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Official study title:

Safety, Tolerability and Efficacy of anti-IL-6 Antibody Clazakizumab in Late Antibody-Mediated Rejection after Kidney Transplantation - a Pilot Trial

NCT number:

Not available yet

Date of the document:

June 25, 2017

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List of abbreviations: ADCC = antibody-dependent cellular cytotoxicity, AE = adverse event, ABMR = antibody-mediated rejection, ALT = Alanin-Aminotransferase, AST = Aspartat-Aminotransferase, BM = basement membrane, CDC = complement-dependent cytotoxicity, cg = transplant glomerulopathy, CNI = calcineurin inhibitor, CRF = Case-Report-Form, CRP = C-reactive protein, CyA = cyclosporine A, CYP = cytochrome P450, DSA = donor-specific antibody, DSMB = data and safety monitoring board, eGFR = estimated glomerular filtration rate, EOS = end-of-study, GCP = Good Clinical Practice, GLP = Good Laboratory Practice, HLA = human leukocyte antigen, IFTA = interstitial fibrosis/tubular atrophy, IgG = Immunoglobulin G, IL-6 = Interleukin-6, IL-6R = Interleukin 6 receptor, IV = intravenous, IVIG = intravenous immunoglobulin, KTX = kidney transplantation, MFI = mean fluorescence intensity, mGFR = measured glomerular filtration rate, MLPTC, multilayering of peritubular capillary basement membranes, MMDx = molecular microscope; MMF = mycophenolate mofetil, mTOR = mammalian target of rapamycin, MUW = Medical University Vienna, PD = pharmacodynamics, PK = pharmacokinetics, PTC = peritubular capillaries, pSTAT3 = phosphorylated signal transducer and activator of transcription 3, RA = rheumatoid arthritis, SAE = serious adverse event, SAFB = single-antigen flow-beads, SC = subcutaneous, SD = standard deviation, STAT3 = signal transducer and activator of transcription 3, TTV = Torque Teno virus, ULN = upper limit of normal

1. BACKGROUND AND RATIONALE

There is emerging evidence that antibody-mediated rejection (ABMR) is a leading cause of kidney allograft dysfunction and failure in the long-term [1-3]. According to current diagnostic standards, the diagnosis of ABMR is based on the detection of donor-specific antibodies (DSA) and renal biopsy results, including characteristic acute and/or chronic morphological lesions in the microcirculation and, in some cases, detection of complement split product (C4d) deposits along peritubular capillaries (PTC) [4,5]. In addition, ABMR was shown to associate with specific gene expression patterns [6], and distinct molecular criteria are now included in the Banff classification of renal allograft pathology [4,5]. While a continuous diagnostic refinement has helped define the role of this rejection type as a major trigger of chronic allograft injury, treatment of late and/or chronic ABMR still represents a major challenge. Our current knowledge is mainly based on the results of uncontrolled observational studies, where a variety of different treatment strategies were evaluated, ranging from modifications in maintenance immunosuppression [7-9] to different immunomodulatory measures, including high dose intravenous immunoglobulin (IVIG) with or without CD20 antibody rituximab [10-13], the proteasome inhibitor bortezomib [14], or anti-C5 antibody eculizumab [15]. Some of these reports have pointed to potential beneficial treatment effects. Nevertheless, the results of recent systematic randomized controlled trials designed to assess the effect of specific interventions, such as eculizumab [15] or bortezomib (Eskandary & Böhmig, manuscript in preparation) in chronic ABMR, have failed to demonstrate a meaningful effect on the course of rejection. For example, in a recent double-blind placebo-controlled phase 2 trial performed at the Medical University Vienna (MUW), we were unable to demonstrate a beneficial effect of two cycles of bortezomib on the progression of late ABMR in 44 kidney allograft recipients. These data clearly demonstrate that there is still an unmet need for an effective treatment of late (chronic) ABMR, and new innovative treatment concepts are required.

