comparable to placebo. No severe or serious infections have occurred in any of the CFZ533 treated subjects. Furthermore, there have been no clinically significant deviations in laboratory parameters and vital signs, including hematology and coagulation parameters (e.g., prothrombin time (PT), activated partial thromboplastin time (aPTT), thromboelastography).

In the Phase 2 program, formal interim data are available from the pSS study (CCFZ533X2203, Section 5.2.1.4), in which clinically active pSS patients received multiple doses (8 doses over 21 weeks) of 3 mg/kg SC or 10 mg/kg IV CFZ533 or placebo. Preliminary data suggest a favorable safety and tolerability profile in both dose cohorts and efficacy data suggest that multiple doses of 10 mg/kg IV CFZ533 have therapeutic benefit in pSS patients. The study in patients with Graves' disease is completed and CFZ533 at 10 mg/kg Q4W for 12 weeks was generally safe and well tolerated. Twelve weeks of treatment with CFZ533 at 10 mg/kg led to significant reductions in the autoantibodies (TRAb) and thyroid hormones (T3 and T4).

Studies in renal transplantation (CFZ533X2201) and myasthenia gravis (CFZ533X2204) are still ongoing; interim data from both studies suggest that CFZ533 is well tolerated, with favorable safety and support further development of the CFZ533 in transplantation and myasthenia gravis.

Overall, based on the events reported (Section 5.2.2 and Section 6) as well as review and recommendations by the Data Monitoring Committees (for the renal transplantation and myasthenia indications), no major new safety signals have emerged.

In the FIH study, in HVs as well as in RA patients, after single IV or SC administration, pharmacokinetic (PK) profiles were consistent with target-mediated disposition of CFZ533, resulting in non-linear PK profiles and more rapid clearance when CD40 receptor occupancy (RO) in whole blood B cells dropped below approximately 90%. The disposition of CFZ533 in healthy Chinese or Japanese subjects was generally similar as compared to Caucasian subjects. In HVs, after SC administration, CFZ533 was rapidly absorbed and distributed in line with what is expected for a typical IgG1 antibody in human. In RA patients, at 10 and 30 mg/kg IV, pharmacokinetic/pharmacodynamic (PK/PD) profiles are consistent with a duration of target engagement of 8 and 16 weeks, respectively.

A single dose of 3 mg/kg (IV or SC) of CFZ533 transiently suppressed anti-KLH (Keyhole Limpet Hemocyanin) responses to KLH immunization, at CFZ533 concentrations corresponding to full RO (≥90%), for about 3-4 weeks. All subjects were able to mount recall responses to a second KLH immunization when CFZ533 is cleared. During the period corresponding to full CD40 occupancy on B cells, CFZ533 prevented rCD154-induced-CD69 expression. When CD40 occupancy was incomplete, the functional activity of rCD154 was restored.

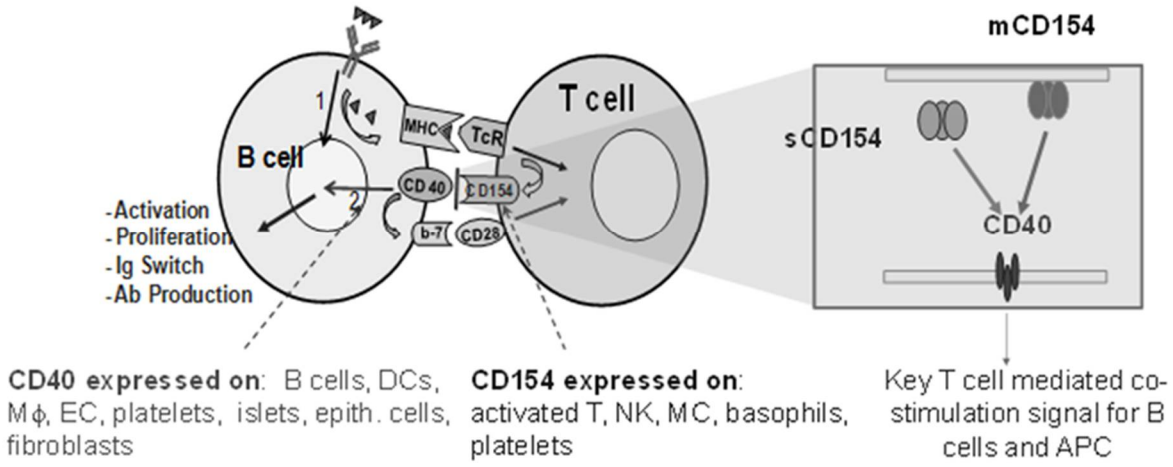
Collectively, current pre-clinical and clinical data support the further development of CFZ533 in clinical trials.

2 Introduction

2.1 CD40 and CD40 ligand biology

CD40 is a member of the tumor necrosis factor (TNF) super-family of proteins. It is a 48 kDa membrane glycoprotein that is predominantly membrane associated but also exists in a soluble form (20.1 kDa). CD40 is constitutively expressed on mature and activated B lymphocytes, as well as other APCs, platelets and eosinophils. CD40 is also upregulated by parenchyma in inflamed tissues, including endothelia, kidney epithelial cells, synovial membranes, keratinocytes and dermal fibroblasts.

Figure 2-1 Roles of CD40-CD154 signaling in the T and B cell



Targeting CD40-154 interactions in transplantation and autoimmune disease. CD40-CD154 interactions are essential for APC activation, T cell priming in the context of APC-T cell interactions and T-cell dependent humoral responses. mCD154=membrane bound CD154; sCD154=soluble CD154. Ig – immunoglobulin; Ab – antibody; DC – dendritic cell; mϕ - macrophage; EC – endothelial cells; NK – natural killer cells; MC – mast cells; APC – antigen presenting cells.

The endogenous ligand for CD40 is CD154 (CD40L) which exists in both membrane-bound and soluble forms. Membrane-bound CD154 is a transmembrane glycoprotein expressed on activated T and B lymphocytes, mast cells, monocytes, basophils, eosinophils, natural killer (NK) cells, and activated platelets. It can also be expressed at low levels on vascular endothelial cells and is up-regulated in areas of local inflammation. Membrane CD154 is cleaved to form soluble CD154 (sCD154) and is shed from lymphocytes and platelets following cellular activation. Both membrane bound and soluble forms of CD154 are biologically active and can stimulate signaling downstream of CD40 following ligation.

The engagement of CD154 on CD40 recruits TNF receptor-associated factors (TRAFs) that trigger downstream activation of multiple signaling pathways (e.g., JNK, ERK1/2, p38). Activation of various kinase cascades stimulates a variety of transcription factors such as NF-κB and AP1 to induce expression of numerous genes involved in cell survival, activation and differentiation (Bishop et al 2007).

CD40 activation by CD154 also appears to be essential for multiple aspects of primary T-cell-dependent antibody responses including GC formation, Ig isotype switching, somatic mutation, and memory B cell and plasma cell differentiation (Figure 2-1; Foy et al 1994; Quezada et al 2004). CD154-mediated activation of APCs also leads to induction of cytokine secretion and expression of surface activation molecules (including CD69, ICAM1, CD80 and CD86) that are involved in the regulation of CD4+ T cell help and CD8+ T-cell cross-priming and activation.

The downstream biological effects of CD40 activation in non-hematologic cells (e.g., endothelial cells, epithelial cells and fibroblasts) has not been as extensively studied and as such, the functional relevance of CD40 expression on these cells is not fully known. There are reports of CD40 engagement on renal epithelial cells inducing the production of chemokines like IL-8 and MCP-1 (Li et al 2008), as well as upregulation of adhesion molecules.

Insights into the role of CD40-CD154 interactions were also provided by the discovery of hyper IgM (HIGM) syndrome; an X-linked immunodeficiency condition linked to loss-of-function mutations in CD154 and CD40. Patients with HIGM lack GCs (as well as a memory B cell repertoire), are unable to mount T-cell dependent antibody responses and display increased susceptibility to certain opportunistic infections (Lougaris et al 2005; Durandy et al 2004). B cells from patients with HIGM are unable to undergo Ig class switching or affinity maturation, thus patients present with little to no circulating IgG, IgA or IgE antibodies. Identical immunological defects are observed in CD40 and CD154-deficient mice (Kawabe et al 1994; Xu et al 1994). Therefore, inhibition of CD40-CD154 interactions with a blocking anti-CD40 antibody would be expected to prevent CD154-mediated activation of CD40 expressing cells. This would then lead to the subsequent suppression of a variety of immune effector functions linked to the pathogenesis of certain autoimmune diseases and transplant rejection. In contrast to HIGM patients in whom the CD40 related deficit exists

from birth, subjects treated with CFZ533 were still able to mount antibody responses after the drug was eliminated (Section 7.2.2).

2.2 Indications being tested or under consideration

2.2.1 Solid organ transplantation: renal allotransplantation

Current immunosuppressive regimens are usually based on combinations of 2 or 3 immunosuppressive drugs. The calcineurin inhibitors (CNI), such as cyclosporine (CsA) or tacrolimus (Tac), are one such class of immunosuppressives used to maximize efficacy and minimize adverse effects. While CNI based standard of care (SoC) has resulted in excellent 1 year patient and graft survival (>95%) with low (10-15%) 1 year biopsy proven acute rejection rates (BPAR), its use is still limited by mechanism-based side effects and poor long-term graft survival. Side effects such as hypertension, dyslipidemia and diabetes as well as gastrointestinal-, hematological-, neuro- and nephrotoxicity are common and result in poor long-term patient survival. In addition, with the current SoC, 5 and 10 year renal allograft survival rates of 67% and 42%, respectively, are common. Hence, a considerable need remains for safer immunosuppressants that can prevent both acute and chronic rejection.

In the search for novel therapeutics, there has been an increasing interest in the role co-stimulation, B cells, plasma cells and antibodies play in the immune response to an allograft, specifically acute cellular rejection and chronic antibody mediated rejection (Clatworthy 2011). The CTLA-4-Fc (Fc: crystalizeable fragment of an antibody) fusion protein (Nulojix®, belatacept,) was approved for clinical use in renal transplant immunosuppression without a CNI (Nulojix® belatacept PI 2013). Belatacept targets the CD80/86-CD28 pathway responsible for T-cell activation, and, when used without a CNI, results in better renal function and decreased cardiovascular risk in comparison to CNI based regimens. Although the benefit in renal function is significant, Belatacept-based treatment regimens have also been found to result in a higher rate of acute rejection (17-22%) compared to the current SoC and have been associated with untoward side effects such as post-transplant lymphomas (PTLD and PML) (Vincenti et al 2010).

Targeting both CD40 and CD154 has shown promise in non-human transplant models, including models for solid organs (liver and kidney), pancreatic islets and graft versus host disease (GVHD). Teneliximab (Chi220, BMS-224819) is a chimeric IgG1 anti-CD40 antibody which is also a partial agonist and was reported to prolong renal allograft survival in rhesus monkeys (Pearson et al 2002). Similarly, the fully human IgG4 anti-CD40 antibody ASKP1240 (4D11) prolonged renal allograft graft survival in cynomolgus monkeys for up to 180 days when given as maintenance therapy and 50 days as induction therapy (Imai et al 2007; Aoyagi et al 2009). NHP studies with CFZ533 are in agreement with these results with survival times of up to 100 days (end of experiment) and normal graft morphology when administered as a monotherapy (Section 4.1.1.2).

In a recent preliminary report of a clinical Phase 2 study in renal transplantation, ASKP1240 was shown to be unable to prevent rejections in a CNI-free setting, however, the doses used are assumed to have been insufficient to achieve full tissue CD40 occupancy (particularly during the first weeks of treatment), due to high target-mediated drug disposition (Harland et al 2015). These results, taken together with data from studies in NHPs and analysis of the ASKP1240 data by Novartis (see also Section 5.2.3), reinforce the approach of targeting the CD40-CD154 axis with sufficient exposure of the CD40 blocking agent both in

tissues and periphery to adequately inhibit this pathway for efficacy (Ma et al 2014; Cordoba et al 2015).

Overall, there is abundant evidence from preclinical allo-transplantation models that support the role of the CD40-CD154 co-stimulation axis in immune function and transplant rejection. Targeting CD40 with CFZ533 in patients following *de novo* renal allo-transplantation may provide an opportunity to develop a treatment regimen that avoids CNI toxicities with similar acute rejection rates and better long term survival.

2.2.2 Autoimmunity

2.2.2.1 Systemic lupus erythematosus and lupus nephritis

Systemic lupus erythematosus (SLE), in particular lupus nephritis, represents a high unmet medical need. Lupus nephritis is a common manifestation of SLE affecting up to 60% of patients, with greater representation in children and young adults (Waldman and Appel 2006). Only about half of the patients that receive intensive induction therapies with IV and/or oral corticosteroids combined with IV cyclophosphamide or oral mycophenolate mofetil (MMF), achieve a satisfactory renal response. Furthermore, these therapies also carry a significant burden of toxicity. Maintenance therapies with lower doses of oral corticosteroids, azathioprine or MMF often fail to maintain remission.

CD40-CD154 interactions have been implicated in the pathology of SLE. For example, anti-CD154 treatment of lupus prone animals was found to ameliorate renal disease (Mohan et al 1995). Elevated sCD154 levels in SLE sera has also been documented and activated T and B cells from the periphery of active SLE patients were found to express CD154 (Desai-Mehta et al 1996). Additionally, augmented CD40 and CD154 expression was observed on renal parenchymal cells from patients suffering from proliferative lupus nephritis (Yellin et al 1997), potentially linking CD40 signaling to organ-specific pathology. Clinical remission of lupus nephritis following rituximab was preceded by downregulation of CD154 on CD4+ T cells (Sfikakis et al 2005). Finally, an anti-CD154 antibody, BG9588, improved serologic activity and decreased hematuria in patients with proliferative lupus nephritis in an open-label Phase 2 study (Boumpas et al 2003). Treatment of SLE patients with BG9588 led to the disappearance of $CD38^{high}$ Ig-secreting plasma cells from the periphery (Grammer et al 2003) and reduced the frequency of peripheral blood anti-dsDNA antibody-producing B cells (Huang et al 2002). Treatment with this compound did however provoke life-threatening thromboembolic events precluding further clinical development. By contrast, another anti-CD154 antibody; IDEC-131, did not show better efficacy than placebo in patients with mild to moderately active SLE in a randomized, double-blind, placebo-controlled Phase 2 study (Kalunian et al 2002). The lack of efficacy was explained by mild severity of disease and insufficient dosing.

2.2.2.2 Primary Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is a common chronic autoimmune disease of unknown etiology. The impact of this disease on quality of life (QoL) measures is substantial and comparative studies indicated that pSS QoL scored quantitatively worse than congestive heart failure or many cancers (Segal et al 2009; Kuenstner et al 2002; Komaroff et al 1996). Moreover, B cell hyper-reactivity in pSS results in an increased risk for malignant transformation with lymphoma development occurring in 5% of pSS patients. Treatment for pSS patients is limited to symptomatic care for the mucosal signs and symptoms, and to date no evidence-based, systemic therapy has been available for pSS patients.

Several lines of evidence suggest that disease pathology driven by or closely related to the CD40-CD154 pathway is essential in pSS. Hallmark diagnostic features of pSS include B cell hyper-reactivity such as formation of GC like structures in salivary glands (observed in 18-59% of patients) and autoantibodies such as SSA, SSB or RF (Vossenkämper et al 2012). In pSS lesions, activated T cells predominate and are capable of provoking B cell hyperactivity, Ig secretion and facilitating destruction of glands through Fas and perforin-mediated cytotoxicity (Manganelli and Fietta 2003). In addition, T and B cell infiltrates in these patients' salivary glands show up-regulation of CD40 and CD154. CD40-CD154 mediated tissue inflammation may also contribute to pSS pathogenesis.

2.2.2.3 Myasthenia gravis

Myasthenia gravis (MG) is a rare T cell-dependent autoantibody-mediated disorder in which pathogenic autoantibodies against muscle antigens such as the acetylcholine receptor (AChR) or muscle-specific kinase (MuSK) directly cause muscle weakness. Although treatment options including anticholinesterase medication, immunosuppressive agents, plasmapheresis and/or thymectomy are available, a high unmet medical need still exists for a subset of patients that are refractory to and/or experience toxicities from the SoC therapy (Berrih-Aknin et al 2014).

Monoclonal anti-CD154 antibodies in chronic experimental autoimmune MG in rats were shown to suppress the clinical progression of the immune mediated process and led to a decrease in the AChR-specific antibodies and delayed-type hypersensitivity (Im et al 2001). Based on the ability of CFZ533 to inhibit T cell-dependent B cell functions and data suggesting the involvement of the CD40/CD154 pathway in the pathogenesis of myasthenia, CFZ533 may offer therapeutic benefit to patients suffering from myasthenia gravis.

2.2.2.4 Graves' disease

Graves' disease (GD), the most common form of hyperthyroidism, is characterized by diffuse goiter and ophthalmopathy and can result in increased morbidity and mortality when left untreated (Weetman 2000, Sundaresh et al 2013). Pathologically, thyroid stimulating hormone (TSH) receptor antibodies (TRAb) activate TSH receptors expressed on thyrocytes and induce unregulated overproduction of thyroid hormone. Furthermore, they can also activate TSH receptors expressed on orbital fibroblasts, which in turn stimulate T cells. Stimulated T-cells secrete glycosaminoglycans and cytokines leading to local tissue inflammation and swelling. This can result in Graves' ophthalmopathy which affects approximately 50% of GD patients, 5% of which are severe and require surgery. Treatment usually involves systemic

corticosteroids however this is often minimally effective resulting in the need for orbital decompression surgery.

The CD40-CD154 signaling pathway has been implicated in the pathogenesis of GD, and in particular, in Graves' ophthalmopathy (Bahn 2010). CD40 expression is increased in the thyroid glands of patients with GD (Hwang et al 2009). Overexpression and activation of the CD40 in the orbital fibroblasts of Graves' ophthalmopathy patients elicits proinflammatory cytokine production (Sempowski et al 1998, Hwang et al 2009). Furthermore, CD154 upregulates the expression of adhesion molecules important for lymphocyte infiltration (ICAM-1, VCAM-1 and E-Selectin) (Wang et al 2015) and induces substantial increases in hyaluronan synthesis in orbital fibroblasts and prostaglandin endoperoxide H synthase-2 expression (Cao and Smith 1999).

CFZ533 has the potential to inhibit T-cell dependent TRAb production in germinal centers and T-cell dependent production of cytokines, adipose and ocular muscle hypertrophy in orbital tissues. Overall, based on the mode of action of CFZ533 and on the pathogenesis of GD, CFZ533 is believed to be capable of attenuating the underlying pathogenesis of GD and may represent a novel therapy in the treatment of Graves' hyperthyroidism and Graves' ophthalmopathy.

2.2.2.5 Type 1 Diabetes

Type 1 diabetes (T1D) is a life-threatening organ specific T-cell mediated auto-immune disease that can manifest at any age, including in seniors. It is also the most common chronic auto-immune disease in children. T1D results from selective auto-immunity against insulin-producing β-cells in the pancreas. This pathologic process results in insulin deficiency and hyperglycemia, requiring lifelong dependence on exogenous insulin therapy. T1D is associated with increased mortality, and acute and long term complications due to inadequate glycemic control and side effects of insulin therapy. To date, there is no available disease modifying therapy and no cure. Some clinical studies with immune modulators, such as Rituximab and anti CD3 antibodies have indicated transient improvements in β-cell function but no lasting remission (Ehlers 2016).

CD40 appears to play an important role in the pathophysiology of T1D. CD40 is expressed in many hematopoetic cells such as B lymphocytes, antigen-presenting cells, macrophages, dendritic cells and has also been identified on T cells, including CD4+ and CD8+ lymphocytes resulting in auto aggressive peripheral T cells in auto-immune disease (Wagner 2017). CD40 is also expressed in non-hematopoetic cells, and is specifically expressed in human pancreatic β cells (Klein 2005). Activation of CD40 in human pancreatic β cells induced the expression and release of inflammatory cytokines and chemokines (Klein 2005). Activation of CD40 in pancreatic β cells of the RIP-CD154 transgenic model of T1D induced the development of local inflammation, insulitis a hallmark of T1D (Haase and Markholst 2007).

T helper cells positive for CD40 (THCD40+ cells) appear to be highly pathogenic in the NOD mouse, a model of spontaneous auto-immune diabetes and in translational human T1D studies (Vaitatis et al 2017). THCD40+ cells purified from diabetic and pre-diabetic NOD mice were shown to be both necessary and sufficient for transferring T1D to NODd recipient mice (Waid

et al 2004). Expansion and activation of TH CD40+ cells was demonstrated in pancreatic lymph nodes before the onset of insulitis in the NOD model (Vaitaitis et al 2017). Thus, CD40 expression on T helper cells and in the pancreas appears to be required not only for the development of diabetes, but also for cell trafficking leading to insulitis, a hallmark of T1D. CD40 blockade has been shown to delay disease progression in the NOD model (NOD). CD40 blockade with a targeted small peptide, KGYY15 was shown to prevent hyperglycemia and also to reverse new-onset hyperglycemia in NOD (Vaitaitis et al 2014). Blockade of B lymphocytes, such as with rituximab has been shown to delay disease progression in the NOD model and in T1D patients, implicating a pathogenic role for B lymphocyte in this disease (Pescovitz at al 2014).

Information on the role of CD40 in human T1D is scarce and is limited to data from peripheral blood samples. Higher levels of soluble CD40, a circulating biomarker of tissue and cell surface CD40 levels were reported in pediatric patients with T1D compared to controls, 109±17.39 pg/mL versus 54.92 ± 3.09 pg/mL, respectively (P = 0.003) (Chatzigeorgiou et al 2010). Differentiation of follicular helper T cells (Tfh), a biomarker of CD40-CD154 interaction and germinal center formation were associated with diabetes in mice. Elevated circulating levels of Tfh were reported in 2 independent cohorts of T1D patients, indicating that expansion of Tfh is also an immunologic feature of the disease (Xu et al 2013, Ferreira et al 2015).

Thus, we hypothesize that CD40 acts as a co-stimulatory molecule that interacts with antigen-presenting cells such as B lymphocytes, activates effector T cell differentiation and expansion and promote and perpetuate auto-immunity in T1D. Additionally, we hypothesize that CD40 activation in pancreatic β cells contribute to insulitis, a local pathologic hallmark of aggressive disease progression in T1D. Blockade of CD40-CD154 activation with CFZ533 in patients with new-onset T1D could halt the auto-immune attack and reduce the insulitis, thus modifying disease progression and improving beta cell function.

3 Physical, chemical and pharmaceutical properties

3.1 Drug substance – physical and chemical properties

CFZ533 is a human monoclonal antibody directed against human CD40. CFZ533 is expressed in Chinese hamster ovary (CHO-K1PD) cell lines and belongs to the IgG1 isotype subclass. CFZ533 consists of 4 polypeptides, 2 heavy chains and 2 light chains, in heterodimeric arrangement. In total, it is composed of 1338 amino acid residues (MW 146 kD).

3.2 Drug product – pharmaceutical properties

3.2.1 Description and composition

Initially, CFZ533 was developed as a lyophilized powder in a vial, requiring reconstitution prior to infusion or injection. The amount of drug per vial is 150 mg. After reconstitution of the lyophilized powder with 1.0 mL water for injection, the resulting solution contains 150 mg/mL CFZ533 and the excipients L-Histidine, Sucrose and Polysorbate 20, pH 6.0 ± 0.5 and is a hyper-osmolar solution. A 20% overfill is added to permit complete removal of the intended dose.

For ease of administration and to improve convenience, CFZ533 was additionally developed as a 'ready to use' aqueous buffered sterile solution. The liquid in vial (LIVi) presentation (also referred to as CFZ533 Concentrate for solution for infusion/solution for injection) has the same composition as the reconstituted powder. The excipients are suitable to maintain the biological activity, purity and conformation of the protein and are suitable for intravenous infusion as well as subcutaneous injection. The same overfill of 20% is included to allow complete removal of the intended dose.

3.2.2 Storage condition

The recommended storage condition of the drug product is 2-8°C; do not freeze, protect from light.

3.2.3 Device / administration kit

No device is currently introduced; however, device development concepts are currently under review.

3.2.4 Hazards and precautions

There are no known hazards or precautions identified at this time.

4 Non-clinical studies

4.1 Pharmacology

4.1.1 Primary pharmacodynamics

CFZ533 is a fully human, non-depleting, blocking monoclonal antibody targeting CD40. By binding to cell surface CD40, CFZ533 prevents rCD154-induced activation of human and NHP leukocytes. CFZ533 contains an Fc-silencing mutation (N297A) which abolishes FcγR binding and associated effector functions like ADCC and CDC (Lund et al 1991).

4.1.1.1 *In vitro* pharmacodynamics

Summary

A summary of the *in vitro* pharmacology profiling data for CFZ533 can be found in Table 4-1. CFZ533 binds to human CD40 with high affinity, however, it was unable to bind CD16 (FcγRIII receptor) or mediate ADCC or CDC. CFZ533 inhibited rCD154-induced activation and proliferation of human leukocytes, but by itself possessed minimal stimulatory activity. Structural data indicated that CFZ533 competed with, and could displace CD154 binding to CD40 ([RD-2015-00436]). Finally, CFZ533 did not induce platelet activation *in vitro* as assessed using platelet aggregometry or thromboelastography (Section 4.1.2.1).

Table 4-1 Summary of *in vitro* properties of CFZ533 (human assays)

Assay	CFZ533 (146 kDa)
CD40 binding, SPR (Biacore) (Kd, M)	$3.05\pm0.26x10^{-10}$
CD16 binding, Biacore (Kd, nM)	No binding detected
ADCC activity (normalized specific lysis)	< 1 % (vs. reference control)
CDC activity (normalized specific lysis)	No activity (vs. positive control)
Agonist activity, human PBMC proliferation (^{3}H-Thy) (EC50) +/- costimulation (e.g. anti-Ig, IL-4)	> 100 µg/ml; > 685 µM
rCD154 inhibition – human PBMC proliferation (IC50)	0.017±0.012 µg/ml; 0.12±0.08 µM (n=12*)
rCD154 inhibition – human whole blood leukocyte proliferation (1:10 dilution) (IC50)	0.020±0.007 µg/ml; 0.14±0.05 µM (n=5)
rCD154 inhibition – human whole blood activation molecule (CD69) expression (IC50)	0.20±0.34 µg/ml; 1.4 +/- 2.3 µM (n=6)

*n indicates the number of independent donors. Sources: [RD-2012-00350], [RD-2011-00519], [RD-2010-00194], [RD-2010-00100], [RD-2012-00243], [RD-2012-00385].

CFZ533 does not stimulate human PBMCs *in vitro*

CFZ533 failed to stimulate proliferation of human PBMCs (Table 4-1), either alone or in combination with other co-stimulatory signals such as IL-4, CpG2006 (Toll-like receptor 9 ligand) or an anti-IgM F(ab')2 fragment. Additionally, CFZ533 did not stimulate cytokine production from human monocyte-derived DCs. Finally, recent experiments using CD40 expressing endothelial cells indicated that CFZ533 (in contrast to rCD154) was unable to induce ICAM1 upregulation or production of the chemokine MCP-1 (see Section 4.3.7). Upon analysis of a larger pool of healthy donors (n ~ 50), CFZ533 was seen to induce partial up-regulation of the activation marker CD69 but not proliferation in 2 donors, after overnight culture on B cells in whole blood cultures (data on file and not shown here). Increases in CD69 expression were not observed using isolated PBMCs from these donors. Results from *in vivo* preclinical studies in NHPs (Section 4.3) failed to demonstrate any evidence or consequence attributable to CD40 pathway activation such as systemic cytokine release. In the FIH study CCFZ533X2101, transient upregulation of CD69 in 1 subject from the 0.1 mg/kg cohort was seen, however, no evidence of cytokine release or clinical sequelae that could be linked to CD40 pathway stimulation was observed (i.e. no febrile response) (see Section 5.2.1.1).

Species cross-reactivity

CFZ533 binds to human and NHP (but not rodent) CD40. Therefore, pharmacology investigations and standard toxicology studies were conducted in NHPs.

Table 4-2 Summary of human and NHP cross-reactivity of CFZ533

Assay	Human	Rhesus	Cynomolgous
CD40 occupancy (CD20+ B cells – FACS) (EC50)	0.22±0.04 µg/ml 1.5±0.3 µM[1] (n=4*)	0.22±0.03 µg/ml 1.5±0.2 µM (n=6)	0.20±0.07 µg/ml 1.4±0.5 µM (n=4)
Inhibition of rCD154 + IL-4-induced proliferation (PBMCs) (IC50)	0.02±0.01 µg/ml 0.1±0.1 µM (n=12)	0.03±0.02 µg/ml 0.2±0.1 µM (n=8)	0.010±0.003 µg/ml 0.07±0.02 µM (n=4)

* n indicates the number of independent donors.

[1] based on molecular weight of 146 kDa

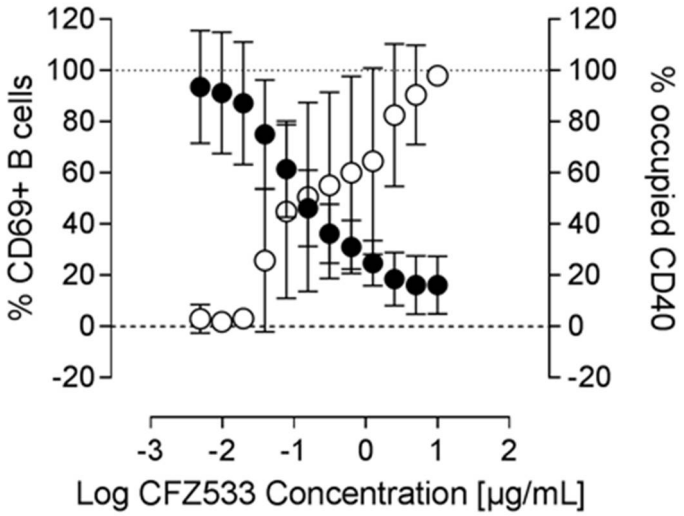
Source: [RD-2011-00519]

Table 4-2 indicates that CFZ533 binds to CD20+ cells (B cells) of all 3 species with almost identical EC50 values (less than 2-fold difference between the 3 tested species). Additionally, CFZ533 inhibited CD154+IL-4 induced proliferation of cynomolgus and rhesus PBMCs from multiple donors at similar potencies to that observed for human PBMCs.

Establishing a relationship between CD40 occupancy and functional inhibition

The simultaneous assessment of CFZ533-related CD40 receptor occupancy and functional inhibition was conducted using human whole blood cultures. Functional inhibition was assessed by examining the ability of CFZ533 to suppress rCD154-induced expression of the activation marker CD69 on CD20 positive cells (B cells). Unbound CD40 and CD69 expression levels on B cells were assessed in human whole blood cultures stimulated overnight with rCD154 in the presence of different concentrations of unlabeled CFZ533. Despite some donor-to-donor variability, we observed that complete CD40 receptor occupancy was required for CFZ533 to fully inhibit rCD154-induced CD69 expression (Figure 4-1).

Figure 4-1 **Relationship between CD40 receptor occupancy by CFZ533 and functional activity (rCD154-induced expression of CD69) in human whole blood cultures**



Simultaneous assessment of CD69 expression (closed symbols) and CD40 receptor occupancy by CFZ533 (open symbols) on CD20+ B cells in human whole blood (healthy subjects) stimulated overnight with rCD154 in the presence of different concentrations of CFZ533. Data are illustrated as CD40 occupancy and functional activity as a function of the Log of CFZ533 dose (µg/ml, x-axis). The data was normalized, with the percentage of CD69 expression in rCD154-only cultures adjusted to 100%. Similarly, CD40 occupancy by CFZ533 was normalized to levels of CD40 expression in rCD154 only cultures (100%).

4.1.1.2 *In vivo* pharmacology to assess the immunosuppressant activity of CFZ533

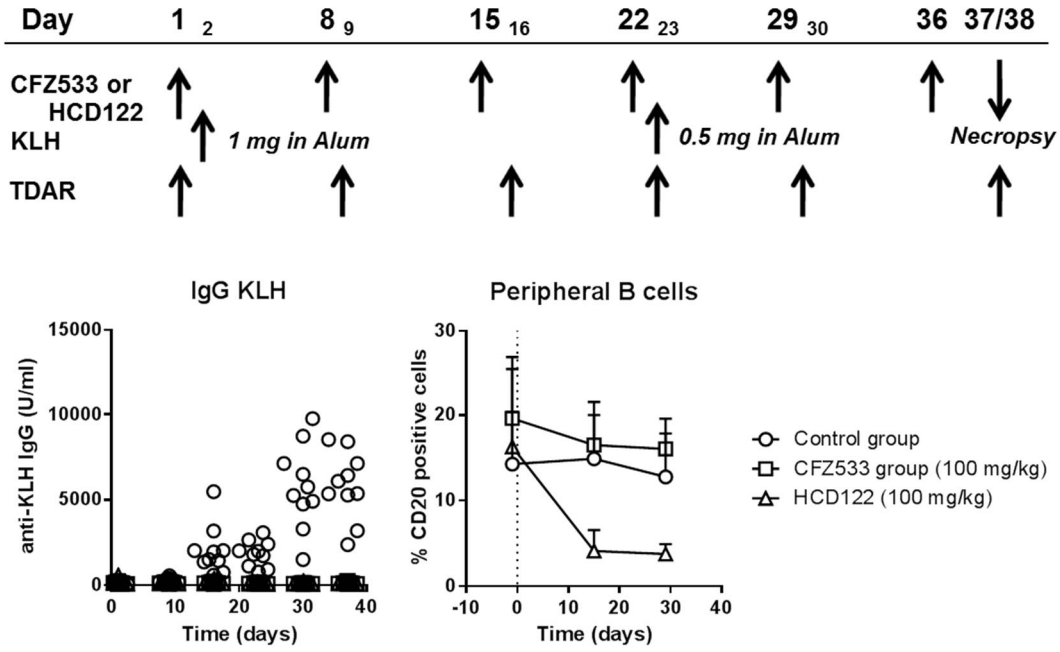
4.1.1.2.1 Neo-antigen immune response: NHP immunization studies

The immunosuppressive activity of CFZ533 on the humoral response to Keyhole Limpet Hemocyanin (KLH)-immunization was investigated in a non-clinical toxicology study (Section 4.2). In this study, cynomolgus monkeys (5/sex/group) were treated with 6 weekly doses of 100 mg/kg (IV) CFZ533, HCD122 (control blocking and depleting anti-CD40 antibody) or vehicle starting on Day 1 (Top panel; Figure 4-2). On Day 2, animals were immunized with 1 mg KLH in Alum followed by a booster injection of 0.5 mg KLH in Alum on Day 23. KLH specific IgM/IgG titers were determined with enzyme-linked immunosorbent assay (ELISA) using sera obtained at various time points after immunization (Top panel; Figure 4-2).

Complete inhibition of KLH-specific IgM (not on file and not shown here) and IgG production was seen after the first dose of CFZ533 or HCD122 (Figure 4-2). In contrast to HCD122, total B cell counts in CFZ533-treated animals were largely unchanged. Thus, CFZ533 abrogated T-dependent antibody responses (TDAR) in the absence of B cell depletion.

For additional *in vivo* vaccine response data in NHP please see Section 4.2.7 and Section 4.2.2.2.

Figure 4-2 Effect of CFZ533 and HCD122 on T cell dependent antibody responses



A schematic outlining experimental details as a function of time is illustrated: anti-CD40 antibody dosing, KLH immunization and sampling for assessment of anti-KLH IgM and IgG antibody at different time points are represented by arrows. The 2 graphs depict anti-KLH IgG responses and percent CD20+ numbers in control (circles), CFZ533 (squares) and HCD122 (triangles) groups. Individual (IgG) or average values (B cells) with standard deviation (SD) values are shown (n = 10 animals per group).

4.1.1.2.2 Renal allotransplantation experiments in NHPs

CFZ533 was evaluated in a life-supporting kidney allotransplantation model in cynomolgus monkeys. Bilaterally nephrectomized animals received an allogeneic donor kidney such that the survival of the recipient depended fully on the function of the transplanted kidney.

Table 4-3 CFZ533: Life-supporting kidney allotransplantation in cynomolgus monkeys

Treatment	Dose [mg/kg/d]	Graft survival times [days] for each individual transplant	Mean survival times in days (SD)
CFZ533 Monotherapy	30 (iv)	76 [1)], >98 [2)], >100 [2)] , >100 [2)], >100 [2)]	94.8 (10.54)
Historical Data			
Control	0	8, 8, 4, 8	7

1) Terminated due to general health status deterioration. Animal presented with clinical symptoms consistent with viral infection and responded partially to anti-viral therapy. Infection could not be confirmed histologically; cause of graft dysfunction was not identified.

2) Terminated with functional graft (end of protocol)

Source: [RD-2012-00330], [RD-2002-02327]

Five animals were selected based on ABO blood type match and major histocompatibility complex (MHC class II) mismatching (MLR index ≥7) and transplanted. All animals received an immunosuppressive treatment regimen consisting of a loading regimen of 30 mg/kg IV CFZ533 on days -1, 0 and 1 post-transplantation, followed by weekly administration of CFZ533 (30 mg/kg IV). Kidney graft function was monitored with regular blood biochemistry analysis, ultrasound examinations and percutaneous kidney biopsies (obtained only in 2 animals, on day 30 post-transplant). The results with CFZ533 are summarized in Table 4-3.

Treatment with CFZ533 (30 mg/kg IV) as a monotherapy resulted in prolongation of survival (mean cohort 94.8 days) in comparison to historical controls (Cordoba et al 2015). Four animals reached the end of protocol (day 98 or 100) without any signs of acute cellular rejection, chronic rejection or unexpected pathology of the graft or other organs. One animal however was euthanized on day 76 due to general health status deterioration, including apathy, weight loss, sustained neutropenia, and progressive increase in urea, alanine aminotransferase (ALT), C-reactive protein (CRP), and alkaline phosphatase (ALP) and ocular secretions. This animal presented with symptoms consistent with viral infection starting on day 42 and partially responded to empirical anti-viral (ganciclovir; day 57-68) and antibiotic (ceftriaxone; day 57-70) therapy. In addition, the animal also received nutritional supplementation and therapy for anemia (iron with erythropoietin) during this time. With ganciclovir and ceftriaxone treatment, the animal's general behavior improved remarkably, ocular secretions resolved and serum ALT and urea returned to normal limits. Despite anti-infective therapy as well as 2 blood transfusions (ABO matched) on days 59 and 72, serum ALP and CRP concentrations remained elevated and there was no improvement in neutropenia. Once treatment was stopped on days 68 and 70, the animal's health status deteriorated again and was euthanized. Viral infection could not be confirmed histologically and cause of graft dysfunction was not identified. There was no histological evidence of graft rejection, and C4d immunostaining was negative in all cases providing evidence that there was no antibody-mediated rejection.

4.1.2 Secondary pharmacodynamics

4.1.2.1 *In vitro* and *ex vivo* effects on platelet function and hemostasis

In vitro effects of CFZ533 on platelet function (Whole Blood Aggregometry, WBA) and blood hemostasis (Thromboelastography, TGE) were investigated in blood samples from healthy human volunteers (studies 1011027 and 1170066). Investigation of *in vivo* effects of CFZ533 on platelet function (WBA) and hemostasis (TGE) was conducted by using blood samples from kidney-transplanted cynomolgus monkeys treated with CFZ533 and CsA (studies 1011093 and 1170029). CFZ533 did not induce platelet aggregation but rather displayed some mild inhibitory effects on platelet aggregation at a high concentration. Further *in vitro* and *in vivo* studies, which are investigating the effects of preformed complexes of either CD40L/anti-CD40L mAb or CD40/anti-CD40 mAb, are described in Section 4.3.7.

Ex vivo investigations in blood samples from cynomolgus monkeys in kidney transplantation studies indicated that CFZ533 did not cause adverse effects on platelet function and hemostasis endpoints in various *in vitro* (human and monkey) and *ex vivo* (monkey) studies.

It is important to note that targeting CD154 with Fc-active (ADCC capable) agents have been associated with an increase in thromboembolic events both pre-clinically (Schuler et al 2004, Kanmaz et al 2004, Pfeiffer et al 2001, Koyama et al 2004, Kawai et al 2000, Shock et al 2015) and in the clinic (Boumpas et al 2003, Kasran et al 2005).

Of note, no instances of thromboembolic events have been observed after treatment with a number of different anti-CD40 antibodies (Goldwater et al 2013, Fanale et al 2014, Bensinger et al 2012, Byrd et al 2012), including CFZ533 (Slade et al 2014, Slade et al 2015). Thus, the risk of hemostatic events are not considered to be increased by the inhibition of CD40-CD154 interactions *per se*, rather these data suggest a target-specific effect of certain anti-CD154 antibodies. More details related to the risk for thrombophilia and on 2 suspected unexpected serious adverse reaction (SUSARs) related to a thromboembolic event that occurred in a patient in the ongoing transplant study, can be found in Section 5.2.2 and Section 7.2.5.

4.1.3 Safety pharmacology

According to the ICH Guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6 (R1) 2011), relevant safety pharmacology endpoints were incorporated in toxicity studies (Section 4.3). No dedicated respiratory, CNS or cardiovascular safety pharmacology studies were conducted.

4.1.4 Pharmacodynamic drug interactions

No studies have been conducted.

4.2 Non-clinical pharmacokinetics and metabolism

4.2.1 Bioanalytical methods

Validated immunoassays measuring CFZ533 in NHPs (serum) and in human (plasma), and anti-CFZ533 antibodies in NHPs (serum) and in human (plasma) are summarized in Table 4-4. Validated PD assays measuring total soluble CD40 and total soluble CD154 (or CD40L) in human plasma are summarized in Table 4-5. CD40 occupancy by CFZ533 on whole blood B cells was assessed by flow cytometry, measuring:

- *Free CD40 on CD19-positive B cells*, using PE-conjugated CFZ533 whose binding is inhibited by unconjugated CFZ533. Binding of CFZ533 resulted in mean fluorescence intensity (MFI) reduction of the drug-sensitive CD40 on B cells. The percentage of CFZ533-positive cells is measured as % of all CD19 positive B cells. MFI for CD40 on B cells is converted into Molecules of Equivalent Soluble Fluorochrome (MESF) using PE-MESF beads.
- *Total CD40 on CD19-positive B cells*, using a PE-conjugated anti-CD40 antibody whose binding is not inhibited by CFZ533. The percentage of CD40-positive cells is measured as % of all CD19- positive B cells. MFI for CD40 on B cells is converted into MESF using PE-MESF beads.

Table 4-4 Validated PK and immunogenicity assays in NHPs and in human

A - PK immunoassays			
	Cynomolgus [a]	**Rhesus [b]**	**Human**
Format	Sandwich, target based		
Capture	Recombinant human CD40/Fc chimera Gp67-CD40 aa20-193 His		Biotinylated hsCD40aa20-193-His6
Detection	- I^{ary}: Mouse monoclonal antibody to human kappa light chain - II^{ary}: HRP-Goat anti-mouse IgG		Peroxidase-conjugated AffiniPure Goat anti-human IgG, Fcγ fragment specific
Chromogenic Substrate	TMB		ortho-phenylenediamine (OPD)
LLOQ-ULOQ	0.3 - 10 µg/mL	0.15 - 5 µg/mL	0.01 [e] or 0.03 - 0.24 µg/mL
Interference Testing	N.A		sCD40 interference observed at ≥ 1.17 ng/mL [c]

B - Immunogenicity assays			
	Cynomolgus [a]	**Rhesus [b]**	**Human**
Format	Bridging assay		
Capture	CFZ533		Biotinylated CFZ533 (pre-incubation step)
Detection	- Biotinylated CFZ533 - Streptavidin-HRP conjugate		- Digoxigenin labelled CFZ533 (pre-incubation step) - Anti-digoxigenin POD antigen binding fragment of an antibody (Fab) fragments (poly)
Chromogenic Substrate	TMB		
Sensitivity [positive control]	0.05 µg/mL [goat anti-human IgG]	25 ng/mL [goat anti-human IgG]	120 ng/mL [rabbit affinity purified anti-HCD122A IgG]
Drug tolerance limit	0.5 µg/mL	1-5 ug/mL	5 µg/mL [d]

[a] 26-week toxicology study, [b] 13-week toxicology study, [c] sCD40 interference at sCD40:CFZ533 molar ratio 2:1 (demonstrates the ability of the method to measure free CFZ533), [d] No interference for spiked sCD40 up to 100 ng/mL, [e] CCFZ533X2101 and CCFZ533X1101 studies.

Table 4-5 Validated PD assays in human

	Total soluble CD40	**Total soluble CD154**
Format	Sandwich assay (MSD streptavidin plate)	Sandwich assay (solid phase Quantikine assay)
Capture	- Samples saturated with CFZ533 - Biotinylated goat anti-human CD40 Ab	Polyclonal Ab specific for CD154
Detection	Sulfo-Tag goat anti-human CD40 Ab	Enzyme linked polyclonal Ab specific for CD154
Readout	Electrochemiluminescence	
LLOQ - ULOQ	0.195 - 200 ng/mL	0.0773 - 2.91 ng/mL

4.2.2 Absorption

4.2.2.1 Absorption and bioavailability

No specific studies have been conducted to assess the absorption and bioavailability of CFZ533 after subcutaneous administration; however, toxicology studies in NHPs were conducted exploring the SC and IV routes of administration (Section 4.2.2.2).

4.2.2.2 Toxicokinetics

A 13-week GLP subcutaneous rhesus monkey study with an intravenous single dose arm and a 30-week recovery period (study S630170)

CFZ533 was administered SC at weekly doses of 10, 50 and 150 mg/kg or IV at weekly doses of 150 mg/kg. Exposure metrics are presented in Table 4-6. At steady state, average CFZ533 concentrations (Cav,ss) throughout all dose groups were 25 to 790-fold higher than the concentration producing full CD40 occupancy on blood B cells (approximately 10 µg/mL; Section 4.2.7).

Table 4-6 Mean (all animals) toxicokinetic parameters of CFZ533 on Day 1 and at steady state on Week 13 following weekly administration for 13 weeks (SC or IV)

Mean (M + F) [c] Weekly dose (Route)		Cmax [a]	Dose normalized Cmax [a]	AUCtau [a, b]	Dose normalized exposure [a]	Cav,ss [a]
10 mg/kg (SC)	Day 1	147	14.7	792	79.2	-
	Week 13	602	60.2	3495	350	499
50 mg/kg (SC)	Day 1	631	12.7	3605	72.1	-
	Week 13	2265	45.3	13800	276	1971
150 mg/kg (SC)	Day 1	1985	13.3	10900	72.5	-
	Week 13	8735	58.3	52900	353	7557
150 mg/kg (IV)	Day 1	4060	27.1	13950	93.2	-
	Week 13	11650	77.6	55300	369	7900

[a] Units: Cmax in ug/mL, Dose normalized Cmax in (µg/ml)/(mg/kg), AUCtau in µg.day/mL, Dose normalized exposure in (µg.day/mL)/(mg/kg), and Cav,ss (calculated as AUCtau/Tau) in µg/mL.
[b] Subscript tau refers to the dosing interval (weekly). Data from Day 1 (single dose) and Week 13 (steady state) are presented. [c] Each group consisted of 3 male and 3 female animals, plus 2 male and 2 female recovery animals in the control and high dose groups.

A 26-week dosing and 30-week recovery period GLP subcutaneous administration toxicology study in cynomolgus monkey (study 1180364)

CFZ533 was administered SC at weekly doses of 1, 50, and 150 mg/kg. At steady state, the average serum CFZ533 concentration over a dosing interval (Cav,ss; Table 4-7) was approximately 2.9 to 840-fold higher than the concentration producing full CD40 occupancy on blood B-cells *in vivo* (about 10 µg/mL).

In this study, the pharmacological action of CFZ533 was confirmed:

- By almost complete absence of TDAR to KLH vaccinations during dosing at 150 mg/kg weekly. No memory B cell induction was observed, indicated by the absence of a memory-related increase of TDAR following challenge after wash-out.
- By a reduction of GC development in lymphoid follicles in all investigated lymph nodes and spleen at 50 and 150 mg/kg/week.

- Three animals dosed at 1 mg/kg weekly had average steady state plasma concentrations ≥38 µg/mL. These concentrations were associated with complete suppression of GC development in cortical B cell areas of lymph nodes. Incomplete or no suppression of GCs was observed in lymphatic tissues in 3 animals with an average steady state plasma concentration below 20 µg/mL. These results indicate that concentrations of CFZ533 required for a pathway-relevant PD effect are at least 10-fold in excess of those required for full CD40 occupancy on peripheral blood CD20-positive B cells.