The pleiotropic pro-inflammatory cytokine interleukin-6 (IL-6), which is known to play a pivotal role not only as a trigger of acute phase responses, but also in the activation and development of B cells and antibody production, may be a promising target for ABMR treatment [16]. Monoclonal antibodies against IL-6 and the IL-6 receptor (IL-6R) have been proven to be effective in the treatment of various autoimmune diseases, including rheumatoid arthritis (RA) [17-19]. More recently, targeting IL-6/IL-6 receptor has gained interest also in the context of organ transplantation. In a recent uncontrolled trial by Choi et al. [20] the anti-IL6R monoclonal antibody tocilizumab was evaluated as treatment of chronic ABMR unresponsive to IVIG, rituximab and/or plasmapheresis in a cohort of 36 kidney transplant recipients. The results of this uncontrolled trial are promising, showing a beneficial safety profile, a reduction

in DSA levels, and stabilization of kidney function at 2 years. A major result of this study was a marked reduction in the extent of microcirculation inflammation in follow-up biopsies. The authors noted graft losses in four recipients in whom tocilizumab was prematurely stopped. For these cases, a role of a rebound effect by accumulated IL-6 [20].

Direct binding and blockade of IL-6 may be an attractive alternative. Clazakizumab (formerly ALD518, BMS945429), is a high affinity humanized monoclonal antibody which binds to IL-6 and prevents interaction and signaling via IL-6R. This antibody is the most potent and longest acting agent in the IL-6/IL-6R blocking category, is free of antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) and does not crosslink any surface receptors. Its half-life is about 30 days [subcutaneous (SC) administration], and monthly SC injections allow for sustained IL-6 blockade. Its safety has so far been established in more than 800 subjects, many of them treated within phase 2 studies performed in RA or psoriatic arthritis (PsA) [18,21-23].

This 12-month pilot trial is primarily designed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of clazakizumab versus placebo in a cohort of 20 kidney transplant recipients diagnosed with late ABMR. The design of the study, which includes early and late follow-up protocol biopsies to decipher the effects on microcirculation inflammation, gene expression profiles and features of chronic transplant injury will also allow for preliminary efficacy assessment (information on effect size and variability), and thus can be expected to provide a valuable foundation of future trials in large populations of transplant patients.

Clazakizumab (anti-IL6 monoclonal antibody): Potential as a therapeutic agent in transplantation

Clazakizumab (Vitaeris Inc., Vancouver, BC Canada) is a humanized monoclonal antibody aimed at the cytokine IL-6 ligand. Clazakizumab has been evaluated extensively in patients with arthritis [18,21-23], but has not yet been approved by the FDA for any condition. Since the introduction of IL-6/IL-6R blocking drugs, reports indicate that inhibition of the IL-6/IL-6R pathway may have significant benefits in systemic lupus erythematosus and other vasculitic disorders and reduces antibody producing cells in treated patients. There is currently no information for clazakizumab in highly sensitized patients awaiting incompatible transplants or for treatment of ABMR. However, preliminary data suggests that clazakizumab exhibits a broad range of immunomodulatory actions that could address the alloantibody response to allografts and be useful as a desensitization agent to improve rates of renal transplantation for highly-HLA sensitized patients. This is based on data obtained from clinical trials of clazakizumab for treatment of RA.

Clazakizumab is a genetically engineered humanized immunoglobulin G1 (IgG1) antibody that binds to human IL-6 with an affinity of 4 pM. Using multiple assays for signaling and cellular functions in response to IL-6 alone (to measure classical signaling) and a combination of IL-6 and sIL-6R (to measure trans-signaling), it was demonstrated that clazakizumab is a potent and full antagonist of IL-6-induced signaling as measured by phosphorylation of signal transducer and activator of transcription 3 (STAT3), as well as cellular functions such as cell proliferation, differentiation, activation, B-cell production of immunoglobulins, and hepatocyte production of acute phase proteins [C-reactive protein (CRP) and fibrinogen]. In addition, clazakizumab is shown to be a competitive antagonist of IL-6-induced cell proliferation. This in vitro pharmacological profile supports the potential of clazakizumab to impact multiple immune and non-immune cellular processes that are central to disease pathogenesis, and thus, to offer a new therapeutic modality in the treatment of autoimmune diseases and other IL-6 mediated diseases.