After a recovery period of 30 weeks no pharmacologically related tissue effects could be detected.

Table 4-7 Toxicokinetic parameters of CFZ533 on Day 1 and at steady state on Week 26 (or Week 26/27) following weekly subcutaneous administration (27 doses) in cynomolgus monkey

Dose [a,c] **Route**		**Cmax** [a]		**Dose normalized Cmax** [a]		**AUCtau** [a, b]		**Dose normalized exposure** [a]		**Cav,ss** [a]	
		F	M	F	M	F	M	F	M	F	M
1	Day 1	6.90	7.06	6.90	7.06	35.8	38.9	35.8	38.9	-	-
(SC)	Week 26	31.3	56.2	31.3	56.2	200	342	200	342	29	49
50	Day 1	589	663	11.8	13.3	3440	3850	68.7	77.0	-	-
(SC)	Week 26	2700	3770	53.9	75.4	16400	23200	328	464	2343	3314
150	Day 1	2180	2100	14.6	14.0	12700	12200	84.4	81.5	-	-
(SC)	Week 26	8680	9130	57.9	60.9	53600	55900	358	373	7657	7986
	Week 26/27	9630	9360	64.2	62.4	58900	57300	393	382	8414	8186

[a] Units: Dose in mg/kg/week, Cmax in µg/mL, dose normalized Cmax in (µg/mL)/ (mg/kg), AUCtau in µg.day/mL, dose normalized exposure in (µg.day/mL)/(mg/kg), and Cav,ss (calculated as AUCtau/Tau) in µg/mL; [b] AUCtau refers to exposure during the dosing interval of 1 week (tau), after a single dose on Day 1 or at steady state at Week 26 (or Week 26/27).[c] Each group consisted of 3 males and 3 females, plus 2 male and 2 female recovery animals in the control and high dose groups.

4.2.3 Distribution

No formal distribution study was conducted with CFZ533. Nevertheless, in the 26-week toxicology study in cynomolgus monkey, pharmacodynamic effects in tissues were demonstrated and correlated with plasma concentrations (see Section 4.2.2.2).

4.2.4 Metabolism

Metabolism studies have not been conducted with CFZ533, as is typical with therapeutic monoclonal antibodies. The main elimination pathway for CFZ533 is believed to be catabolism by peptidases/proteases across the body including liver and kidneys.

4.2.5 Excretion/elimination

The elimination of CFZ533 was investigated in a single dose PK/PD study in cynomolgus monkey (see Section 4.2.7).

4.2.6 Drug-drug interactions

Traditional *in vitro* metabolism and drug metabolizing enzyme inhibition and induction assays have not been performed as is typical for a therapeutic monoclonal antibody. CFZ533 would be expected to be metabolized by normal physiologic proteolytic processes as occurs with endogenous antibodies and pharmacokinetic drug interactions would not be expected.

4.2.7 Other PK/PD studies

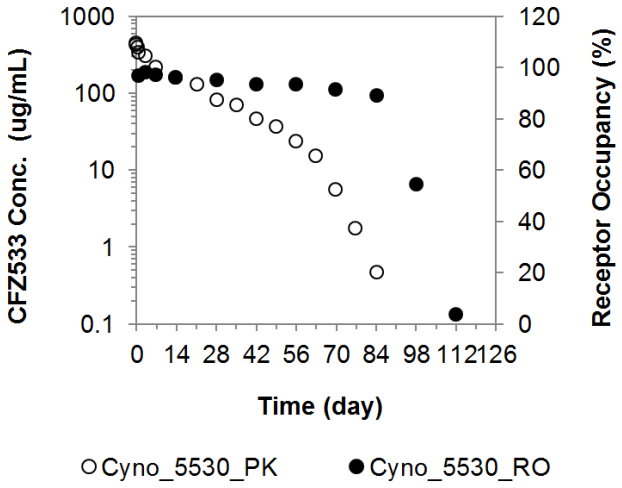
A single dose intravenous PK/PD study in cynomolgus monkey

CFZ533 was administered as an IV bolus in 3 cynomolgus monkeys (calculated dose of 16.2, 18.5 and 20 mg/kg).

Typical for a monoclonal antibody targeting a membrane bound protein, the time course of CFZ533 concentration exhibited target-mediated disposition, resulting in non-linear PK profiles. The inflection point observed in the PK profiles (at about 10-20 µg/mL),

- Is a marker of target engagement,
- Is associated with an increased contribution of CD40 to the overall clearance of CFZ533, in addition to faster elimination clearance (Figure 4-3),
- Is associated with a drop of CD40 saturation on peripheral B cells (for all monkeys, there was no loss of CD40 receptor expression on cells; [RD-2010-01108]).

Figure 4-3 Representative pharmacokinetic profile and CD40 receptor occupancy (RO) time course by CFZ533 in cynomolgus monkey after CFZ533 administration at 16-20 mg/kg (IV single dose)



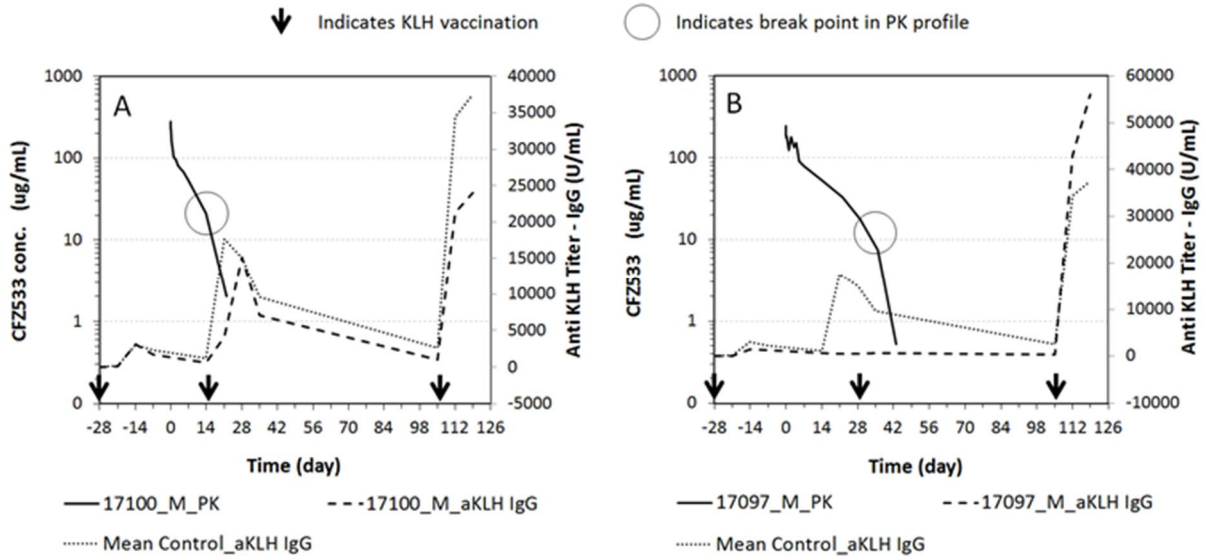
Pharmacokinetics: concentration-time profiles are designated by open symbols and left y-axis; CD40 occupancy (isolated PBMCs; % occupancy normalized to 100%)-time profiles are designated by filled symbols and right y-axis. Reports: BxSD RS653225, BxSD RS653225B.

A single dose intravenous PK/PD investigation in rhesus monkey

As part of the 13-week rhesus monkey study (PCS RS630170), 2 male and 2 female animals were administered with a single dose of CFZ533 at 10 mg/kg IV on Day 1. All animals were immunized with KLH on Study Day -28, 15 and 106. Blood samples were obtained for KLH specific IgG titers in order to assess the TDAR before and after CFZ533 treatment.

Target-mediated disposition was demonstrated, resulting in non-linear PK profiles (Figure 4-4). CD40 occupancy by CFZ533 at serum concentrations >40 µg/mL at the time of KLH challenge (Day 15) completely prevented recall antibody responses (panel B). Serum concentrations at or below the inflection point (progressive drop of CD40 occupancy on peripheral blood B cells) at time of KLH challenge (Day 15), were associated with a partial recall response (panel A). Upon elimination of CFZ533 a normal memory antibody response to a third challenge with KLH (Day 106) could be mounted in all animals.

Figure 4-4 Pharmacokinetic profiles and anti-KLH titers (IgG) in the rhesus monkey after CFZ533 administration at 10 mg/kg IV single dose



On Day 1, rhesus monkeys received a single dose of CFZ533 at 10 mg/kg IV. The inflection point in the PK profiles (transition to higher elimination clearance with an associated drop of CD40 saturation) is highlighted with a circle on the PK profiles. All monkeys were immunized with KLH (SC) before treatment (Day -28, priming), followed by a second and a third immunization at Study Day 15 and 106. Control animals from the 13-week rhesus monkey study (PCS RS630170), were used as control animals for the KLH TDAR. Panel A: serum concentrations at or below the inflection point (progressive drop of CD40 occupancy on peripheral blood B cells) at the time of KLH challenge (Day 15), were associated with a partial recall response. Panel B: CD40 occupancy by CFZ533 at serum concentrations >40 µg/mL at the time of KLH challenge completely prevented recall antibody responses. Data source for PK and anti-KLH IgG levels in PCS RS630170.

4.2.7.1 Conclusion on non-clinical pharmacokinetics and pharmacodynamics

In cynomolgus or rhesus monkeys, the disposition of CFZ533 was mainly the consequence of CFZ533 binding to FcRn receptors (a high capacity receptor responsible for IgG homeostasis by recycling/salvage) and constitutive expression of CD40, leading to target-mediated disposition.

Typical for IgG immunoglobulins, the primary route of elimination of CFZ533 is likely via proteolytic catabolism, occurring at sites that are in equilibrium with plasma. In addition to proteolysis, binding and internalization of CFZ533-CD40 complexes resulted in rapid and saturable clearance routes. This was illustrated by non-linear concentration-time profiles showing an inflection point at about 10-20 µg/mL. The contribution of CD40-mediated clearance to the overall clearance depended on CFZ533 concentration, together with levels of CD40 expression, internalization and receptor turnover rates. Above the inflection point, the target was saturated and clearance via normal IgG pathways predominated. At lower concentrations, where the inflection point in PK profiles was associated with a drop of CD40 occupancy in peripheral B cells, target-mediated clearance predominated and faster elimination was demonstrated. For serum concentrations of CFZ533 >20 µg/mL, linear kinetics are expected.

In a PK/PD study in cynomolgus monkeys, CFZ533 concentrations below the inflection point (approx. 10-20 µg/mL) in the PK profiles were associated with a loss of CD40 occupancy. As such this inflection point is viewed as a marker for the level of saturation of CD40, and as evidence for target engagement. The link between CD40 occupancy and pharmacodynamic activity was further demonstrated in rhesus monkeys immunized with KLH (Figure 4-4). These data suggest that the loss of CFZ533-CD40 occupancy after the inflection point correlated with the ability to mount a partial recall and memory immune response to the second KLH vaccination. Conversely, CD40 occupancy by CFZ533 at plasma concentrations >40 µg/mL at the time of the second KLH vaccination completely prevented recall antibody responses. However, once CFZ533 was cleared, recall responses in all animals appeared normal, suggesting that the function of pre-existing memory B cells were not affected.

4.3 Toxicology

Toxicology studies were conducted in cynomolgus and rhesus monkeys as they represent cross-reacting species suitable for toxicology investigation with CFZ533. Binding of CFZ533 to cynomolgus and rhesus CD40, as well as inhibitory activity in a functional B cell proliferation assay was very similar to that observed using human leukocytes (Table 4-2). Polymorphism analysis of 6 rhesus monkeys from the colony designated for the toxicity study did not show deviations in the target epitope sequence. CFZ533 does not cross-react with rodent CD40 therefore a rodent species was not selected.

Previous clinical experience with anti-CD154 antibodies indicated a potential for thromboembolic complications. While these thromboembolic complications could be reproduced in rhesus monkeys, cynomolgus monkeys appeared to be less sensitive to this effect (Shock et al 2015). Consequently, the rhesus monkey was used as the most sensitive species to investigate the potential for CFZ533 to produce thromboembolic events in a 13-week repeated dose toxicity study. Following the absence of such effects and, in accordance

with ICH S6, a 26 week toxicity study was conducted in cynomolgus monkeys in order to support chronic clinical use of CFZ533. A summary of the completed and ongoing toxicology studies can be found in Table 4-8.

4.3.1 Single dose toxicity studies

No single dose toxicity studies with CFZ533 have been performed.

4.3.2 Repeated dose toxicity studies

Three repeated dose toxicity studies have been completed, a 5-week non-GLP, a 13-week GLP and a 26-week GLP study in cynomolgus, rhesus and cynomolgus monkeys respectively. The details of these studies are summarized in Table 4-8 and discussed in an integrated section to follow.

Table 4-8 Repeated dose toxicity studies

Species, Study no. GLP Status	Method of administration	Duration of dosing (Weeks)	Dose levels (mg/kg)	Gender and No. per group	Major findings
Cynomolgus S630171 CFZ533 Non-GLP	IV	5 wks, q.wk., 6 inj. in total	100	5/sex/ group	No mortality. No clinical findings. No changes in hemostasis. No clinical pathology changes indicative of CFZ533-mediated effect. Histologically, absence of GC and reduced size of splenic lymphoid follicles and CD20+- B cell depletion in spleen and lymph node (LN). Complete inhibition of primary and secondary TDAR to KLH **NOAEL = 100 mg/kg**

Species, Study no. GLP Status	Method of administration	Duration of dosing (Weeks)	Dose levels (mg/kg)	Gender and No. per group	Major findings
Rhesus S630170 GLP	SC IV (high dose only)	13 wks, q.wk., 14 inj. in total	10, 50, 150	3/sex/dose (main study) 2/sex/150mg/kg (recovery incl control and IV/SC)	No mortality. No clinical findings. Reduced CD20 B cell counts from D 49 on at all dose levels. Absence of germinal centers with reduced CD20 B cells at all dose levels in line with pharmacological activity of CFZ533. Enlarged LN (mesenteric, tracheobronchial, axillary, inguinal) with increased lymphocytes in high endothelial venules (HEVs), paracortical & medullary T cell regions in animals across the dose-range were considered reactive to detected Cryptosporidium and Adenovirus infections. Two males at mid-dose with slight signs of inflammation during in-life phase as indicated by slightly reduced RBC counts, cholesterol and albumin levels as well as slightly elevated reticulocyte counts, coagulation parameters and triglycerides as well as two episodes of increased EOS in 1 M. Inflammatory infiltrates were noted in several organs including lung and kidney. Inflammation in the trachea and eyes of 1 animal was also noted in addition to elevated liver and kidney weights, renal tubular atrophy and proteinuria. Considered reactive to infection. **Recovery**: Increased cellularity in axillary, mesenteric, mandibular LN and spleen predominantly in B cell areas (CD20 stain) with increase in Ki67+ GC indicates a compensatory reaction leading to recovery. **NOAEL = 10 mg/kg** based on infectious findings in 2 M at 50mg/kg

Species, Study no. GLP Status	Method of administration	Duration of dosing (Weeks)	Dose levels (mg/kg)	Gender and No. per group	Major findings
Cynomolgus 1180364 GLP	SC	26 wks q.wk., 27 inj. in total	1, 50, 150	3/sex/dose (main study) 2/sex/150mg/kg (recovery incl control)	No clinical findings. No clinical pathology findings. Trend to reduced blood B cell numbers (CD20+) at all doses. Absence of germinal centers in axillary, mesenteric, mandibular Ln and spleen. Decreased cellularity of PALS at all doses. Increase in vacuolated macrophages at all doses in axillary and mesenteric LN. Increased LYM in paracortex/medulla in mesenteric LN at all doses incl control but with higher incidence at mid and high dose presumably in response to ongoing infection. No findings after recovery, lymphatic tissue with normal architecture **NOAEL = 150 mg/kg**

Abbreviations: LYM=lymphocyte; PALS=periarteriolar lymphatic sheath; GC=germinal center; NOAEL=no observed adverse effect level; RBC: red blood cells; EOS: eosinophils; LN: lymph node; TDAR: T-dependent antibody response; KLH: keyhole limpet hemocyanin

As SC administration is the currently preferred route of administration in the clinic, the SC route was selected for administration in the 13- as well as 26-week toxicity studies in NHPs. However, a comparison between IV and SC routes was made in the 13-week toxicity study at the highest dose. In addition, the IV route was initially used in the 5-week exploratory toxicity study in NHP. See Section 4.2.2.2 and Section 4.2.7 for complete details on PK / PD results, relationships and toxicokinetics.

Treatment with CFZ533 was generally well-tolerated. The effects observed in the repeated dose toxicity studies in NHPs were related to the pharmacological mode of action of CFZ533.

Safety pharmacology assessment was applied in the 13- and 26-week toxicity studies and no adverse effects were noted for cardiovascular, respiratory and neurobehavioral endpoints.

No thromboembolic events were seen in the 13-week rhesus toxicity study. Blood coagulation was not affected by treatment with CFZ533 as assessed by prothrombin time, activated partial prothrombin time and measurement of serum fibrinogen. Platelet counts were within normal limits and neither P-selectin or sCD40L concentrations in plasma indicated platelet activation.

Blood lymphocyte counts were found normal in all toxicity studies throughout the treatment phase. Blood CD20-positive B cells appeared on a normal level after 6 weekly administrations of CFZ533 (100 mg/kg) in a 5-week toxicity study. After 7 weeks of treatment in the 13-week toxicity study, a moderate reduction of CD20-positive B cells in the blood could be detected at 10 mg/kg and higher doses of CFZ533. This was confirmed after 13 weeks of treatment and returned to normal values after 30 weeks of recovery. In the 26-week toxicity study only a trend towards reduced blood CD20-positive B cell count could be detected. In contrast,

administration of the ADCC-capable antibody HCD122 in a parallel group in the 5-week toxicity study led to a prominent decrease in CD20-positive B cells. CD16-positive NK cells were also reduced in these monkeys reflecting their marked involvement in ADCC activity. This was in line with reduced relative B cell counts in total cell preparations of spleen and lymph nodes, whereas the effect of CFZ533 on lymphatic tissue CD20 B cell count was much less pronounced after 5 weeks of treatment.

Complete suppression of GC development in cortical B cell areas of lymph nodes and spleen was the most prominent result of histological evaluation in all toxicity studies (see Section 4.2.2.2 for further details). In the 13-week toxicity study, 5 animals across all dose levels showed enlarged lymph nodes (mesenteric, tracheobronchial, axillary, inguinal) with increased presence of T cells in the paracortical, HEVs and medullary T cell regions as identified by immunohistochemistry (Ki67, CD3, CD4, CD8). In the 26-week toxicity study in cynomolgus monkeys, this increased cellularity of lymphocytes was seen in the mesenteric lymph node of some animals in all groups including controls. A higher incidence and severity was observed in group 3 and 4 (50 and 150 mg/kg SC) and could be related to increased CD20 B cells in the medulla associated with CD8 T cells in the medulla and paracortex. In the 26-week toxicity study, an increased incidence of vacuolated macrophages was seen in the axillary and mesenteric lymph nodes of dosing groups 2, 3 and 4 (1, 50, and 150 mg/kg SC) and in the mandibular lymph node of group 2 animals. In the spleen a decreased cellularity of the PALS was obvious in groups 3 and 4.

Although no clinical findings were noted, 2 mid-dose rhesus monkeys (50 mg/kg/week SC) of the 13-week toxicity study who were group-housed, presented with slightly reduced RBC counts, cholesterol and albumin levels as well as slightly elevated reticulocyte counts, coagulation parameters and triglycerides. Inflammatory infiltrates were noted in several organs including lung and kidney. Inflammation in the trachea and eyes of 1 animal was also noted in addition to elevated liver and kidney weights, renal tubular atrophy and proteinuria. Mononuclear inflammatory cell infiltrations in the lung and kidney of these group 3 males were comprised mainly of CD8+ T cells. Consistent with an inflammatory response, 1 male from group 3 presented with increased serum concentrations of IL-6 and IL-8. IL-8, (detected in measurements before start of dosing), was also found at considerable levels in all animals. All other cytokines tested (e.g., IFN-γ, TNF-α, IL-1β) were below the LLOQ. Some CD40 expression was also seen at sites of kidney pathology (low in proximal tubules, moderate intensity in intercalated cells of collecting ducts) and in the mononuclear cell infiltrations in the kidney and lung. As CFZ533 is an Fc silent antibody, direct ADCC is not considered to be a reason for the observed pathology. The observed inflammatory responses indicate that the presence of opportunistic pathogens are a likely explanation for the paradoxical increase in lymph node size and increased cellularity of the predominantly T cell regions of the lymph nodes.

In the 13-week toxicity study in rhesus monkeys, Adenovirus intranuclear inclusion (confirmed by immunohistochemistry) was identified in the intestine in 1 low dose female. Typical Cryptosporidium organisms focally infecting the enterocytes of the intestinal mucosa could be identified in 1 low dose and 3 mid dose males, as well as in 1 high dose female. A partial concordance between these infections and the lymph node enlargements, as well as the increased cellularity in paracortical, medullary and HEV regions was established and is

likely related to the different stages of elimination of infectious agents. The lung and kidney findings of mononuclear cell infiltrations in addition to the presence of CD40-positive DCs in the 2 group 3 (50 mg/kg/week SC) males of the 13-week toxicity study in rhesus monkeys, may also be driven by opportunistic infection, although no infectious lesions were detected in the lung or kidney sections on H&E, Gomori silver stain or on Gram's stained sections. Noteworthy, EBNA-2 staining of lymph nodes did not reveal a Lymphocryptovirus (LCV) reactivation in the 2 affected group 3 males. In addition, there was no histological evidence for LCV reactivation as this would involve the proliferation of infected B cells.

In the recovery animals an increased cellularity, predominantly in the B cell areas of the lymphatic tissues, was observed. This was confirmed by CD20+ staining in the cortical and medullary follicles. There was an increase in the number and size of Ki67 positive GCs, which could be indicative of compensatory B cell proliferation after reversal of CFZ533-mediated inhibition of B cells. It is noteworthy that no signs of active Cryptosporidium, Adenovirus, or any other active infection were found in the recovery animals. This indicates that the immune system regained control over infectious agents after elimination of CFZ533. Please refer to Section 4.2.2.2 for further details.

The NOAEL of the 13-week toxicity study in rhesus monkeys was set to 10 mg/kg because of the 2 males found with multiple inflammatory lesions, which were most probably due to an infectious background. The NOAEL derived from this rhesus study is considered less relevant for supporting clinical dose regimen because respective findings are most likely related to the pharmacological activity of CFZ533. The NOAELs of the toxicity studies in cynomolgus monkeys were established at 100 mg/kg (5-week toxicity study) and 150 mg/kg (26-week toxicity study).

4.3.3 Genotoxicity / mutagenicity studies

Genotoxicity studies have not been conducted for CFZ533.

4.3.4 Carcinogenicity studies

No carcinogenicity studies have been conducted. Generally immunosuppressive drugs pose a risk of tumor induction (e.g., skin cancer, lymphoma) by reactivation of viruses, which are normally controlled by the immune system. A thorough carcinogenic risk assessment will be provided at a later stage of development.

4.3.5 Reproductive toxicity studies

A dose-range finding, embryo-fetal development (EFD) study in rabbits has been conducted in order to confirm the rabbit as a relevant reproductive toxicology species. In an *in vitro* study, CFZ533 could inhibit rabbit PMBC stimulation by recombinant human CD154 (IC50 = 0.05 µg/mL) indicating that the rabbit is a relevant species for reproductive toxicity studies. This was corroborated by histologically detected decreases in GCs in spleen and lymph nodes from females of the dose-range finding EFD study. At 100 mg/kg, a complete suppression of GCs was observed, whereas at 1 and 10 mg/kg, incomplete suppression was noted. Immunogenicity was seen at 1 and 10 mg/kg, which led to a disproportional exposure of the females after the second and third injection (Table 4-9). No effects on embryo-fetal

development were seen and there was no treatment-related fetal external malformation in any group Table 4-9.

Based on the results of this preliminary study in rabbits, a full reproductive toxicity assessment will be conducted in parallel to future clinical development.

Table 4-9 Reproductive toxicity studies

Study number, Species, Study type, GLP status	Method of administration (Vehicle / Formulation)	Duration of dosing (Weeks)	Dose levels (mg/kg)	Gender and No. per group	Major findings
Study 1381156 Rabbit DRF EFD Non-GLP	IV	GD 7, 14, 21	1, 10, 100	6 F (mated)	Well tolerated, no deaths, no clinical signs. No change in b.w. and food consumption. Hematology: no findings, no changes in blood B and T cells. No effects on gravid uterus weight. Histology: partial (at 1 and 10mg/kg) and complete (at 100mg/kg) suppression of GCs in lymphatic tissues (Spleen and LN). All dams were pregnant and live foetuses did not show effects on embryo-fetal development nor external malformations at Caesarian section (GD 29). Fetal weight was equivocally lower at 100mg/kg while mean litter size was increased.

DRF: dose-range finding; EFD: embryo-fetal development; GD: days of gestation

4.3.6 Juvenile toxicity studies

No juvenile toxicity studies have been conducted

4.3.7 Other toxicity studies

Assessment of tissue cross reactivity

Immunohistochemical tissue cross-reactivity testing with CFZ533 on cryo-sections from human, rhesus and cynomolgus monkey tissues revealed binding to CD40 on lymphocytes in all investigated lymphatic tissues. Blood mononuclear cells and platelets also stained positive as well as megakaryocytes and mononuclear cells, consistent with B cell precursors (cynomolgus and rhesus monkey only). Furthermore, staining was also identified on connective tissue components, on blood vessel endothelium of most tissues and on epithelial components of many tissues. Specific positive staining of nerve fibers in human peripheral nerve (2 of 3 donors) and spinal cord tissue (1 of 3 donors) sections was also seen.

In addition, tissue cross-reactivity studies revealed that CD40 receptors are also present on endothelial and epithelial cells across human, rhesus and cynomolgus monkeys. CD40 on endothelial cells serves as a major mediator of cell activation by production of adhesion

molecules, cytokines, chemokines, and inflammatory mediators important for wound healing (Phipps 2008). Stimulation of CD40 also leads to a down-regulation of the vasodilator apelin, which may have consequences in cardiovascular function and fluid-homeostasis for kidney grafts (Pluvinet et al 2008). As a non-agonistic antibody, CFZ533 is not considered to mediate such reactions. The same authors showed that CD40 activation resulted in the up-regulation of genes involved in virus defense like TLR3, IFIH1 etc., which may suggest interference in virus defense as seen in the rhesus study described above. CD40 expressed on epithelial cells can also stimulate the expression of inflammatory mediators upon engagement by its ligand (Dugger et al 2009). Activation of CD40 on renal proximal tubular epithelial cells stimulates expression of IL-6, IL-8, RANTES, MCP-1, and IL-15, which in turn contribute to tubular injury and kidney graft rejection. CFZ533 is an antagonistic anti-CD40 monoclonal antibody and is therefore not expected to exert any further stimulus to endothelial cell inflammatory responses. This was confirmed by *in vitro* studies using human umbilical vein endothelial cell (HUVECs) which demonstrated complete CFZ533-mediated suppression of rCD154-mediated upregulation of the chemo-attractant MCP-1 and of ICAM-1, facilitating migration of lymphocytes to inflamed tissues. The unexpected staining of nerve fibers in human peripheral nerve and spinal cord tissue sections is of unclear significance at present, however, CD40 staining of microglia and Schwann cells are a known phenomenon during autoimmune neuritis and Guillain-Barre-Syndrome (Mao et al 2010).

Assessment of CFZ533 activity on HUVEC

CFZ533 at up to 150 µg/mL did not exert agonistic activity on IL-6, IL-8, MCP-1 and RANTES release in a 24 hour culture of HUVEC. Upon co-incubation with IL-4, CFZ533 did not cause an upregulation of IL-6 nor an increased expression of ICAM-1 and VCAM-1. In contrast, soluble CD40L induced upregulation of MCP-1 as well as IL-8 and RANTES at low levels. In combination with IL-4, CD40L markedly increased the expression of ICAM-1, and of VCAM-1.

CFZ533 tested in a concentration range of 1-150 µg/mL completely inhibited the upregulation of MCP-1 and ICAM-1 observed when treating with 100 ng/mL soluble CD40L, but did not affect IL-6, IL-8 and RANTES secretion and expression of VCAM-1.

Demonstration of the absence of thromboembolic potential of anti-CD40 mAb *in vitro* and *in vivo*

Previous data indicated that soluble CD40L/anti-CD40L mAb immune complexes could activate platelets *in vitro* via the FcγRIIa present on platelet surface (Langer et al 2005), and had pro-aggregatory effects on platelets (Mirabet et al 2008a, Mirabet et al 2008b). In addition, pulmonary thrombi consisting of platelet aggregates and fibrin and thrombocytopenia were found in FcγRIIa transgenic mice (as mouse platelets do not express FcγRIIa), but not wild type mice after injection of pre-formed immune complexes consisting of soluble CD40L and anti-CD40L mAb (Robles-Carrillo et al 2010). No such experiments have been performed using anti-CD40 antibodies. We therefore used human FcγR transgenic mice (Smith et al 2012) to investigate the ability of CFZ533 to induce thromboembolic events in comparison to anti-CD40L mAb as positive control. Mice were injected either with single proteins (soluble CD40L, soluble CD40) or antibodies (isotype controls, anti-CD40L mAb, anti-CD40 mAb),

or with immune complexes (of matched recombinant protein and antibody) and were followed for 10 minutes prior to analyses [Study 1620309]. Animals injected with soluble CD40L/anti-CD40L mAb immune complexes showed severe signs of sickness, a significant decrease in platelets and had to be sacrificed. Post-mortem histology revealed thrombi formation in the lung as sentinel organ for this effect. In contrast, mice injected with soluble CD40/anti-CD40 mAb immune complexes were not affected and showed no signs of TE in post-mortem histopathology.

In vitro platelet aggregation (whole blood aggregometry) was performed using blood from FcγR transgenic mice and human healthy donors [Study 1720250]. Whole blood samples from FcγR transgenic mice were treated with the same proteins and antibodies as in the *in vivo* study. Similar to the in vivo experiments, no blood aggregation was observed in the presence of all anti-CD40, whereas anti-CD40L mAbs promoted blood aggregation.

4.4 Overall assessment of non-clinical studies

CFZ533 is a fully human, non-depleting anti-CD40 antibody with minimal stimulatory activity that blocks CD154-mediated activation of CD40 signaling in B cells, other APCs, and parenchymal cells. CFZ533 prevented rCD154+IL-4-induced proliferation of human, rhesus, cynomolgus and rabbit PBMCs with similar potency. Furthermore, full CD40 occupancy was required for CFZ533 to completely inhibit CD154-induced activation of B cells in human whole blood.

In vivo, CFZ533 prolonged renal allograft survival in cynomolgus monkeys. In most cases, transplanted animals reached *a priori* defined endpoints with high quality of graft and no evidence of CFZ533-mediated AEs, including thromboembolic complications. In addition, CFZ533 suppressed primary and secondary antibody responses and GC formation following immunization with a T cell-dependent antigen. The ability to mount TDARs was regained after clearance of CFZ533. It is also important to note that serum concentrations of CFZ533 of >40 µg/mL were required for complete suppression of GCs; at least 10-fold higher than that required for full CD40 occupancy on B cells in peripheral blood. Collectively this data provided an experimental basis for selection of relevant disease indications as well as selection of CFZ533 doses that would result in a pathway-relevant PD effect in tissue. Furthermore, it also helped guide the selection of suitable species for toxicity studies.

In toxicology studies plasma concentrations of CFZ533 were sufficient to cause full CD40 occupancy on blood B cells at all doses. Complete pharmacological tissue effects were observed at all doses of 10 mg/kg and higher in rhesus and cynomolgus monkeys. At 1 mg/kg in the 26 week toxicity study, full CD40 occupancy was achieved on blood B cells, however the pharmacological tissue effect, manifesting as GC reduction, was not seen in all animals at this dose level indicating incomplete tissue exposure. In the clinical situation where patients are likely to present with disease specific enhanced CD40 expression levels, the dose and regimen of administration should be selected such as to prevent rapid elimination of CFZ533 by receptor-mediated clearance, and to ensure full CD40 occupancy, not only on peripheral blood B cells, but in target tissues as well.

Tissue cross-reactivity studies have revealed CD40 receptor expression on immune cells, endothelial cells and epithelial cells in human, rhesus and cynomolgus monkeys. Treatment of NHPs, including rhesus monkeys, with CFZ533 was generally well-tolerated and no specific organ toxicities occurred. No thromboembolic events were observed. The rhesus monkey was selected specifically to investigate thrombophilia, as it is considered the most sensitive species for this endpoint based on the work by Shock et al 2015. In addition, investigation of platelet aggregation and hemostatic function in human whole blood and from cynomolgus monkeys did not show abnormalities. Investigation in human FcγR transgenic mice revealed the absence of TE activity of a blocking, non-depleting anti-CD40 mAb, whereas anti-CD154 mAb caused thrombocytopenia and thrombi formation. In an *in vitro* study (whole blood aggregation) this result could be confirmed. This data collectively suggests that the thromboembolic risk is very low. Safety pharmacology assessment was applied in the 13- and 26-week toxicity studies and no adverse effects were noted for cardiovascular, respiratory and neurobehavioral endpoints.

Pharmacological activity could be detected as reduction in blood B cells observed after Day 49 in the 13-week rhesus toxicity study, whereas in the 26 week toxicity study only a trend towards reduced blood B cells was observed after long-term treatment. Post-mortem histological evaluation revealed a decrease in GCs in cortical B-cell areas of the spleen and lymphatic tissues. The decrease in B cell counts in blood and lymphatic organs was considered a consequence of the pharmacological inhibition of T-B cell interaction and reduced B cell survival, rather than antibody-mediated cell killing, as CFZ533 was incapable of mediating ADCC. Macroscopic enlargement and/or increased lymph node cellularity affecting the paracortex, HEVs and medulla regions, were associated with T-cell populations in these regions with Ki67, CD3, CD4 and CD8 positivity and were considered to be related to an infectious background. Active Adenovirus and *Cryptosporidium* were identified in the intestine. Involvement of the latter is corroborated by the finding that CD154-CD40 signaling is involved in intestinal immunity to *Cryptospodium* infection in man (Pantenburg et al 2008).

The recovery animals showed some cases of increased lymph node cellularity with normal T cell areas and increased B cell areas, which is consistent with reconstitution of GCs after drug withdrawal.

Collectively, the findings in the rhesus toxicity study were most probably of infectious nature and were therefore considered secondary to immunosuppression mediated by CFZ533.

In the toxicity studies, NOAEL were established at 10 mg/kg (13-week), 100 mg/kg (5-week) and 150 mg/kg (26-week). The NOAEL of 10 mg/kg for the 13-week toxicity study was set in view of the inflammatory findings with infectious background in different organs at 50 mg/kg.

Overall, results of the preclinical evaluation presented above support continued investigation of CFZ533 in human volunteers and patients.

5 Human studies

The current CFZ533 clinical program comprises 3 completed and 3 ongoing studies, as detailed in Table 5-1. In addition, clinical data for a similar anti-CD40 antibody, ASKP1240, currently in Phase 2 development by another sponsor is presented in Section 5.2.3.

Table 5-1 Summary of ongoing human studies as of 15-Nov-2017

Study	Population (No. of enrolled subjects)	No. of Subjects exposed to CFZ533/ Placebo	Study Title	Dose/Frequency/ Formulation
Healthy volunteer studies				
Patient studies				
CCFZ533 X2201 (Part 1) (Part 2 started May 2016)	7 (Part 1 completed) (52 in Part 2)	7 CFZ533 No placebo in Part 1 Part2: 34 on CFZ533; 18 on SoC	A randomized, two-part, 6- or 12-month, sequential, adaptive, controlled, open-label, multicenter, clinical proof-of-concept study to evaluate the efficacy, safety, tolerability, PK and PD of CFZ533 + MMF + CS, with standard exposure (Part 1) or no tacrolimus (Part 2, 3), for initial and maintenance prophylaxis of organ rejection in adult *de novo* renal transplant recipients as compared to SoC.	Part 1: CFZ533 3 mg/kg IV (Day 1) followed by CFZ533 3 mg/kg SC administration on Days 15, 29, 43 and 71 Part 2: Randomization 2: 1 to either CFZ533 10mg/kg on Days 1, 3, 7, 15, 29, 43, 57,85,113,141,169, 197,225, 253, 281, 309, 337 or control arm Standard of Care (SoC) including oral Tacrolimus (Tac)
CCFZ533 X2203	44 (12 with 3 mg/kg SC and 32 with 10mg/kg IV)	Cohort 1: 8 CFZ533 (3 mg/kg SC) +4 Placebo all pts on CFZ533 in follow-up Cohort 2: 32 randomization 2:1; all pts on CFZ533 in follow-up Cohort 3: 16 enrolled/24 planned, all on CFZ533 (open label) in two treatment arms	A multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CFZ533 in patients with primary Sjögren's syndrome	CFZ533 3.0 mg/kg SC (Cohort 1) or 10 mg/kg IV (Cohort 2) or placebo on Days 1,15, 29, 57, 85, 99, 113, 141 Cohort 3: Arm 1: CFZ533 at 600 mg SC weekly on 4 occasions (loading regimen), followed by 300 mg SC weekly on 9 occasions (maintenance) regimen starting on study Day 29). Arm 2: single IV dose of 10 mg/kg CFZ533 on study Day 1 (loading), followed by 300 mg SC weekly on 12 occasions (maintenance) starting on Day 8).
CCFZ533 X2204	44	44 CFZ533 or Placebo; randomization 1:1	A multi-center, randomized, double-blind, placebo-controlled, parallel group study to preliminarily evaluate the safety, tolerability, pharmacokinetics and efficacy of CFZ533 in patients with moderate to severe myasthenia gravis	CFZ533 10 mg/kg IV or placebo on Days 1, 29, 57, 85, 113, 141

5.1 Pharmacokinetics, metabolism and pharmacodynamics in humans

The pharmacodynamic consequences of CD40 engagement by CFZ533 and the pharmacokinetic properties of CFZ533 are tightly linked. They are discussed together in this section.

5.1.1 A randomized, double-blind, placebo-controlled, single ascending dose first-in-human study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of CFZ533 in healthy subjects and rheumatoid arthritis patients (CCFZ533X2101)

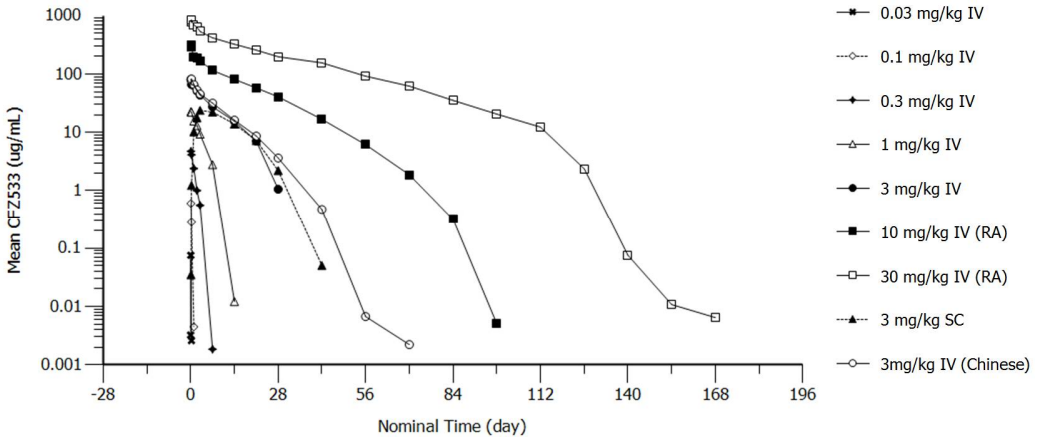
In HVs as well as in patients with rheumatoid arthritis (RA), after single IV or SC administration, PK profiles were consistent with target-mediated disposition of CFZ533, resulting in non-linear PK profiles (Figure 5-1 Plot A) and more rapid clearance when CD40 receptor occupancy (RO) dropped below approximately 90% (Figure 5-1 Plot B).

Despite some inter-individual variability in the PK profiles from Chinese subjects, the disposition of CFZ533 in Chinese subjects was generally similar as for non-Chinese subjects.

At 3 mg/kg IV, similar PK/PD properties were demonstrated in Chinese and non-Chinese subjects through free CFZ533 profiles in plasma, CD40 occupancy on whole blood peripheral B cells (measuring free and total CD40; 4 weeks of RO), and total sCD40 profiles in plasma (Figure 5-1Plot C) showing 4 weeks of target engagement through the accumulation of CFZ533-sCD40 complexes. The increase in total sCD40 concentration in plasma with time correlated well with CD40 occupancy by CFZ533 on peripheral B cells.

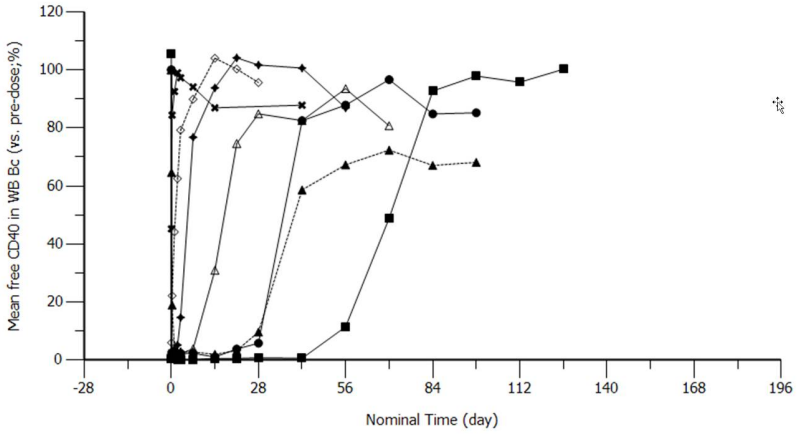
Figure 5-1 First-in-human study (CCFZ533X2101): Pharmacokinetics and target engagement

Plot A: Mean free CFZ533 plasma concentration-time profiles in HVs and RA patients



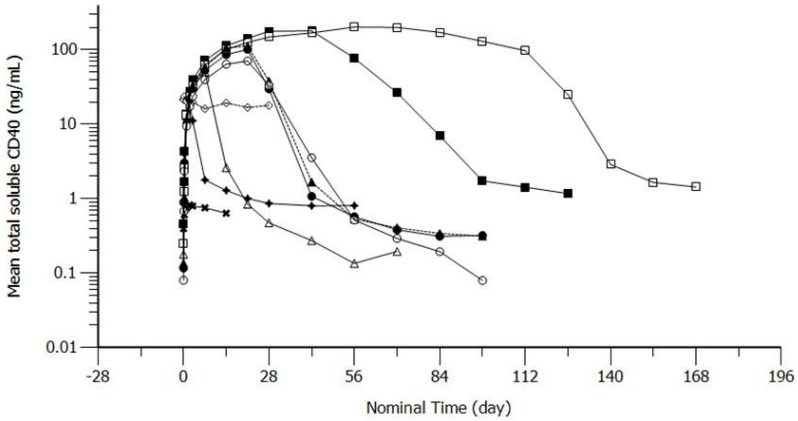
Free CFZ533 concentrations were measured in plasma using a validated target-based sandwich ELISA method (Section 4.2.1). Samples were collected from non-Chinese (when not specified) or Chinese healthy volunteers and rheumatoid arthritis (RA) patients, after intravenous (IV) or subcutaneous (SC) administration. Mean concentration data are presented.

Plot B: Percentage unbound CD40 receptor on B cells in whole blood from HVs and RA patients (mean free CD40 compared to mean pre-dose)



Whole blood samples were collected from non-Chinese healthy volunteers (symbols and lines as in Plot A) after intravenous (IV) or subcutaneous (SC) administration. CD40 receptor occupancy by CFZ533 was determined, at baseline and post-dose, on peripheral B cells using flow cytometry analysis (Section 4.2.1). Mean data (free CD40 on B cells compared to pre-dose) are presented.

Plot C: Mean total soluble CD40 plasma profiles (target engagement) in HVs and RA patients



Total soluble CD40 concentrations (free plus bound soluble CD40) were measured in plasma using a validated ELISA method (Section 4.2.1). Samples were collected, at baseline and post-dose, from non-Chinese (when not specified) or Chinese healthy volunteers and rheumatoid arthritis (RA) patients, after intravenous (IV) or subcutaneous (SC) administration. Symbols and lines as in Plot A. Mean concentration data are presented.

After SC administration in HVs, CFZ533 was rapidly absorbed and distributed in line with what is expected for a typical IgG1 antibody in human. At 3 mg/kg SC, CFZ533 generally peaked at 3 days post-dose (7 days for 2 subjects), and 1 week after dosing plasma concentrations were in the same range as for after IV. At 3 mg/kg SC, duration of target engagement was also about 4 weeks. In this and subsequent studies, CFZ533 plasma concentrations of 0.3-0.4 µg/mL were associated with full (≥90%) CD40 occupancy on whole blood B cells.

Full (≥90%) CD40 occupancy was generally maintained for 8 weeks in RA patients dosed with 10 mg/kg IV (as measured by free CD40 on whole blood B cells compared to mean pre-dose, and total sCD40 profiles in plasma). At 30 mg/kg IV, PK and total sCD40 profiles in plasma were consistent with a duration of target engagement of 16 weeks.

In HVs CD40 engagement by CFZ533 generally led to a decrease in total CD40 on peripheral B cells by about 50% (not shown), tracking CD40 occupancy on B cells. This could be due to a combination of internalization and/or shedding of membrane-bound CD40 following binding of CFZ533. In patients with RA the decrease in total CD40 on peripheral B cells was not confirmed.

More generally, non-specific and specific elimination pathways regulate the clearance of CFZ533. The non-specific and high capacity pathway mediated by FcRn receptors is commonly shared by endogenous IgGs. The specific target-mediated disposition of CFZ533 occurred as a consequence of mAb engagement with CD40, likely resulting in internalization and/or membrane shedding of the mAb-target complex.

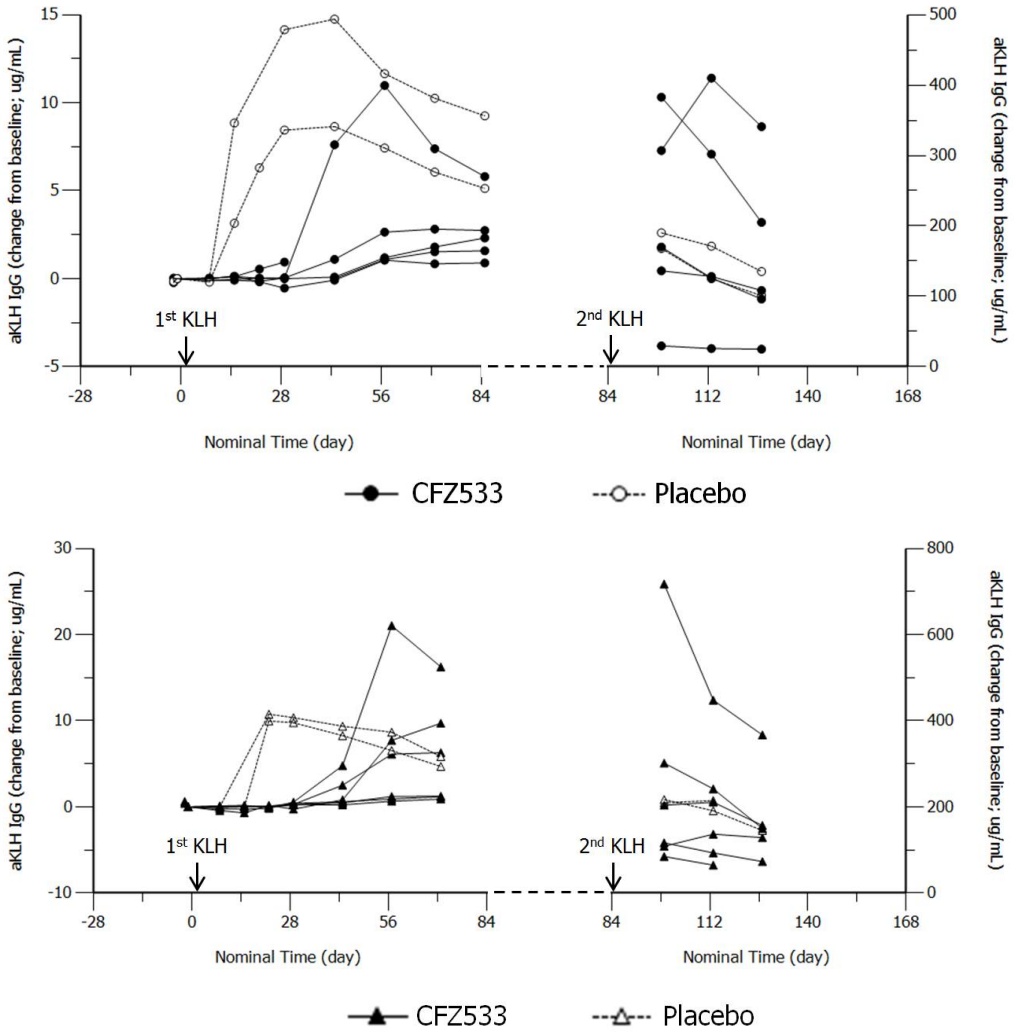
Target-mediated processes resulted in saturable and nonlinear disposition of CFZ533. The formation of CFZ533-CD40 complexes was dose/concentration-dependent, with saturation occurring at high concentrations of CFZ533. Overall, the disposition of CFZ533 is dependent on the relative contribution of the specific (target-mediated) and non-specific elimination pathways to the overall clearance of CFZ533. Nonlinear PK behavior was observed when CFZ533 concentrations were lower than that of the target, while at higher concentrations with CD40 receptors being saturated, the non-specific pathways predominate and the elimination of CFZ533 was linear.

As expected for a typical IgG1 antibody targeting a membrane bound receptor and demonstrating target-mediated disposition, the extent of exposure of CFZ533 (AUClast) increased more than the increase in dose (hyper-proportionality). This is expected to be associated with a decrease in the volume of distribution and clearance of CFZ533 at higher doses.

One subject at 1 mg/kg IV (1 week full CD40 occupancy) developed specific antibodies to CFZ533 detected 6 weeks after CFZ533 plasma concentrations were below the limit of quantification, and definitively too low to block any CD40 pathway-relevant effects in tissue. The presence of anti-drug antibodies (ADAs) in this subject did not compromise exposure, and was not associated with an immune related safety signal. This corresponds to an ADA incidence of 2% in this study.

A single dose of 3 mg/kg (IV or SC) of CFZ533 transiently suppressed anti-KLH (Keyhole Limpet Hemocyanin) responses to the first KLH immunization (Day -3) (Figure 5-2), at CFZ533 concentrations corresponding to full RO (≥90%), for about 3-4 weeks (Figure 5-2). Anti-KLH primary responses were detected in all subjects as CFZ533 concentration, and accompanying RO declined. All subjects were able to mount recall responses to a second KLH immunization (administered at Day 85, after loss of receptor occupancy was anticipated).

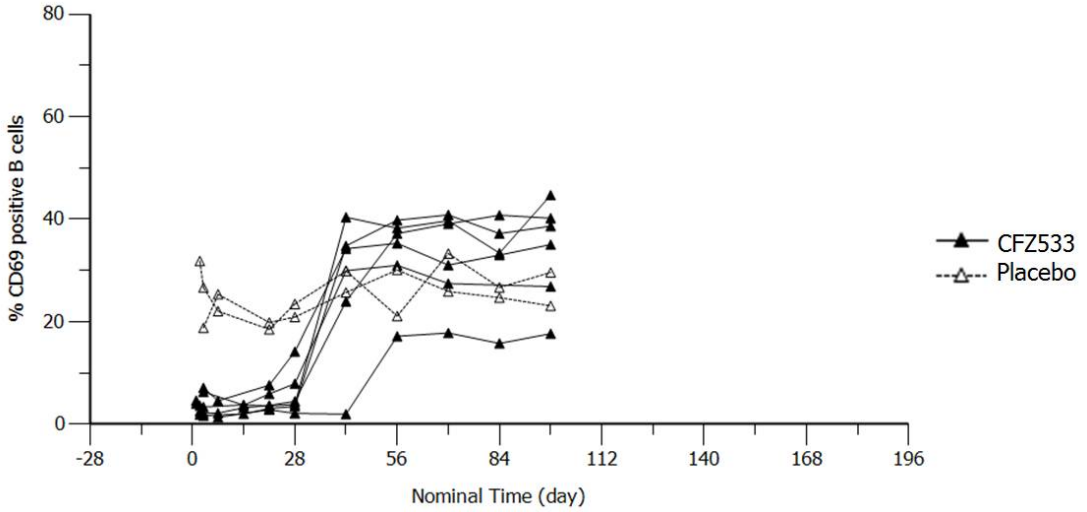
Figure 5-2 First-in-human study (CCFZ533X2101): Anti-KLH IgG responses in HVs at 3 mg/kg IV (upper panel), SC (lower panel) or placebo



HVs were immunized with the T-dependent neo-antigen KLH on Day 3 and 85 (CFZ533 was administered on Day 1). The change from baseline in anti-KLH IgG responses following KLH immunization is presented. CFZ533 transiently and completely suppressed anti-KLH responses at concentrations providing full CD40 occupancy on peripheral B cells (for about 4 weeks after 3 mg/kg IV/SC). After complete CFZ533 washout, all subjects mounted a robust anti-KLH response following a KLH challenge on Day 85. Lower doses of CFZ533 (shorter period of full RO) did not prevent anti-KLH responses

CD40 engagement by CFZ533 prevented recombinant human CD154 (rCD154) mediated B cell activation in human whole blood. The rCD154-induced-CD69 expression on B cells was generally suppressed during a period corresponding to full CD40 occupancy on B cells (Figure 5-3, 3 mg/kg SC). When CD40 occupancy was incomplete, the functional activity of rCD154 was restored.

Figure 5-3 **First in human study (CCFZ533X2101): recombinant human CD154 (rCD154) mediated B cell activation in human whole blood at 3 mg/kg SC in HVs.**



Whole blood samples were collected from non-Chinese healthy volunteers to measure the capacity of CFZ533 to block functional activity via T-cell activation. Samples were stimulated *ex-vivo* and overnight with recombinant CD154. CD69 is an activation marker that is rapidly expressed on B cells following stimulation with CD154. Functional activity (CD154-induced expression of CD69 on CD19+ cells) was assessed using flow cytometry. The percentage of CD69 positive B cells in whole blood is presented for HVs receiving 3 mg/kg SC CFZ533.

There was no evidence of any effect of CFZ533 on immunophenotyping data.

5.1.2 A randomized, double-blind, placebo-controlled, single ascending intravenous doses and single subcutaneous dose study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of CFZ533 in Japanese healthy male subjects (CCFZ533X1101)

CFZ533 was administered at 0.3, 1 and 3 mg/kg IV, and 3 mg/kg SC in Japanese healthy subjects. As for study CCFZ533X2101 in non-Japanese healthy volunteers, following IV infusion, CFZ533 plasma concentration-time profiles showed non-linear kinetics due to target-mediated disposition. Full (>90%) CD40 occupancy was observed as indicated by free CD40 on peripheral B cells, and the duration was dose-dependent, e.g. 3 days, 1 and 4 weeks after single doses of 0.3, 1 and 3 mg/kg of CFZ533, respectively.

One week after dosing at 3 mg/kg SC, plasma concentrations were in the same range as for IV, suggesting rapid absorption and distribution of CFZ533 after SC. At 3 mg/kg SC, Tmax was observed at Day 7.

No changes in the major cell populations (T cells, B cells, monocytes and NK cells) were observed.

No immunogenicity was reported in Japanese healthy volunteers.

Similar PK/PD characteristics were observed in Japanese and Caucasian healthy volunteers.

5.1.3 A multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CFZ533 in patients with primary Sjögren's syndrome (CCFZ533X2203)

This study is ongoing and preliminary data are presented below. CFZ533 was administered at 3 mg/kg SC in Cohort 1 (on days 1, 15, 29, 57 in the placebo-controlled period, and on days 85, 99, 113, 141 in the open-labelled period), and at 10 mg/kg IV (same dosing scheme) in Cohort 2.

In the SC Cohort 1, the dose/regimen was expected to deliver trough CFZ533 concentrations ≥10 µg/mL to overcome target-mediated disposition (TMD) of CFZ533. At interim analysis, most patients demonstrated lower than expected PK profiles and only a few patients had CFZ533 concentrations ≥10 µg/mL. PK/PD (soluble CD40 in plasma) profiles in this cohort suggest efficient pre-systemic TMD, possibly in the interstitium, lymphatic capillaries and/or lymph nodes. The occurrence of efficient pre-systemic elimination of CFZ533 when given SC at start of treatment is supported by the fact that pSS patients with an EULAR Sjögren Syndrome Disease Activity Index (ESSDAI) ≥6 (inclusion criterion) had systemic disease with extraglandular/systemic manifestations and lymph node enlargement in addition to glandular manifestations. As CD40 has been reported to be upregulated on parenchyma in inflamed tissues, an increased level of this receptor could be responsible for TMD.

In Cohort 2 the IV regimen was introduced to offer higher plasma exposures throughout the treatment period in order to ensure complete and sustained CD40 pathway blockade in target tissues under conditions where CD40 expression may be increased. The data show mean trough levels ≥100 µg/mL (steady state conditions) in the placebo-controlled and open-labelled periods (Figure 5-4 upper panel).

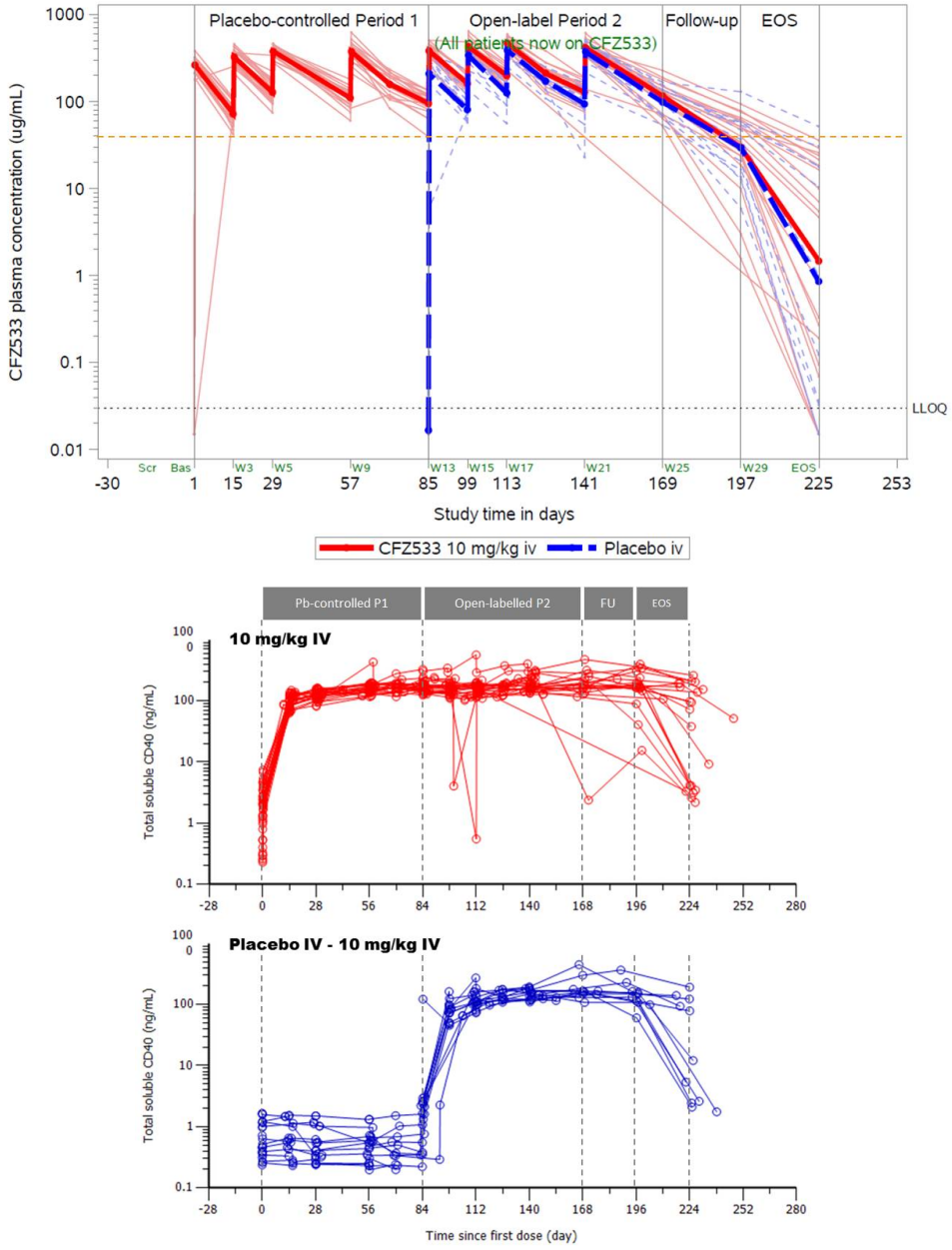
Collectively these data support the idea that an efficient dosing regimen in pSS patients may require a loading regimen (IV or SC), providing early full CD40 saturation and minimal target-mediated disposition followed by a SC maintenance regimen.

Cohort 3 is currently testing 2 dosing regimens, to explore whether either an IV or a SC loading regimen, both followed by a SC maintenance regimen, is needed to overcome TMD, and to deliver steady state plasma concentrations similar to the IV Cohort 2.

- Arm 1 (n=10): CFZ533 is administered at 600 mg SC weekly on 4 occasions (loading regimen), followed by 300 mg SC weekly on 9 occasions (maintenance regimen starting on study Day 29).
- Arm 2 (n=10): the loading regimen consisted of a single IV dose of 10 mg/kg CFZ533 (study Day 1), followed by 300 mg SC weekly on 12 occasions (maintenance regimen starting on study Day 8).

In pSS patients, total soluble CD40 profiles in plasma (Figure 5-4 lower panel) demonstrated sustained target engagement (accumulation of sCD40-CFZ533 complexes) in Cohort 2 (10 mg/kg IV regimen) throughout the placebo controlled and the open-labelled period, but not in Cohort 1 (3 mg/kg SC regimen; not shown).

Figure 5-4 **Study CCFZ533X2203 (primary Sjögren's Syndrome patients): free CFZ533 (upper panel) and total soluble CD40 (lower panel) plasma concentration-time profiles for the 10 mg/kg IV regimen (Cohort 2) - Preliminary data**



In Cohort 2, CFZ533 was administered at 10 mg/kg IV on Study Day 1, 15, 29, and 57 (placebo-controlled period), and on Study Day 85, 99, 113, 141 (open-labelled period). In the upper panel (PK profiles) the line at 40 µg/mL represent the CFZ533 plasma level above which complete suppression of GC development was observed in NHPs (26-week toxicology study; Section 4.2.2.2). The lower panel is presenting the duration of target engagement through total soluble CD40 profiles in plasma.

5.1.4 A 12-month randomized, multiple dose, open-label, study evaluating safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD) and efficacy of an anti-CD40 monoclonal antibody, CFZ533, in combination with mycophenolate mofetil (MMF) and corticosteroids (CS), with and without tacrolimus (Tac), in *de novo* renal transplant recipients (CCFZ533X2201)

This is an on-going Phase 2 study in patients undergoing kidney transplantation.

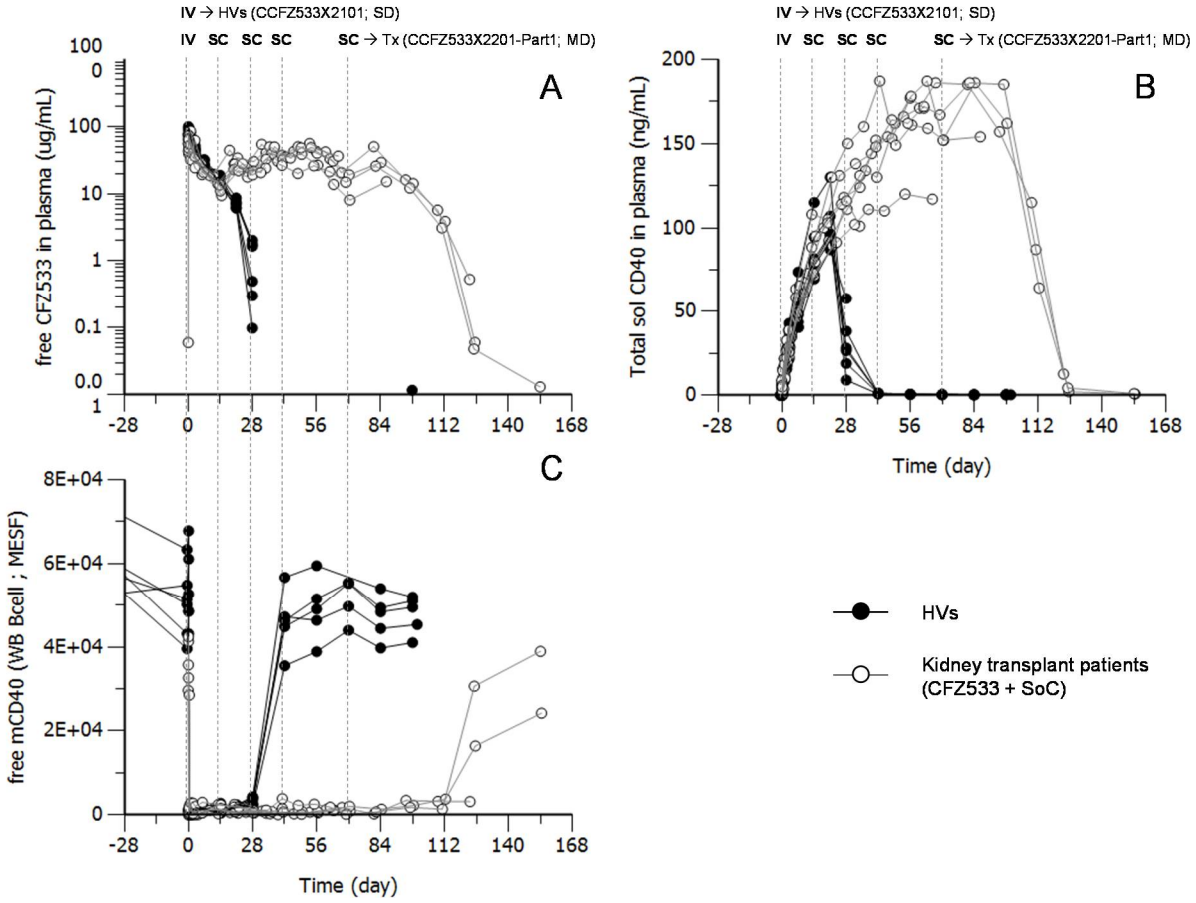
- Part 1 has been completed (PK/PD study; 7 patients): CFZ533 was administered at 3 mg/kg IV/SC (first dose is IV, then SC administration on Day 15, 29, 43 and 71) on top of SoC (tacrolimus, mycophenolate mofetil and corticosteroids).
- Part 2 is still on-going (proof-of-concept study): 10 mg/kg IV on Day 1, 3, 7, 15, 29, 43 and 57, followed by a maintenance regimen at 10 mg/kg IV Q4W.
- Part 3 (dose range finding), initially planned, will not be pursued in the scope of the present study, but will be conducted as a separate study.

Preliminary PK/PD data from Part 1 are presented in Figure 5-5, together with PK/PD profiles from HVs at 3 mg/kg IV (CCFZ533X2101).

CFZ533 PK profiles in transplant (Tx) patients under SoC (Figure 5-5, panel A) are in agreement with the disposition characteristics of CFZ533 in HVs. Under these conditions, the biology of CD40 (expression and turnover) appeared to be similar in HVs and Tx patients. In contrast to available data from a Ph2 trial with ASKP1240 in kidney Tx patients (Harland et al 2015), there was no evidence for faster target-mediated elimination during the first month. To explain the similarity between Tx patients in Part 1 (CFZ533 + SoC) and HVs, it is hypothesized that exposures resulting in full tissue CD40 occupancy prevent feed-forward loops leading to increased receptor expression.

In Part 1, as shown in Figure 5-5 (panel C), target engagement in whole blood was obtained up to Day 112 as measured through total soluble CD40 profiles in plasma (panel B), and free CD40 in whole blood B cells.

Figure 5-5 **Study CCFZ533X2201-Part 1 (kidney transplant patients): PK/PD profiles at 3 mg/kg IV/SC (on top of SoC) plotted together with HV profiles (3 mg/kg IV; from study CCFZ533X2101) – Preliminary data**



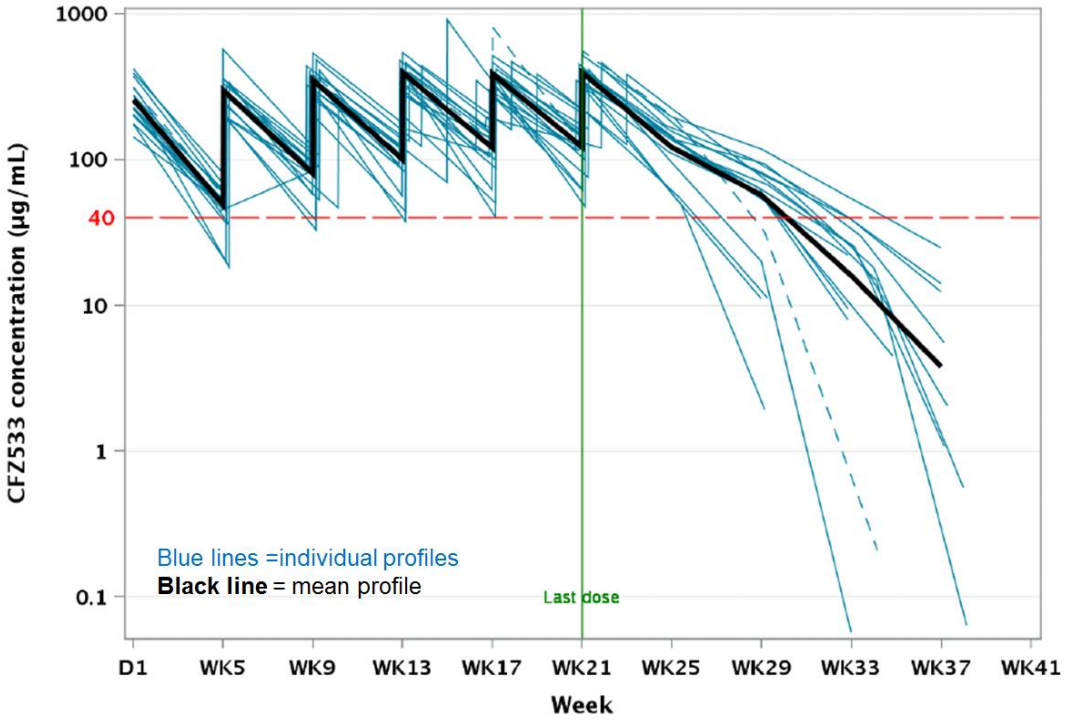
Panel A - PK (free CFZ533) profiles: typical target-mediated profiles showing non-linearity as an evidence of target engagement. Panel B - PD profiles: total soluble CD40 in plasma showing extent and duration of target engagement by CFZ533. Panel C - PD profiles: free membrane bound CD40 in whole blood B cells (MESF is Molecules of Equivalent Soluble Fluorochrome) showing target occupancy on peripheral B cells, extend and duration of target engagement. In HVs (closed symbols, black lines) CFZ533 was administered (vertical dashed bars) on Day 1 (IV), and in Tx patients (Part 1), CFZ533 was administered IV on Day 1, and SC on Day 15, 29, 43 and 71.

5.1.5 A multi-center, randomized, double-blind, placebo-controlled, parallel group study to preliminarily evaluate the safety, tolerability, pharmacokinetics and efficacy of CFZ533 in patients with moderate to severe myasthenia gravis (CCFZ5332204).

This is an ongoing study where CFZ533 is administered at 10 mg/kg IV at Week 1/Day 1, Week 5, 9, 13, 17 and 21. Similar to pSS patients (Figure 5-4), at end of the treatment period (steady state conditions), PK profiles in myasthenia gravis patients (Figure 5-6) showed mean trough levels at about 100 µg/mL. During the treatment period and for 1 or 2 months post last dose, individual PK profiles were generally >40 µg/mL, a concentration above which

complete suppression of GC development was observed in NHPs (Section 4.2.2.2), and which is also associated with inhibition of TDAR (Section 4.2.7).

Figure 5-6 Study CCFZ533X2204 (myasthenia gravis): PK profiles of CFZ533 at 10 mg/kg IV regimen - Preliminary data.

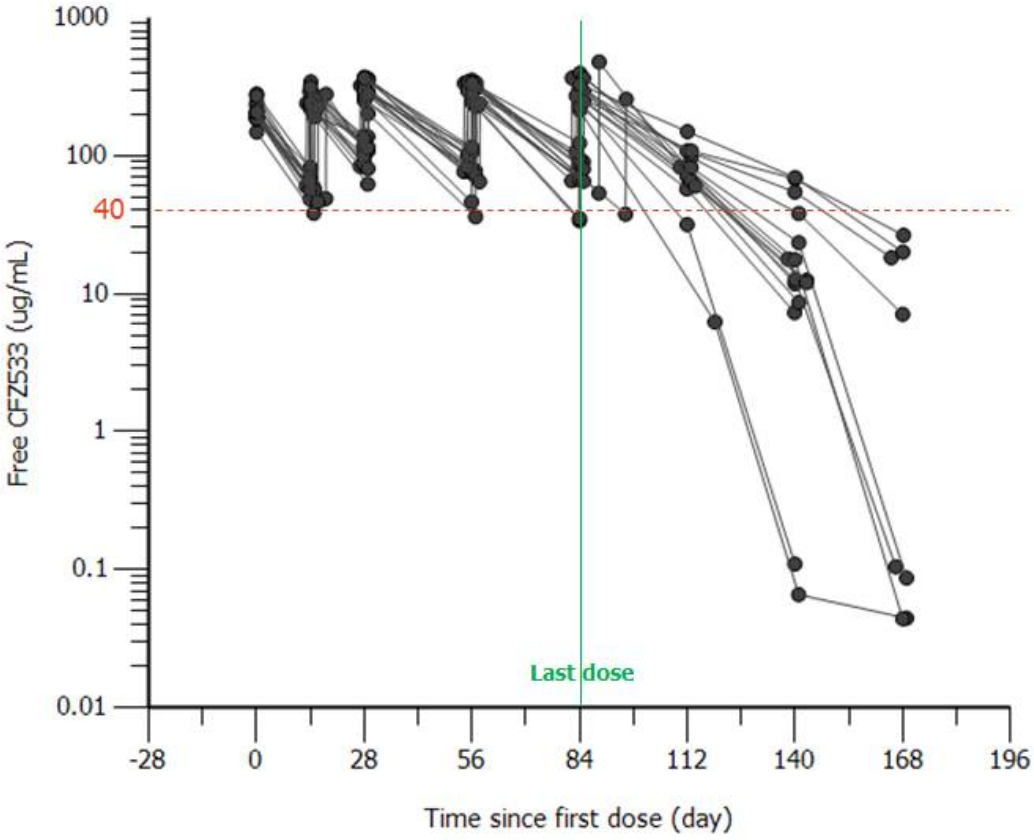


Free CFZ533 concentrations were measured in plasma. CFZ533 was administered at 10 mg/kg IV on Study Day 1 (Week 1), 29 (Week 5), 57 (Week 9), 85 (Week 13), 113 (Week 17), and 141 (Week 21). The line at 40 µg/mL represents the CFZ533 plasma level above which complete suppression of GC development was observed in NHPs (26-week toxicology study; Section 4.2.2.2).

5.1.6 An open label study to evaluate the safety and efficacy of 12 week treatment with CFZ533 in patients with Graves' disease (CCFZ533X2205)

The CCFZ533X2205 study has been completed. CFZ533 was administered at 10 mg/kg IV at Week 1/Day 1, Day 15, Week 5/Day 29, Week 9/Day 57, and Week 13/Day 85. Trough CFZ533 plasma levels in Graves' disease patients (Figure 5-7) were only slightly lower compared to trough levels in pSS patients (Figure 5-4). Nevertheless, at the end of the treatment period trough concentrations were also at *ca*. 100 µg/mL. CFZ533 exposure levels in individual subjects were generally >40 µg/mL during the treatment period, and for up to 1 or 2 months post last dose.

Figure 5-7 Study CCFZ533X2205 (Graves' disease): Pharmacokinetic profiles at 10 mg/kg IV regimen



Free CFZ533 concentrations were measured in plasma. CFZ533 was administered at 10 mg/kg IV on Study Day 1, 15, 29, 57 and 85. The line at 40 µg/mL represents the CFZ533 plasma level above which complete suppression of GC development was observed in NHPs (26-week toxicology study; Section 4.2.2.2).

5.1.7 Biopharmaceutical properties

In HVs, the bioavailability of the SC route of administration is at least 75% (preliminary data).

5.1.8 Absorption and distribution

The FIH study in HVs and RA patients (CCFZ533X2101) and the Ethnicity Sensitivity Study in Japanese HVs (CCFZ533X1101) have assessed the rate and extent of exposure for CFZ533 administered by the IV or SC route. Details are available in Section 5.1.1 and Section 5.1.2, respectively.

As expected for a typical IgG1 antibody the tissue distribution of CFZ533 is a slow process which is achieved by convective transport through capillary pores and through transcytosis into the extracellular space (a process guided by size, polarity and solubility properties), but also the consequence of CD40 mediated disposition of CFZ533.

5.1.9 Metabolism

This is not applicable to therapeutic antibodies like CFZ533. Metabolism studies have not been conducted, as is typical with therapeutic antibodies. The main elimination pathway for CFZ533 is believed to be catabolism by peptidases/proteases across the body including liver and kidneys, and breakdown products are mainly peptides and amino-acids that are expected to have no activity.

5.1.10 Excretion

See Section 5.1.7.

5.1.11 Drug-drug interactions

As is typical for therapeutic monoclonal antibodies, no *in vivo* or *in vitro* PK/PD drug interaction studies were conducted with CFZ533. Also, *in vitro* studies have limited value in the qualitative and quantitative projection of clinically relevant drug-drug interactions. CFZ533 does not undergo metabolism by CYP450 enzymes, and the risk of clinically relevant therapeutic protein drug interaction leading to dose adjustment is considered as low.

Classical ('small molecule entity-like') drug interaction trials are not anticipated to be conducted with CFZ533. Instead, a mechanism-driven and risk-based strategy is planned for CFZ533 in targeted patient populations.

5.1.12 Pharmacokinetics in special patient populations

A dedicated hepatic impairment study has not been conducted with CFZ533 based on the rationale that CFZ533 is a typical IgG1 antibody mainly cleared through catabolism. This is supported by recent publications (Yang et al 2013, Zhao et al 2012), where hepatic dysfunction showed no major impact on the PK of therapeutic proteins, and no dose modification was recommended.

However, continued used of population PK analyses, aiming to evaluate the potential effect of hepatic impairment is still viewed as important, in case specific inflammatory conditions have liver specific manifestations with clinically relevant consequences on CFZ533 disposition.

Similarly, no dedicated renal impairment study was conducted with CFZ533 considering the minimal role of renal clearance for CFZ533. The effect of renal impairment on the PK of biologics is dependent on the ability of the compound to undergo glomerular filtration, which is largely driven by molecular weight (MW). CFZ533 has a MW of *ca*. 146 kD, and renal clearance usually plays a minimal role in the elimination of biologics with MW greater than 69 kDa (Meibohm and Zhou 2012). Despite the fact that there is evidence that in some forms of renal disease, such as diabetic nephropathy, there may be an increase in the renal elimination of IgGs (Bakoush et al 2002), no specific trial is anticipated with CFZ533 in patients with impaired renal function. However, continued used of population PK analyses to further evaluate the potential effect of renal impairment is still viewed as important.

Similarly, the effect of age, gender, and race on the disposition of CFZ533 will be explored through population-based PK/PD analysis.

5.1.13 Pharmacodynamics and exposure-response relationship

The pharmacodynamic consequences of CD40 engagement by CFZ533 are discussed in Section 5.1, together with pharmacokinetics.

5.2 Safety and efficacy in humans

5.2.1 Summary of clinical trials

5.2.1.1 CCFZ533X2101- final

Study CCFZ533X2101 is a randomized, double-blind, placebo-controlled, single-ascending dose study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of CFZ533 in healthy subjects and patients with RA. In healthy subjects, doses up to 3 mg/kg IV and SC were assessed (Cohorts 1-5 and 8), in patients with RA, doses up to 30 mg/kg IV (Cohort 6 and 7) were assessed. In addition, a single dose of 3 mg/kg IV CFZ533 or placebo was administered to healthy Chinese subjects (Cohort 9). This study is completed and the study report is available (CFZ533X2101)

A total of 56 healthy subjects were enrolled, 42 of whom received single doses of CFZ533 up to 3 mg/kg. A total of 20 patients with mild to moderate RA were enrolled, 10 of whom received single doses of CFZ533 at 10 mg/kg (n=6) or 30 mg/kg (n=4) with the same number of patients received placebo in a blinded manner. The cumulative AEs to date are presented in Table 5-2 (Cohorts 1-5 and 8; non-Chinese healthy volunteers), Table 5-3 (Cohort 9 and 5; Chinese vs. non-Chinese) and Table 5-4 (Cohort 6-7; RA patients).

Healthy subjects (dose range: 0.03 to 3 mg/kg)

There have been no deaths, SAEs or discontinuations due to AEs. Two subjects from the healthy volunteer cohorts discontinued the study early due to administrative problems as they failed to return to the center for follow-up visits.

For the non-Chinese healthy volunteers (see Table 5-2), all reported AEs were mild to moderate in severity, transient and did not re-occur. When data was pooled from all treatment groups, 28 out of 36 active treated subjects experienced at least 1 AE (75%), whereas 8 out of 12 placebo treated subjects experienced at least 1 AE (66.7%). The most common reported AEs in subjects receiving CFZ533 included headache (7/36; 19.4%) and injection site pain (5/36; 13.9%) but neither these nor other individual AEs were particularly more frequent at higher doses or compared to placebo. Considering the immunosuppressive nature of CFZ533, the overall rate of infection, reported as an AE in subjects receiving CFZ533 was relatively low. For the Chinese healthy subjects cohort (Table 5-3), all reported AEs were mild to moderate in severity, transient and did not re-occur. Five of 6 Chinese subjects reported at least one AE, while 3 of 6 non-Chinese subjects received the same dose of 3 mg/kg reported at least one AE. No major or apparent differences were observed between Chinese and non-Chinese healthy subjects.

Table 5-2 Incidence of AEs reported by >5 percent subjects, by preferred term n(percent) of subjects (Cohort 1-5, and 8)

	CFZ533 0.03 mg/kg IV NC-HVs N=6 n (%)	CFZ533 0.1 mg/kg IV NC-HVs N=6 n (%)	CFZ533 0.3 mg/kg IV NC-HVs N=6 n (%)	CFZ533 1 mg/kg IV NC-HVs N=6 n (%)	CFZ533 3 mg/kg IV NC-HVs N=6 n (%)	CFZ533 3 mg/kg SC NC-HVs N=6 n (%)	Placebo NC-HVs N=12 n (%)	Total N=48 n (%)
Subjects with AE(s)	5 (83.3)	4 (66.7)	6 (100.0)	5 (83.3)	3 (50.0)	5 (83.3)	8 (66.7)	36 (75.0)
Preferred term								
Headache	3 (50.0)	0	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	6 (50.0)	13 (27.1)
Injection site pain	1 (16.7)	0	2 (33.3)	0	2 (33.3)	0	2 (16.7)	7 (14.6)
Oropharyngeal pain	1 (16.7)	1 (16.7)	0	0	0	3 (50.0)	1 (8.3)	6 (12.5)
Sinus congestion	1 (16.7)	0	0	0	1 (16.7)	2 (33.3)	1 (8.3)	5 (10.4)
Musculoskeletal pain	2 (33.3)	0	0	0	0	1 (16.7)	1 (8.3)	4 (8.3)
Rhinorrhoea	0	1 (16.7)	1 (16.7)	0	0	1 (16.7)	1 (8.3)	4 (8.3)
Back pain	1 (16.7)	0	0	0	0	1 (16.7)	1 (8.3)	3 (6.3)
Cough	1 (16.7)	0	0	0	0	1 (16.7)	1 (8.3)	3 (6.3)
Nausea	1 (16.7)	1 (16.7)	1 (16.7)	0	0	0	0	3 (6.3)
Pain in extremity	1 (16.7)	0	0	1 (16.7)	0	1 (16.7)	0	3 (6.3)

Arranged in descending order of frequency (in total group) and by preferred term.
Source: Table 14.3.1-1.1a

Table 5-3 Incidence of AEs by preferred term n(percent) of subjects (Cohort 9 and 5)

	CFZ533 3 mg/kg IV NC-HVs N=6 n (%)	Placebo NC-HVs N=2 n (%)	CFZ533 3 mg/kg IV C-HVs N=6 n (%)	Placebo C-HVs N=2 n (%)	Total N=16 n (%)
Subjects with AE(s)	3 (50.0)	1 (50.0)	5 (83.3)	0	9 (56.3)
Preferred term					
Headache	1 (16.7)	1 (50.0)	0	0	2 (12.5)
Hyperglycaemia	0	0	2 (33.3)	0	2 (12.5)
Injection site pain	2 (33.3)	0	0	0	2 (12.5)
Abnormal weight gain	0	0	1 (16.7)	0	1 (6.3)
Anxiety	1 (16.7)	0	0	0	1 (6.3)
Blood bilirubin increased	0	0	1 (16.7)	0	1 (6.3)
Blood triglycerides increased	0	0	1 (16.7)	0	1 (6.3)
Cough	0	1 (50.0)	0	0	1 (6.3)
Gamma-glutamyltransferase increased	0	0	1 (16.7)	0	1 (6.3)
Herpes zoster	0	0	1 (16.7)	0	1 (6.3)
Nasopharyngitis	1 (16.7)	0	0	0	1 (6.3)
Oral herpes	1 (16.7)	0	0	0	1 (6.3)
Productive cough	1 (16.7)	0	0	0	1 (6.3)
Respiratory tract congestion	1 (16.7)	0	0	0	1 (6.3)
Sinus congestion	1 (16.7)	0	0	0	1 (6.3)
Toothache	0	1 (50.0)	0	0	1 (6.3)

	CFZ533 3 mg/kg IV NC-HVs N=6 n (%)	Placebo NC-HVs N=2 n (%)	CFZ533 3 mg/kg IV C-HVs N=6 n (%)	Placebo C-HVs N=2 n (%)	Total N=16 n (%)

Arranged in descending order of frequency (in total group) and by preferred term.
Source: Table 14.3.1-1.1b

In addition, there were no clinically significant deviations in laboratory evaluations, including coagulation parameters (e.g., PT, aPTT) over the course of the trial. All notable laboratory deviations were transient, resolved spontaneously and did not require treatment or result in an AE report. Similarly, there were no clinically relevant changes in ECG parameters, vital signs or special laboratory assessments such as thromboelastography (TEG), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen and multiplex cytokine assessments. In addition, there was no effect on % of CD19+ B-cells or other leukocyte- and B cell subsets nor was there a significant change in total IgM or IgG concentrations during the trial as compared to baseline in healthy volunteers.

Patients with rheumatoid arthritis (10 mg/kg and 30 mg/kg IV)

A total of 12 patients with RA were enrolled to Cohort 6 (10 mg/kg IV) and a total of 8 patients with RA were enrolled to Cohort 7 (30 mg/kg IV) in this study. Six or four patients were assigned to receive either 10 mg/kg or 30 mg/kg CFZ533 single IV dose in cohort 6 and cohort 7, respectively, with equal numbers of patients with RA receiving placebo in each cohort.

There have been no deaths, study medication-related SAEs or discontinuations due to AEs in any of the subjects who received CFZ533. Three SAEs were reported by two patients, one patient received placebo (diverticulitis) and the other patients received 30 mg/kg CFZ533 (vasovagal syncope and episode of confusion). None of these SAEs was suspected to be related to the study. The overall incidence of AEs is shown by preferred term in Table 5-4. Out of 20 RA patients, 19 (95.0%) experienced at least 1 AE. All patients (100%) who received CFZ533 and 9 out of 10 patients (90%) who received the placebo experienced an AE.

A single dose of CFZ533 at 10 and 30 mg/kg were generally well tolerated in patients with rheumatoid arthritis, and there was no evidence of dose-related increases in the incidence of any AE. The majority of patients reported only mild (30%, 6 out of 20 patients) or moderate (45%, 9 out of 20 patients) AEs, with 20% (4 out of 20 patients) reporting severe (Grade 3) AEs. The incidence of severe AEs was similar between treatment groups (10 mg/kg and 30 mg/kg CFZ533 and placebo), and none were considered to be treatment-related. The severe AEs included increased lipase (up to 2xULN in one patient on 10 mg/kg CFZ533), syncope and an episode of confusion (1 patient on 30 mg/kg CFZ533, also reported as an SAE), hypertriglyceridaemia (up to 9.7xULN in one patient on placebo) and arthralgia (one patient on placebo). AEs of infection were reported by 8 patients receiving CFZ533 10 or 30 mg/kg (mostly mild or moderate in severity) and 7 patients receiving placebo (mild or moderate in severity). No severe or serious infection has been observed with CFZ533. There were no clinically relevant changes in ECG parameters, vital signs or clinical laboratory parameters, including coagulation parameters (e.g., PT, aPTT).

Table 5-4 Incidence of AEs reported by >5 percent subjects by preferred term n(percent) of subjects (Cohort 6 and 7)

	CFZ533 10 mg/kg IV RA N=6 n (%)	CFZ533 30 mg/kg IV RA N=4 n (%)	Placebo RA N=10 n (%)	Total N=20 n (%)
Subjects with AE(s)	6 (100.0)	4 (100.0)	9 (90.0)	19 (95.0)
Preferred term				
Upper respiratory tract infection	2 (33.3)	2 (50.0)	3 (30.0)	7 (35.0)
Urinary tract infection	1 (16.7)	0	4 (40.0)	5 (25.0)
Headache	1 (16.7)	1 (25.0)	2 (20.0)	4 (20.0)
Nasopharyngitis	2 (33.3)	1 (25.0)	0	3 (15.0)
Nausea	1 (16.7)	0	2 (20.0)	3 (15.0)
Bronchitis	0	0	2 (20.0)	2 (10.0)
Hypokalaemia	1 (16.7)	0	1 (10.0)	2 (10.0)
Vomiting	2 (33.3)	0	0	2 (10.0)

Arranged in descending order of frequency (in total group) and by preferred term.
Source: Table 14.3.1-1.1c

Overall, in the Phase 1 study, single doses up to 3 mg/kg CFZ533 in healthy volunteers and single doses of 10 and 30 mg/kg CFZ533 in RA patients have been safe and well tolerated. No study medication-related SAE occurred in any of the subjects who received CFZ533 up to 30 mg/kg.

5.2.1.2 CCFZ533X1101- Completed study data

This was a double-blind, randomized, placebo-controlled, non-confirmatory study to assess the safety and tolerability of single IV (0.3, 1 and 3 mg/kg), and SC (3 mg/kg) doses of CFZ533 in Japanese healthy male subjects. As secondary endpoints, PK and PD of CFZ533 as well as immunogenicity after single doses of CFZ533 were also investigated.

A similar incidence of AEs in the CFZ533 treated subjects and in the placebo treated subjects was observed with no death, SAE, or AE of special interest or clinically relevant alterations of laboratory, vital sign or ECG data with the exception of an AE related to elevated creatine kinase (CK). All reported AEs were mild to moderate in severity. Only two AEs were reported in subjects treated with CFZ533. All notable laboratory deviations were transient, resolved spontaneously and did not require treatment or result in an AE report (except one AE of CK increase). Similarly, there were no clinically relevant changes in ECG parameters, vital signs or special laboratory assessments such as evaluation of IgG. As compared to baseline, there was no effect of CFZ533 on the immunophenotyping parameters such as B cells or T cells and no difference was observed between CFZ533 treated and placebo subjects. Antibodies against CFZ533 were not detected.

Of 32 subjects enrolled, only five (15.6%) subjects experienced at least one AE. The overall incidence of AEs was seen in three (37.5%) subjects in the placebo group and in two (8.3%) subjects in CFZ533 dose groups. The incidence of AEs by preferred term is summarized in Table 5-5.

Table 5-5 Incidence of AEs by preferred term - n (percent) of subjects: Safety analysis set

	0.3 mg/kg iv CFZ533 N=6 n (%)	1 mg/kg iv CFZ533 N=6 n (%)	3 mg/kg iv CFZ533 N=6 n (%)	3 mg/kg sc CFZ533 N=6 n (%)	Placebo N=8 n (%)	Total N=32 n (%)
Subjects with AEs	0	0	1 (16.7)	1 (16.7)	3 (37.5)	5 (15.6)
Blood creatine phosphokinase increased	0	0	0	0	1 (12.5)	1 (3.1)
Headache	0	0	1 (16.7)	0	0	1 (3.1)
Nausea	0	0	1 (16.7)	0	0	1 (3.1)
Oral herpes	0	0	0	0	1 (12.5)	1 (3.1)
Pharyngitis	0	0	0	0	1 (12.5)	1 (3.1)
Thermal burn	0	0	0	1 (16.7)	0	1 (3.1)

Arranged by frequency in the total column
Source: CSR Table 14.3.1-1.2

Overall, single doses of 0.3-3 mg/kg CFZ533 were safe and well tolerated in Japanese healthy volunteers. The study has been completed and the full Clinical Study Report is available.

5.2.1.3 CCFZ533X2201 preliminary safety and efficacy data

CCFZ533X2201 is a two-part, randomized, multiple dose, open-label, study evaluating safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD) and efficacy of CFZ533, in combination with mycophenolate mofetil (MMF) and corticosteroids (CS), with and without tacrolimus (Tac), in de novo renal transplant recipients. Part 1 of this trial has been completed (n=7 subjects). It focused on profiling the multiple dose pharmacokinetics (PK), pharmacodynamics (PD) and tolerability of a 3mg/kg dose for both IV and SC CFZ533 administration on top of standard-of-care, calcineurin-inhibitor (CNI)-based immunosuppression. The review of PK/PD data confirmed expected exposure.

Part 2 of the trial is currently ongoing to evaluate the safety and efficacy of CFZ533 in the absence of CNI in combination with adjunct MMF and steroids. All subjects received basiliximab induction therapy and are followed for up to 12 months either on SoC or CFZ533. Interim analysis of Part 2 was done at 3 and 6 months of treatment and the preliminary results of the latter are presented here. A total of 52 patients were included and randomized, of which 51 received a kidney transplant (34 received CFZ533 and 18 patients received tacrolimus).

There were no deaths, no thromboembolic events in the CFZ533 group (1 in the Tac arm), no cases of post-transplant lymphoproliferative disease (PTLD), and no cases of progressive multifocal leukoencephalopathy (PML).

During the first 6 months of the trial, CFZ533 seemed to provide similar efficacy in terms of preventing acute rejection (treated BPAR) as the conventional Tac-based therapy. Two grafts were lost in the Tac arm (11%), but none in the CFZ533 group. The safety profile is presented

in Table 5-6. Fewer patients experienced serious adverse events on CFZ533 compared to Tac (approximately 47% vs. 61%).

Table 5-6 Summary of Adverse events in the CFZ533X2201 study

	CFZ+MMF N=34 nE, nS (%)	Tac+MMF N=18 nE, nS (%)	Total N=52 nE, nS (%)
AEs, Patients with AEs	432, 33 (97.1)	291, 18 (100.0)	723, 51 (98.1)
AEs of mild intensity	272, 33 (97.1)	176, 18 (100.0)	448, 51 (98.1)
AEs of moderate intensity	149, 29 (85.3)	108, 16 (88.9)	257, 45 (86.5)
AEs of severe intensity	11, 7 (20.6)	7, 4 (22.2)	18, 11 (21.2)
Study drug-related AEs	40, 17 (50.0)	36, 9 (50.0)	76, 26 (50.0)
Serious AEs	31, 16 (47.1)	25, 11 (61.1)	56, 27 (51.9)
AEs leading to discontinuation of study treatment	10, 9 (26.5)	5, 5 (27.8)	15, 14 (26.9)
SAEs leading to discontinuation of study treatment	9, 9 (26.5)	3, 3 (16.7)	12, 12 (23.1)
Study drug related AEs leading to discontinuation of study treatment	8, 7 (20.6)	3, 3 (16.7)	11, 10 (19.2)
Deaths	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

Source: 14.3.1-1.6

A separate dose range finding trial is planned and will employ an exposure-response modeling approach using data from Parts 1 and 2 to enable CFZ533 regimens for the active treatment arms.

5.2.1.4 CCFZ533X2203- Interim safety and efficacy data

A multi-center, randomized, double-blind, placebo controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CFZ533 in patients with primary Sjögren's syndrome (pSS) is currently ongoing.

Three interim analyses have been conducted and included data from a total of 44 patients with pSS who were enrolled to Cohort 1 (3 mg/kg SC) and Cohort 2 (10 mg/kg IV) in this study. All patients (n=12) in Cohort 1 completed Period 1 (12 weeks, double blind, placebo-controlled period) and 11 patients completed Period 2 (additional open label [all-CFZ533]12 weeks extension). Thirty-two patients were enrolled (dosed) in Cohort 2 and 31 completed Period 1 (one patient in Cohort 2 (CFZ533 group) did not complete Period 2 due to an AE). At the time of writing, Periods 1 and 2 have been completed for both Cohorts. One patient in Cohort 2 in the CFZ533 group did not complete Period 2 due to an AE. Cohort 3 is currently ongoing to test different s.c. dosing regimens.

In both cohorts, CFZ533 or placebo was administered at Weeks 1, 3, 5 and 9 in Period 1 followed by Period 2 when CFZ533 was administered at Weeks 13, 15, 17 and 21.

Based on the preliminary data available from these three interim analyses, the adverse events that occurred were mainly of mild or moderate severity and no new safety signal emerged.

There was one SAE (bacterial conjunctivitis) in Cohort 1 in Period 2 (3 mg/kg SC), which was not suspected to be related to study drug by the investigator. There was one SAE (atrial fibrillation) in Cohort 2 in Period 2 which was not suspected to be related to the study drug and the patient had a pre-disposing medical condition. Both SAEs occurred several weeks after the last dose of CFZ533 in the safety follow-up period near the End of Study visit.

The incidence of AEs by preferred term in Cohort 1 and Cohort 2 is summarized in Table 5-7 and Table 5-8, respectively.

Table 5-7 Incidence of AEs by preferred term - n (percent) of subjects (Safety analysis set) in Cohort 1 (3 mg/kg SC)

	CFZ533 3 mg/kg s.c N=8 n (%)	Placebo -> CFZ533 N=4 n (%)	Total N=12 n (%)
Subjects with AE(s)	8 (100.0)	4 (100.0)	12 (100.0)
Preferred term			
Upper respiratory tract infection	2 (25.0)	2 (50.0)	4 (33.3)
Arthralgia	2 (25.0)	1 (25.0)	3 (25.0)
Dizziness	2 (25.0)	1 (25.0)	3 (25.0)
Lower respiratory tract infection	2 (25.0)	1 (25.0)	3 (25.0)
Rash	2 (25.0)	1 (25.0)	3 (25.0)
Diarrhoea	1 (12.5)	1 (25.0)	2 (16.7)
Nausea	1 (12.5)	1 (25.0)	2 (16.7)
Toothache	1 (12.5)	1 (25.0)	2 (16.7)
Urinary tract infection	2 (25.0)	0 (0.0)	2 (16.7)
Vomiting	2 (25.0)	0 (0.0)	2 (16.7)
Abdominal pain upper	0 (0.0)	1 (25.0)	1 (8.3)
Abdominal wall neoplasm	1 (12.5)	0 (0.0)	1 (8.3)
Abdominal distension	0 (0.0)	1 (25.0)	1 (8.3)
Alopecia	0 (0.0)	1 (25.0)	1 (8.3)
Amenorrhoea	1 (12.5)	0 (0.0)	1 (8.3)
Appetite disorder	1 (12.5)	0 (0.0)	1 (8.3)
Arthropod bite	1 (12.5)	0 (0.0)	1 (8.3)
Blepharitis	0 (0.0)	1 (25.0)	1 (8.3)
Carpal tunnel syndrome	0 (0.0)	1 (25.0)	1 (8.3)
Cataract	1 (12.5)	0 (0.0)	1 (8.3)
Cerumen impaction	1 (12.5)	0 (0.0)	1 (8.3)
Chills	0 (0.0)	1 (25.0)	1 (8.3)
Conjunctivitis	1 (12.5)	0 (0.0)	1 (8.3)
Conjunctivitis bacterial	1 (12.5)	0 (0.0)	1 (8.3)
Corneal abrasion	1 (12.5)	0 (0.0)	1 (8.3)
Cough	0 (0.0)	1 (25.0)	1 (8.3)
Cutaneous vasculitis	0 (0.0)	1 (25.0)	1 (8.3)
Cyst	0 (0.0)	1 (25.0)	1 (8.3)
Depressed mood	1 (12.5)	0 (0.0)	1 (8.3)
Diplopia	1 (12.5)	0 (0.0)	1 (8.3)
Dry eye	0 (0.0)	1 (25.0)	1 (8.3)
Dry throat	0 (0.0)	1 (25.0)	1 (8.3)
Dysphonia	0 (0.0)	1 (25.0)	1 (8.3)
Ear infection	1 (12.5)	0 (0.0)	1 (8.3)

	CFZ533 3 mg/kg s.c N=8 n (%)	Placebo -> CFZ533 N=4 n (%)	Total N=12 n (%)
Epicondylitis	1 (12.5)	0 (0.0)	1 (8.3)
Erythema	1 (12.5)	0 (0.0)	1 (8.3)
Eye pain	1 (12.5)	0 (0.0)	1 (8.3)
Fatigue	1 (12.5)	0 (0.0)	1 (8.3)
Gingivitis	0 (0.0)	1 (25.0)	1 (8.3)
Headache	0 (0.0)	1 (25.0)	1 (8.3)
Hypersensitivity	0 (0.0)	1 (25.0)	1 (8.3)
Hyperventilation	0 (0.0)	1 (25.0)	1 (8.3)
Hypoacusis	1 (12.5)	0 (0.0)	1 (8.3)
Increased tendency to bruise	0 (0.0)	1 (25.0)	1 (8.3)
Inflammation	1 (12.5)	0 (0.0)	1 (8.3)
Influenza	0 (0.0)	1 (25.0)	1 (8.3)
Localised infection	1 (12.5)	0 (0.0)	1 (8.3)
Lymph gland infection	1 (12.5)	0 (0.0)	1 (8.3)
Lymphadenopathy	1 (12.5)	0 (0.0)	1 (8.3)
Lymphopenia	1 (12.5)	0 (0.0)	1 (8.3)
Mental disorder	0 (0.0)	1 (25.0)	1 (8.3)
Myalgia	1 (12.5)	0 (0.0)	1 (8.3)
Nail bed infection	1 (12.5)	0 (0.0)	1 (8.3)
Nodule	1 (12.5)	0 (0.0)	1 (8.3)
Non-cardiac chest pain	0 (0.0)	1 (25.0)	1 (8.3)
Ocular hyperaemia	1 (12.5)	0 (0.0)	1 (8.3)
Onychoclasis	1 (12.5)	0 (0.0)	1 (8.3)
Oropharyngeal pain	0 (0.0)	1 (25.0)	1 (8.3)
Osteoarthritis	1 (12.5)	0 (0.0)	1 (8.3)
Paraesthesia	0 (0.0)	1 (25.0)	1 (8.3)
Parotid gland enlargement	0 (0.0)	1 (25.0)	1 (8.3)
Pharyngitis	0 (0.0)	1 (25.0)	1 (8.3)
Procedural nausea	1 (12.5)	0 (0.0)	1 (8.3)
Red blood cells urine positive	1 (12.5)	0 (0.0)	1 (8.3)
Rhinitis	1 (12.5)	0 (0.0)	1 (8.3)
Rosacea	1 (12.5)	0 (0.0)	1 (8.3)
Seasonal allergy	1 (12.5)	0 (0.0)	1 (8.3)
Sinusitis	0 (0.0)	1 (25.0)	1 (8.3)
Sjogren's syndrome	1 (12.5)	0 (0.0)	1 (8.3)
Skin infection	1 (12.5)	0 (0.0)	1 (8.3)
Swelling face	1 (12.5)	0 (0.0)	1 (8.3)
Tongue ulceration	1 (12.5)	0 (0.0)	1 (8.3)
Tooth infection	0 (0.0)	1 (25.0)	1 (8.3)
Tremor	0 (0.0)	1 (25.0)	1 (8.3)
Uterine prolapse	1 (12.5)	0 (0.0)	1 (8.3)
Viral upper respiratory tract infection	0 (0.0)	1 (25.0)	1 (8.3)
White blood cell count decreased	1 (12.5)	0 (0.0)	1 (8.3)
White blood cells urine positive	1 (12.5)	0 (0.0)	1 (8.3)

Arranged in descending order of frequency (in total group) and alphabetically by preferred term
Source: PT-Table 14.3.1-1.1

Table 5-8 Incidence of AEs by preferred term - n (percent) of subjects (Safety analysis set) in Cohort 2 (10 mg/kg IV)

	CFZ533 10 mg/kg i.v. N=21 n (%)	Placebo -> CFZ533 N=11 n (%)	Total N=32 n (%)
Subjects with AE(s)	11 (52.4)	7 (63.6)	18 (56.3)
Preferred term			
Upper respiratory tract infection	2 (9.5)	2 (18.2)	4 (12.5)
Contusion	2 (9.5)	1 (9.1)	3 (9.4)
Diarrhoea	2 (9.5)	1 (9.1)	3 (9.4)
Headache	2 (9.5)	1 (9.1)	3 (9.4)
Iron deficiency anaemia	1 (4.8)	1 (9.1)	2 (6.3)
Lipase increased	0 (0.0)	2 (18.2)	2 (6.3)
Nasopharyngitis	0 (0.0)	2 (18.2)	2 (6.3)
Photosensitivity reaction	1 (4.8)	1 (9.1)	2 (6.3)
Rash	1 (4.8)	1 (9.1)	2 (6.3)
Abdominal discomfort	1 (4.8)	0 (0.0)	1 (3.1)
Abnormal dreams	1 (4.8)	0 (0.0)	1 (3.1)
Amnesia	1 (4.8)	0 (0.0)	1 (3.1)
Anaemia	1 (4.8)	0 (0.0)	1 (3.1)
Anxiety	1 (4.8)	0 (0.0)	1 (3.1)
Arthralgia	0 (0.0)	1 (9.1)	1 (3.1)
Arthritis	1 (4.8)	0 (0.0)	1 (3.1)
Arthropod bite	1 (4.8)	0 (0.0)	1 (3.1)
Atrial fibrillation	1 (4.8)	0 (0.0)	1 (3.1)
Benign breast neoplasm	0 (0.0)	1 (9.1)	1 (3.1)
Blood alkaline phosphatase increased	0 (0.0)	1 (9.1)	1 (3.1)
Body tinea	0 (0.0)	1 (9.1)	1 (3.1)
Bronchitis	0 (0.0)	1 (9.1)	1 (3.1)
Constipation	0 (0.0)	1 (9.1)	1 (3.1)
Deafness	1 (4.8)	0 (0.0)	1 (3.1)
Depression	1 (4.8)	0 (0.0)	1 (3.1)
Dermatitis allergic	0 (0.0)	1 (9.1)	1 (3.1)
Dizziness	1 (4.8)	0 (0.0)	1 (3.1)
Dysphagia	0 (0.0)	1 (9.1)	1 (3.1)
Endometrial disorder	0 (0.0)	1 (9.1)	1 (3.1)
Gamma-glutamyltransferase increased	0 (0.0)	1 (9.1)	1 (3.1)
Gastroenteritis viral	1 (4.8)	0 (0.0)	1 (3.1)
Hemianopia homonymous	0 (0.0)	1 (9.1)	1 (3.1)
Herpes zoster	1 (4.8)	0 (0.0)	1 (3.1)
Hyperhidrosis	0 (0.0)	1 (9.1)	1 (3.1)
Incision site hypoaesthesia	0 (0.0)	1 (9.1)	1 (3.1)
Inflammation	1 (4.8)	0 (0.0)	1 (3.1)
Intraocular pressure increased	1 (4.8)	0 (0.0)	1 (3.1)
Limb injury	1 (4.8)	0 (0.0)	1 (3.1)
Menstruation irregular	1 (4.8)	0 (0.0)	1 (3.1)
Nasal congestion	0 (0.0)	1 (9.1)	1 (3.1)
Nausea	1 (4.8)	0 (0.0)	1 (3.1)
Neck pain	0 (0.0)	1 (9.1)	1 (3.1)
Oropharyngeal pain	0 (0.0)	1 (9.1)	1 (3.1)

	CFZ533 10 mg/kg i.v. N=21 n (%)	Placebo -> CFZ533 N=11 n (%)	Total N=32 n (%)
Osteoarthritis	0 (0.0)	1 (9.1)	1 (3.1)
Palpitations	1 (4.8)	0 (0.0)	1 (3.1)
Pharyngitis	1 (4.8)	0 (0.0)	1 (3.1)
Plantar fasciitis	0 (0.0)	1 (9.1)	1 (3.1)
Rash macular	0 (0.0)	1 (9.1)	1 (3.1)
Salivary gland enlargement	1 (4.8)	0 (0.0)	1 (3.1)
Sinusitis	1 (4.8)	0 (0.0)	1 (3.1)
Skin injury	0 (0.0)	1 (9.1)	1 (3.1)
Spinal compression fracture	0 (0.0)	1 (9.1)	1 (3.1)
Tinnitus	1 (4.8)	0 (0.0)	1 (3.1)
Tooth fracture	1 (4.8)	0 (0.0)	1 (3.1)
Tooth infection	1 (4.8)	0 (0.0)	1 (3.1)
Toothache	1 (4.8)	0 (0.0)	1 (3.1)
Urogenital infection bacterial	1 (4.8)	0 (0.0)	1 (3.1)
Urticaria	1 (4.8)	0 (0.0)	1 (3.1)
Vitreous detachment	1 (4.8)	0 (0.0)	1 (3.1)
Vitreous floaters	1 (4.8)	0 (0.0)	1 (3.1)
Vomiting	1 (4.8)	0 (0.0)	1 (3.1)

Arranged in descending order of frequency (in total group) and alphabetically by preferred term
Source: PT-Table 14.3.1-1.1

Based on preliminary efficacy data, clear improvements in the primary endpoint (i.e. ESSDAI) were seen after 12 weeks of treatment in the 10 mg/kg IV CFZ533 group as compared to placebo (ΔESSDAI=5.6) but not in the 3 mg/kg SC CFZ533 group. Trends in most secondary endpoints also favored CFZ533 with more pronounced effects seen in the 10 mg/kg IV vs. the 3 mg/kg SC group. Efficacy (ESSDAI changes) seen in Period 1 at 10 mg/kg IV was sustained in the open label Period 2. Some improvements were observed in the Placebo group when patients were switched to 10 mg/kg IV CFZ533.

Overall, based on interim data, multiple doses of 3 mg/kg SC and 10 mg/kg IV CFZ533 including a total of eight doses over 21 weeks have been safe and well tolerated in patients with primary Sjögren`s syndrome. Furthermore, preliminary efficacy data suggest that multiple doses of 10 mg/kg IV CFZ533 have improved the signs and symptoms of primary Sjögren`s syndrome as measured by ESSDAI and other efficacy endpoints. At the time of writing, Cohort 3 of the study is still ongoing.

5.2.2 Investigator Notifications

During the reporting period two Investigators Notifications were issued for SUSARs received for CFZ533 studies. Both cases were received from study CCFZ533X2201 with event PTs of Polyomavirus-associated nephropathy and Gastroenteritis.

The details of six Investigator Notifications submitted to date are summarized in Table 5-9.

Table 5-9 Investigator Notifications issued to date

Indication	Study	SAE number	SUSAR event (PT)	Initial IN sent

Indication	Study	SAE number	SUSAR event (PT)	Initial IN sent
Renal transplant	CCFZ533 X2201	PHHO2017DE003040	Gastroenteritis	09 Mar 2017
Renal transplant	CCFZ533 X2201	PHHO2016US017713	Polyomavirus-associated nephropathy	21 Dec 2016
Renal transplant	CCFZ533 X2201	PHHO2016NL015402	Enterobacter bacteraemia	03 Nov 2016
Renal transplant	CCFZ533 X2201	PHHO2016NL011480	Amylase increased	17 Aug 2016
Myasthenia gravis	CCFZ533 X2204	PHHO2016DK004392	Neutropenia	15 Jun 2016
Renal transplant	CCFZ533 X2201	PHHO2015US01343	Deep vein thrombosis, Pulmonary embolism	02 Sep 2015

5.2.3 ASKP1240 (Astellas Pharma)

As reported by Goldwater et al, ASKP1240 is a fully human anti-CD40 monoclonal antibody which has been administered to 109 healthy volunteers in a single dose double-blind, safety, tolerability, and pharmacokinetic study. Doses of ASKP1240 were 0.00003, 0.0001, 0.0003, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10 mg/kg and subjects were followed-up for 60 days in all dose groups except 10 mg/kg group which was followed for 90 days (Goldwater et al 2013).

One hundred and four (104) of 109 randomized subjects completed the study. One subject was randomized but not treated, 3 subjects were lost to follow up between days 8 and 15, and 1 subject withdrew consent on day 8. Doses of 1, 3 and 10 mg/ kg resulted in quantifiable serum ASKP1240 in all subjects through days 8, 29 and 43, respectively, with 5 out of 6 subjects in 10 mg/kg treatment group sustaining PK levels through day 60. In the 3 and 10 mg/kg ASKP1240 groups, maximal CD40 receptor occupancy was sustained through days 29 and 60, respectively. Dose proportionality was not met for either Cmax or AUC. No subjects experienced cytokine release syndrome (CRS) or thromboembolic event. No subjects discontinued due to an AE.

AEs reported in the combined ASKP1240 treatment groups vs. placebo included headache in 9.7% vs. 11.1%, upper respiratory tract infection in 8.3% vs. 2.8% and cough in 6.9% vs. 2.8%. One mild rash occurred in a subject who received ASKP1240 10 mg/kg. Incidence of treatment emergent anti-ASKP1240 antibodies was 6.9%. Laboratory evaluations did not indicate platelet or endothelial cell activation nor activation of coagulation or fibrinolytic cascades (Goldwater et al 2013).

The first results of a randomized open-label non-inferiority study of ASKP1240 in *de novo* kidney transplantation recipients were presented at the American Transplant Congress in May 2015 (Harland et al 2015). Subjects (n=138) were randomized to SoC comprising tacrolimus + mycophenolate mofetil + cyclosporine, (n=48), ASKP1240 + mycophenolate mofetil + cyclosporine (CNI-free, n=46) or ASKP + tacrolimus + mycophenolate mofetil + CsA (tacrolimus "minimization", n=44).

The main outcome after 6 months was an increased rate of rejection in the CNI-free arm with 17 cases of biopsy proven acute rejection rates compared to 3 in SoC (37% vs. 6.3%).

However, based on Novartis analysis (data on file), the doses used were assumed to have been insufficient to achieve full tissue CD40 occupancy during the first weeks of treatment, which may explain inefficacy. Furthermore, the tacrolimus levels were not reduced in the tacrolimus "minimization" cohort, which may account for the increased number of BK virus infections of 12 compared to 6 cases on SoC (27 vs. 12 %). Importantly, no subjects experienced thromboembolic events (Harland et al 2015).

5.3 Post-marketing experience

Not applicable.

5.4 Publications

The following publications relating to CFZ533 have been published:

Cordoba F, Wieczorek G, Audet M, et al (2015) A Novel, Blocking, Fc-Silent Anti-CD40 Monoclonal Antibody Prolongs Nonhuman Primate Renal Allograft Survival in the Absence of B Cell Depletion. Am J Transplant; 15(11):2825-36.

Slade A, Koo P, Espie P, et al (2014) OM11-62MF: Safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of a novel anti-CD40 antibody in healthy volunteers. Transplantation; 98:115.

Slade A, Doucet J, Koo P, et al (2015) CFZ533: Assessment of immunomodulatory activity following single doses of a novel anti-CD40 mAb in healthy volunteers. American Transplant Congress 2015, Abstract number 252026.

6 Reference Safety Information

No serious adverse reactions (SARs) are considered expected by the sponsor for the purpose of expedited reporting and identification of SUSARs in the Development Safety Update Report (DSUR) for the CFZ533 IMP.

7 Summary of the data and guidance for the investigator

7.1 General

CFZ533 is a new molecular entity currently in Phase 2 evaluation with limited clinical experience using either single IV infusions and subcutaneous doses of CFZ533 in healthy subjects, patients with RA, or during 12 week treatment at a dosing regimen of Q4W in patients with Graves' disease. The FIH study in healthy subjects and patients with RA (CFZ533X2101), and the clinical study in patients with Graves' disease (CFZ533X2205) have been completed. Interim data are available from patients with primary Sjögren`s syndrome (Phase 2). The potential human safety concerns and the investigator guidance are based on data from the clinical trials with CFZ533, preclinical and toxicological data, as well as experience from other compounds of the same class.

Currently, CFZ533 is not approved for clinical use. Eligible patients for treatment are specified in the respective study protocols. The drug must only be used as instructed by a clinical study protocol, and the conduct of these study protocols is restricted to qualified clinical sites with personnel experienced in the conduct and monitoring of early phase clinical studies.

Subjects who receive CFZ533 must be informed about the nature of the clinical study and provide written consent. Subjects participating in CFZ533 studies should be informed to report any adverse signs or symptoms occurring during the study.

7.2 Potential human safety concerns

7.2.1 Infusion and injection related reactions

The intended route of CFZ533 (recombinant IgG_1 subtype monoclonal antibody) administration is by IV infusion or SC administration, as indicated in the specific clinical study protocol. The duration of study drug infusions are specified in the study protocol and will depend on the dose administered.

Non-serious injection site pain has been reported by subjects following SC administration of CFZ533. To date there have been no infusion related reactions including cytokine release syndrome in subjects receiving IV doses of CFZ533 up to 30 mg/kg or SC doses of CFZ533 at 3 mg/kg. In general, hypersensitivity or infusion reactions can manifest with itching, flushing, headache, nausea/vomiting, hypotension, urticaria, bronchospasm, or angioedema. In the event of a hypersensitivity reaction, stop the infusion. Assess and treat for anaphylaxis if indicated and initiate supportive care per local practice. Fluids, vasopressors, corticosteroids, antihistamines, bronchodilators, and oxygen should be on hand.

The use of plasma exchange may be considered to facilitate removal of the CFZ533 antibody from the peripheral circulation, although the benefit for patients following subcutaneous administration may be limited.

7.2.2 Infections

Administration of CFZ533 doses that result in full tissue receptor occupancy is expected to result in general immunosuppression with a decreased capacity to mount a humoral immune response to immunogens, including those of bacterial, viral, fungal and parasitic origin. Subjects receiving CFZ533 may be immune suppressed from hours to weeks depending on the dose. During this time of immunosuppression subjects may be at a higher risk for infection.

In vivo data from NHPs, where animals maintained a serum concentration ≥10-20 ng/mL CFZ533 resulted in impaired TDAR to a neoantigen (KLH) (Section 4.1.1.2). CFZ533 did not cause ADCC or CDC mediated immune cell depletion in clinical (Section 5.2) and non-clinical studies (Section 4.1.1). Upon antibody elimination, NHPs were able to mount a normal primary and secondary response to tetanus toxoid (TTx) or KLH (See Section 4.2.2.2 and Section 4.2.7). In clinical studies, although the ability to mount a primary immune response may be affected by CFZ533 administration, based on the mechanism of action the preexisting memory B-cell repertoire should remain intact and protective. In addition, adult subjects will have adequate preformed antibody to maintain protective humoral response for extended periods of time (months). Similarly, cytotoxic T lymphocyte (CTL) responses to viral infections may be reduced due to impairment of antigen presentation, but are expected to remain intact.

The overall rate of mild-moderate infections following single doses CFZ533 up to 30 mg/kg, reported as an AE in healthy subjects and patients with RA, was low (see Section 5.2.1.1). To date, eleven cases of infectious SAEs have been reported in patients receiving CFZ533 across all CFZ533 studies. All these SAEs have been reported in the CCFZ533X2201 (transplant) study in which the patient was on multiple immunosuppressants along with CFZ533.

It has been shown that patients with HIGM syndrome, a genetic dysfunction in CD40-CD154 signaling, are at an increased risk for recurrent bacterial infections and infection with intracellular pathogens such as *Cryptosporidium* and *Pneumocystis jiroveci* pneumonia (PCP) (Van Kooten and Banchereau 2000). In fact, intestinal *Cryptosporidae* infections were identified in 1 low dose (10 mg/kg/week), 3 mid-dose (50 mg/kg/week), and 1 high dose (150 mg/kg/week) animals from the 13-week GLP toxicology study. Considering the pharmacology of CFZ533, induction of a transient HIGM-like phenotype in subjects receiving CFZ533 is possible and would limit their ability to mount an immune response to new infectious pathogens and induce long-lasting immune memory to new immunogens. Patients 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 this risk. Of note, subjects treated with CFZ533 can mount recall immune responses after the drug has been eliminated.

The risk of infection may increase if CFZ533 is combined with immunosuppressive drugs. Subjects with current, active or latent infection susceptible to reactivation should be excluded

from entry into early clinical studies unless otherwise allowed per protocol (treated latent TB infection may be acceptable with documentation).

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

7.2.3 Vaccination

Vaccination of subjects during treatment with CFZ533 and prior to clearance of the antibody is likely to result in therapeutic failure (i.e., non-protective antibody titers) due to the pharmacologic activity of CFZ533. Administration of live attenuated agents should be avoided while receiving CFZ533 treatment and for up to 6 months thereafter, depending on the dose and time for reconstitution of humoral immune function. For subjects participating in clinical studies, all vaccinations should be up to date based on local guidelines.

7.2.4 Immunogenicity

There is a risk that anti-CFZ533 antibodies are formed in human subjects which may lead to loss of efficacy or allergic/immune-mediated inflammatory reactions. Anti-CFZ533 antibodies are assessed in all studies with CFZ533.

In the FIH study, one subject at 1 mg/kg IV (1 week full CD40 occupancy) developed specific antibodies to CFZ533 detected 6 weeks after CFZ533 plasma concentrations were below the limit of quantification. The presence of ADAs in this subject did not compromise exposure, and was not associated with an immune related safety signal. This corresponds to an ADA incidence of 2% in this study.

No immunogenicity was reported in Japanese healthy volunteers (CCFZ533X1101).

7.2.5 Thrombophilia

Currently, a theoretical risk without clinical evidence exists for CFZ533 to cause thromboembolic events based on previous experience with monoclonal antibodies that bind to CD154. Such antibodies have been associated with a risk of thrombophilia in both clinical and non-clinical studies in primates (Schuler et al 2004; Kanmaz et al 2004; Pfeiffer et al 2001; Koyama et al 2004; Kawai et al 2000; Wakefield et al 2010; Boumpas et al 2003; Kuwana et al 2004; Kalunian et al 2002; Kasran et al 2005). These thromboembolic events have been linked to the direct activation of platelets which express both CD154 (Henn et al 1998) and a low affinity, activating Fc receptor FcγRIIA. Upon binding to CD154, the Fc-domains of the anti-CD154 mAb may interact with the platelet FcγRIIA receptors, induce cross-linking and aggregation (Law and Grewal 2009; Kawai et al 2000).

In contrast, binding to the CD40 receptor and blocking ligation of CD154 with an Fc-silent mAb, as is the case for CFZ533 and other anti-CD40 antibodies under development (e.g., HCD122 and ASKP1240), does not appear to carry the same risk of thrombophilia as evidenced by the following:

- In repeat dose toxicology studies, CFZ533 was administered to cynomolgus (5 and 26-week) and rhesus (13-week) monkeys at doses up to 150 mg/kg. No thromboembolic complications or signs of thrombophilia were observed (See Section 4.3.2).
- In repeat dose kidney transplantation studies in cynomolgus monkeys using doses of 30 mg/kg CFZ533 monotherapy (n=5) or combination therapy with non-therapeutic doses of Cyclosporine A (n=6) no evidence of thrombophilia was observed (See Section 4.1.1.2.2).
- Absence of thromboembolic potential of anti-CD40 mAb was demonstrated in vitro and in vivo in FcγR transgenic mice where anti-CD40L moAb as a positive control showed clear sign of thrombosis (Section 4.3.7).
- In healthy volunteers and patients with RA, single doses of CFZ533 (up to 10 mg/kg, resulting in >90% peripheral CD40 occupancy on B cells for 6-8 weeks) did not induce clinical or laboratory evidence suggestive of thrombophilia in any CFZ533 treated study subject.
- Safety data with HCD122 (lucatumumab), a fully human anti-CD40 monoclonal antibody, is available from 165 patients enrolled across three Phase 1/2 studies in patients with hematological malignancies. Doses from 0.3 to 6 mg/kg HCD122 IV were administered every week for up to 4 weeks with no thromboembolic events noted in any of the patients (Fanale et al 2014; Bensinger et al 2012; Byrd et al 2012).
- ASKP1240 (Astellas Pharma), an anti-CD40 antibody with a similar pharmacology profile as CFZ533, has also been tested in healthy volunteers (single doses), psoriasis patients (multiple doses) and patients undergoing renal transplant (multiple doses). Based on the data available to date, no thromboembolic events have been reported (Goldwater et al 2013, Harland et al 2015).

Of note, an increased incidence of deep venous thrombosis after kidney transplantation -an indication for CFZ533 - has previously been noted (up to 8.3%) and approximately 25% of these patients suffer from pulmonary embolism (Andrassy et al 2004); therefore, 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 clinical and preclinical data have not indicated an associated risk with CFZ533. However, a larger clinical dataset will be required to fully exclude the thromboembolic risk for CFZ533.

7.2.6 Lymphoproliferative disorders

A hypothetical risk for lymphoproliferative disorders for some patients under strong immunosuppression cannot be excluded for CFZ533. To date, however, no lymphoproliferative disorders have been detected in NHP studies, or in clinical trials in healthy volunteers or patients where CFZ533 was evaluated. In the ASKP1240 trials, no lymphoproliferative disorders were reported to date.

Epstein-Barr virus (EBV) infection is commonly associated with lymphoproliferative disorders in transplant and immunosuppressed patients. Inclusion of patients who are EBV negative will be defined by the specific clinical trial protocol where applicable. The clinician should monitor hematology regularly for changes consistent with a lymphoproliferative disorder.

7.3 Overdose

There has not been any experience with CFZ533 overdose in human clinical trials. Single doses of 3.0 mg/kg IV and SC have been administered to a total of 12 healthy volunteers and single doses of 30 mg/kg IV have been administered to a total of 6 patients with RA with good safety and tolerability. Phase 2 trials using multiple doses of 10 mg/kg IV are ongoing. Should an overdose occur, the subject or patient should be carefully monitored for any potential symptoms, and if necessary, appropriate supportive care should be provided until the subject recovers.

The use of plasma exchange may be considered to facilitate removal of the CFZ533 antibody from the peripheral circulation, although the benefit for patients following subcutaneous administration may be limited.

8

8 References

References are available upon request.

Andrassy J, Zeier M, Andrassy K (2004) Do we need screening for thrombophilia prior to kidney transplantation? Nephrol Dial Transplant: 19(Suppl 4): iv64.

Aoyagi T, Yamashitaa K, Suzukia T, et al (2009) A human anti-CD40 monoclonal antibody, 4D11, for kidney transplantation in cynomolgus monkeys: induction and maintenance therapy. American Journal of Transplantation;9:1732-1741.

Bakoush O, Tencer J, Tapia J, Rippe B, Torffvit O. (2002) Higher urinary IgM excretion in type 2 diabetic nephropathy compared to type 1 diabetic nephropathy. Kidney Int.; 61:203-208.

Bensinger W, Maziarz RT, Jagannath S, et al (2012) A phase 1 study of lucatumumab, a fully human anti-CD40 antagonist monoclonal antibody administered intravenously to patients with relapsed or refractory multiple myeloma. Br J Haematol; 159:58-66.

Berrih-Aknin S, Frenkian-Cuvelier M and Eymard B (2014) Diagnostic and clinical classification of autoimmune myasthenia gravis. J Autoimmun; 48-9:143-8.

Bahn RS. (2010) Graves' Ophthalmopathy. N Engl J Med; 362: 726–738.

Bishop GA, Moore CR, Xie P, et al (2007) TRAF proteins in CD40 signaling. Adv Exp Med Biol; 597:131-51.

Boumpas DT, Furie R, Manzi S, et al (2003) A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. Arthritis Rheum; 48(3):719-27.

Byrd JC, Kipps TJ, Flinn IW, et al (2012) Phase I study of the anti-CD40 humanized monoclonal antibody lucatumumab (HCD122) in relapsed chronic lymphocytic leukemia. Leuk Lymphoma; 53(11):2136-42.

Cao HJ and Smith TJ (1999) Leukoregulin upregulation of prostaglandin endoperoxide H synthase-2 expression in human orbital fibroblasts. Am J Physiol; 277(6 Pt. 1):1075-85.

Chatzigeorgiou A, Harokopos V, Mylona-Karagianni C, et al. (2010) The pattern of inflammatory/anti-inflammatory cytokines and chemokines in type 1 diabetic patients over time. Annals of Medicine;42:426-438.

Clatworthy MR (2011) Targeting B cells and antibody in transplantation. American Journal of Transplantation; 11:1359-67.

Cordoba F, Wieczorek G, Audet M, et al (2015) A novel, blocking Fc-silent anti-CD40 monoclonal antibody prolongs non-human primate renal allograft survival in the absence of B cell depletion. Am. J. Transplant.15(11); 2825-36.

Desai-Mehta A, Lu L, Ramsey-Goldman R, et al (1996) Hyperexpression of CD40 ligand by B and T cells in human lupus and its role in pathogenic autoantibody production. J Clin Invest; 97(9):2063-73.

Dugger K, Lowdera TW, Tuckerb TA, et al (2009) Epithelial cells as immune effector cells: the role of CD40. Sem.Immunol; 21:289.

Durandy A, Revy P and Fischer A (2004) Human models of inherited immunoglobulin class switch recombination and somatic hypermutation defects (hyper-IgM syndromes). Adv Immunol; 82:295-330.

Ehlers MR. Immune Interventions to Preserve Beta Cell Function in Type 1 Diabetes (2016) Journal of investigative medicine : the official publication of the American Federation for Clinical Research;64(1):7-13.

Fanale M, Assouline S, Kuruvilla J, et al (2014) Phase IA/II, multicentre, open-label study of the CD40 antagonistic monoclonal antibody lucatumumab in adult patients with advanced non-Hodgkin or Hodgkin lymphoma. Br J Haematol; 164(2):258-65.

Ferreira RC, Simons HZ, Thompson WS et al (2015) IL-21 production by CD4 effector T cells and frequency of circulating follicular helper T cells are increased in type 1 diabetes patients. Diabetologia; 58:781–90.

Foy TM, Laman JD, Ledbetter JA, et al (1994) gp39-CD40 interactions are essential for GC formation and the development of B cell memory. Journal Exp Med; 180(1):157-63.

Goldwater R, Keirns J, Blahunkab P, et al (2013) A phase 1, randomized ascending single-dose study of antagonist anti-human CD40 ASKP1240 in healthy subjects. American Journal of Transplantation; 13:1040-6.

Grammer AC, Slota R, Fischer R, et al (2003) Abnormal GC reactions in systemic lupus erythematosus demonstrated by blockade of CD154-CD40 interactions. J Clin Invest; 112(10):1506-20.

Haase C, Markholst H (2007) CD40 is required for development of islet inflammation in the RIP-CD154 transgenic mouse model of type 1 diabetes. Ann N Y Acad Sci.

Harland R, Klintmalm G, Yang H, et al (2015) ASKP1240 in *De Novo* Kidney Transplant Recipients. Am J Transplant; 15(S3), pp. Abstract # 3012.

Henn V, Slupsky JR, Gräfe M, et al (1998) CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. Nature; 391:591-4.

Huang W, Sinha J, Newman J, et al (2002) The effect of anti-CD40 ligand antibody on B cells in human systemic lupus erythematosus. Arthritis Rheum; 46(6):1554-62.

Hwang CJ, Afifiyan N, Sand D, et al (2009) Orbital fibroblasts from patients with thyroid-associated ophthalmopathy overexpress CD40:CD154 hyperinduces IL-6, IL-8 and MCP-1. Invest Ophthalmol Vis Sci; 50(5):2262-8.

ICH S6(R1) (2011) International Conference on Harmonization of Technical requirements for Registration of Pharmaceuticals for Human Use: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. Adopted by CHMP, July 2011, issued as EMA/CHMP/ICH/731268/1998; MHLW: Adopted March 2012, PFSB/ELD Notification No. 0323-1; FDA: Published in the Federal Register, 18 May 2012, Vol. 77, No. 97, p. 29665-6.

Im SH, Barchan D, Maiti PK, et al (2001) Blockade of CD40 ligand suppresses chronic experimental myasthenia gravis by down-regulation of Th1 differentiation and up-regulation of CTLA-4. J Immunol;166:6893-8.

Imai A, Suzuki T, Sugitani A, et al (2007) A novel fully human anti-CD40 monoclonal antibody, 4D11, for kidney transplantation in cynomolgus monkeys. Transplantation; 84(8):1020-8.

Kalunian KC, Davis JC Jr, Merrill JT, et al (2002) IDEC-131 Lupus Study Group. Treatment of systemic lupus erythematosus by inhibition of T cell costimulation with anti-CD154: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum; 46(12):3251-8.

Kanmaz T, Fechner JJ Jr, Torrealba J, et al (2004) Monotherapy with the novel human anti-CD154 monoclonal antibody ABI793 in rhesus monkey renal transplantation model. Transplantation; 77(6):914-20.

Kasran A, Boon L, Wortel CH, et al (2005) Safety and tolerability of antagonist anti-human CD40 Mab ch5D12 in patients with moderate to severe Crohn's disease. Aliment Pharmacol Ther; 22(2):111-22.

Kawabe T, Naka T, Yoshida K, et al (1994) The immune response in CD40-deficient mice: impaired immunoglobulin class switching and GC formation. Immunity; 1(3):167-78.

Kawai T, Andrews D, Colvin RB, et al (2000) Thromboembolic complications after treatment with monoclonal antibody against CD40 ligand. Nat Med; 6(2):114.

Klein D, Barbé-Tuana F, Pugliese A et al. (2005) A functional CD40 receptor is expressed in pancreatic beta cells.Diabetologia; 48(2):268-276.

Komaroff AL, Fagioli LR, Doolittle TH, et al (1996) Health status in patients with chronic fatigue syndrome and in general population and disease comparison groups. Am J Med; 101:281-90.

Koyama I, Kawai T, Andrews D, et al (2004) Thrombophilia associated with anti-CD154 monoclonal antibody treatment and its prophylaxis in nonhuman primates. Transplantation; 77(3):460-62.

Kuenstner S, Langelotz C, Budach V, et al (2002) The comparability of quality of life scores. A multitrait multimethod analysis of the EORTC QLQ-C30, SF-36 and FLIC questionnaires. Eur J Cancer; 38:339-48.

Kuwana M, Nomura S, Fujimura K, et al (2004) Effect of a single injection of humanized anti-CD154 monoclonal antibody on the platelet-specific autoimmune response in patients with immune thrombocytopenic purpura. Blood; 103(4):1229-36.

Langer F, Ingersoll SB, Amirkhosrave A, et al (2005) The role of CD40 in CD40L- and antibody-mediated platelet activation. Thromb Haemost. 93: 1137.

Law CL and Grewal IS (2009) Therapeutic interventions targeting CD40L (CD154) and CD40: the opportunities and challenges. Adv Exp Med Biol; 647:8-36.

Li XL, Ménoret S, Le Mauff B, et al (2008) Promises and obstacles for the blockade of CD40-CD40L interactions in allotransplantation. Transplantation; 86(1):10-5.

Lougaris V, Badolato R, Ferrari S, et al (2005) Hyper immunoglobulin M syndrome due to CD40 deficiency: clinical, molecular, and immunological features. Immunol Rev; 203:48-66.

Lund J, Winter G, Jones PT, et al (1991). Human Fc gamma RI and Fc gamma RII interact with distinct but overlapping sites on human IgG. J Immunol; 147(8):2657-62.

Ma A, Dun H, Song L, et al (2014) Pharmacokinetics and pharmacodynamics of ASKP1240, a fully human anti-CD40 antibody, in normal and renal transplanted Cynomolgus monkeys. Transplantation; 97(4):397-404.

Manganelli P and Fietta P (2003) Apoptosis and Sjögren syndrome. Semin Arthritis Rheum; 33(1):49-65.

Mao XJ, Zhang XM, Zhang HL, et al (2010) TNF-receptor 1 deficiency reduces antigen-presenting capacity of Schwann cells and ameliorates experimental autoimmune neuritis in mice. Neuroscience Letters; 470:19-23.

Meibohm B, Zhou H. (2012) Characterizing the impact of renal impairment on the clinical pharmacology of biologics. J. Clin. Pharmacol.; 52:54S-62S.

Mirabet M, Barrabes JA, Quiroga A, Garcia-Dorado D. (2008a) Platelet pro-aggregatory effects of CD40L monoclonal antibody. Mol.Immunol. 45:937.

Mirabet M, Barrabes JA, Quiroga A, Garcia-Dorado D. (2008b) Corrigendum to "Platelet pro-aggregatory effects of CD40L monoclonal antibody". Mol.Immunol. 45:2721.

Mohan C, Shi Y, Laman JD, et al (1995) Interaction between CD40 and its ligand gp39 in the development of murine lupus nephritis. J Immunol; 154(3):1470-80.

Nulojix® (belatacept) Package Insert (2013) Bristol-Meyers Squibb Company, Princeton, NJ.

Oura T, Yamashita K, Suzuki T, et al (2010) Long-term hepatic allograft acceptance mediated by a novel human anti-CD40 monoclonal antibody, ASKP1240 (4D11), in a NHP. [abstract] XIII International Congress of The Transplantation Society, Session Immunosuppression-preclinical agents, Vancouver, BC.

Pantenburg B, Dann SM, Wang HC, et al (2008) Intestinal immune response to human Cryptosporidium sp. infection. Infect Immun; (1):23-9.

Pearson TC, Trambley J, Odom K, et al (2002) Anti-CD40 therapy extends renal allograft survival in rhesus macaques. Transplantation; 74(7):933-40.

Pescovitz MD, Greenbaum CJ, Bundy B, et al. (2014) B-Lymphocyte Depletion With Rituximab and β-Cell Function: Two-Year Results. Diabetes Care;37(2):453-459.

Pfeiffer S, Iii GL, Azimzadeh AM, et al (2001) Monotherapy with anti-CD40 ligand antibody (IDEC 131) for NHP allograft heart transplantation. J Heart Lung Transplant; 20(2):250.

Phipps PP (2008) CD40: Lord of the endothelial cell. Blood; 112(9):3531.

Pluvinet R, Olivar R, Krupinski J, et al (2008) CD40: an upstream master switch for endothelial cell activation uncovered by RNAi-coupled transcriptional profiling. Blood; 112(9):3624.

Quezada SA, Jarvinen LZ, Lind EF, et al (2004) CD40/CD154 interactions at the interface of tolerance and immunity. Annu Rev Immunol; 22:307-28.

Robles-Carillo L, Meyer T, Hatfield M, et al. (2010) Anti-CD40L Immune Complexes Potently Activate Platelets In Vitro and Cause Thrombosis in FCGR2A Transgenic Mice. J.Immunol. 185:1577.

Schuler W, Bigaud M, Brinkmann V, et al (2004) Efficacy and safety of ABI793, a novel human anti-human CD154 monoclonal antibody, in cynomolgus monkey renal allotransplantation. Transplantation; 77(5):717-26.

Segal B, Bowman SJ, Fox PC, et al (2009) Primary Sjögren's Syndrome: health experiences and predictors of health quality among patients in the United States. Health Qual Life Outcomes; 7:46.

Sempowski GD, Rozenblit J, Smith TJ, Phipps RP (1998) Human orbital fibroblasts are activated through CD40 to induce proinflammatory cytokine production. Am J Physiol; 274(3 Pt 1):707-14

Sfikakis PP, Boletis JN, Lionaki S, et al (2005) Remission of proliferative lupus nephritis following B cell depletion therapy is preceded by down-regulation of the T cell costimulatory molecule CD40 ligand: an open-label trial. Arthritis Rheum; 52(2):501-13.

Shock A, Burkly L, Wakefield I, et al. (2015) CDP7657, an anti-CD40L antibody lacking an Fc domain, inhibits CD40L-dependent immune responses without thrombotic complications: an in vivo study. Arthritis Res.Ther. 17:234.

Slade A, Koo P, Espie P, et al (2014) OM11-62MF: Safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of a novel anti-CD40 antibody in healthy volunteers. Transplantation; 98:115.

Slade A, Doucet J, Koo P et al (2015) CFZ533: Assessment of immunomodulatory activity following single doses of a novel anti-CD40 mAb in healthy volunteers. American Transplant Congress 2015, Abstract number 252026.

Smith P, DiLillo DJ, Bournazos S, et al. (2012) Mouse model recapitulating human Fcγ receptor structural and functional diversity. PNAS 109(16):6181.

Sundaresh V, Brito JP, Wang Z, et al (2013) Comparative effectiveness of therapies for Graves hyperthyroidism: a systematic review and network meta-analysis. Journal of Clinical endocrinology Metabolism; 98(9) 3671-7.

Vaitaitis GM, Olmstead MH, Waid DM, et al. (2014) A CD40-targeted peptide controls and reverses type 1 diabetes in NOD mice. Diabetologia;57(11):2366-2373.

Vaitaitis GM, Waid DM, Yussman MG, et al (2017) CD40-mediated signaling influences trafficking, T-cell receptor expression, and T-cell pathogenesis, in the NOD model of type 1 diabetes. Immunology;152: 243–254.

Van Kooten C and Banchereau J (2000) CD40-CD40 ligand. J Leukoc Biol; 67(1):2-17.

Vincenti F, Charpentier B, Vanrenterghem Y, et al (2010) A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT Study). American Journal of Transplantation; 10:535-46.

Vossenkämper A, Lutalo PM, Spencer J (2012) Translational mini-review series on B cell subsets in disease. Transitional B cells in systemic lupus erythematosus and Sjögren's syndrome: clinical implications and effects of B cell-targeted therapies. Clin Exp Immunol; 167:7-14.

Waid DM, Vaitaitis GM, Wagner DH Jr. (2004) Peripheral $CD4^{lo}CD40^{+}$ auto-aggressive T cell expansion during insulin-dependent diabetes mellitus. Eur J Immunol;34:1488–97.

Wagner DH (2017). Overlooked Mechanisms in Type 1 Diabetes Etiology: How Unique Costimulatory Molecules Contribute to Diabetogenesis. Frontiers in Endocrinology;8:208:1-10.

Waldman M, Appel GB (2006) Update on the treatment of lupus nephritis. Kidney Int; 70(8):1403-12.

Wang H, Zhu LS, Cheng JW, et al (2015) CD40 ligans induces expression of vascular cell adhesion molecule-1 and E-selectin in orbital fibroblasts from patients with Graves' orbitopathy. Graefes Arch Clin Exp Ophthalmol; 253(4):573-82.

Watanabe M, Yamashita K, Fukumori D, et al (2010) Effect of ASKP1240 (4D11), a fully human anti-CD40 monoclonal antibody, on a single donor-derived allogeneic islet transplantation in cynomolgus monkeys. XIII International Congress of The Transplantation Society, Session Clinical Islet Transplantation, Vancouver, BC.

Weetman AP (2000) Graves' disease. N Engl J Med; 343(17):1236-48.

Xu J, Foy TM, Laman JD, et al (1994) Mice deficient for the CD40 ligand. Immunity; 1(5):423-31.

Xu X, Shi Y, Cai Y, et al (2013) Inhibition of increased circulating Tfh cell by anti-CD20 monoclonal antibody in patients with type 1 diabetes. PLOS ONE; 8:e79858

Yang J, Shord S, Zhao H, Men Y, Rahman A. Are hepatic impairment studies necessary for therapeutic proteins. Clin. Ther. 2013; 35:1444-1451.

Yellin MJ, D'Agati V, Parkinson G, et al (1997) Immunohistologic analysis of renal CD40 and CD40L expression in lupus nephritis and other glomerulonephritides. Arthritis Rheum; 40(1):124-34.

Zhao L, Ren TH, Wang DD. (2012) Clinical pharmacology considerations in biologics development. Acta Pharmacol. Sin.;33:1339-1347.