The clazakizumab development program includes a comprehensive nonclinical development program and clinical studies conducted in healthy subjects and in subjects with RA, PsA, Crohn's disease, graft-versus-host disease, and oncology. To date, no studies with clazakizumab have been conducted in subjects with highly sensitized patients undergoing renal transplant, although supporting safety data are available from the previous clinical studies.

Nonclinical Studies. A comprehensive nonclinical development program has been completed. Clazakizumab was shown to be a potent inhibitor of IL-6-induced acute phase proteins. In pharmacokinetic (PK)/pharmacodynamic (PD) studies, a single dose of clazakizumab resulted in full inhibition of IL-6 activity as measured by the inhibition of IL-6-induced phosphorylated STAT3 (pSTAT3) activity in whole blood treated ex vivo with IL-6. The results of this functional PD assay correlated with drug exposures where full inhibition of pSTAT3 activity was observed when drug levels exceeded 50 ng/mL (approximately 0.3 nM). In a tissue cross-reactivity study, tissue binding of clazakizumab was observed in multiple tissues in both human and cynomolgus monkey, was generally cytoplasmic in nature, and was consistent with the known expression of IL-6 by cells and tissues. Results from both single- and repeat-dose nonclinical toxicology studies of up to 6 months in cynomolgus monkeys demonstrated an acceptable safety profile for clazakizumab. In a preliminary enhanced pre- and post-natal development study conducted in cynomolgus monkeys, an increase in the number of monkeys with retention of the placenta at parturition was observed at clazakizumab doses of 3 mg/kg (n=2) and 30 mg/kg (n=3), corresponding to doses 11 and 110 times the planned human dose of 50 mg. There were no other safety findings of clinical concern.

Clinical studies. Clinical studies have been conducted in healthy subjects and in the following patient populations: RA, PsA, Crohn's disease, graft-versus-host disease, and oncology. These clinical studies include a total of 1,223 subjects, of which 888 subjects were exposed to clazakizumab with doses ranging from 1 mg to 640 mg given by either intravenous (IV) or SC injection for up to 48 weeks.

Clinical Pharmacology. Following the administration of clazakizumab as a 1-hour IV infusion, the PK of clazakizumab were linear over the dose ranges of 30 mg to 640 mg in healthy subjects and 80 mg to 320 mg in subjects with RA as indicated by consistent clearance at these dose levels. The T-half of clazakizumab at all doses was very similar in healthy male subjects and in subjects with RA and was consistent with that expected for a humanized IgG1 antibody. Across the doses studied, the mean T-half of clazakizumab ranged from 19.5 to 31.0 days in healthy male subjects and from 26.4 to 30.9 days in subjects with RA. The T-half of clazakizumab after SC administration in healthy male subjects was similar to the IV administration. In a Phase 1 study comparing IV and SC dosing in healthy male subjects, the mean T-half of clazakizumab was 30.7 days after a single IV dose and 31.1 to 33.6 days after SC administration. The bioavailability of clazakizumab after SC administration was 60% of the IV formulation. As expected, Cmax was lower and Tmax was longer for the SC administration relative to IV administration. Population PK analysis of the data from clinical studies in RA, PsA and healthy subjects have indicated that body weight affects the PK of clazakizumab such that both clearance and central volume of distribution increase with increasing body weight. Therefore, heavier subjects will have lower drug exposure compared with less heavy subjects.

Clinical Efficacy and Safety Studies. Efficacy and safety data for clazakizumab is available from clinical studies conducted in RA, PsA, and oncology. Studies conducted in GVHD and Crohn's disease were prematurely terminated due to safety concerns and therefore no efficacy conclusions are available for these studies. The GVHD study was terminated after only 3 subjects were enrolled, due to 2 subjects with severe GVHD experiencing similar serious adverse events (SAEs) (i.e., acute renal failure) which led to death. These 2 subjects had received single doses of clazakizumab 160mg intravenously. The Crohn's disease study was terminated early because of gastrointestinal (GI) perforation in 3 subjects who had received clazakizumab intravenously at doses of 150 mg or greater. These subjects had multiple confounding medical issues, and the disease itself has an inherent risk of mucosal perforation. Gastrointestinal perforations were also observed during the clinical studies with tocilizumab in subjects with RA.

2. HYPOTHESIS AND OBJECTIVE OF THE STUDY

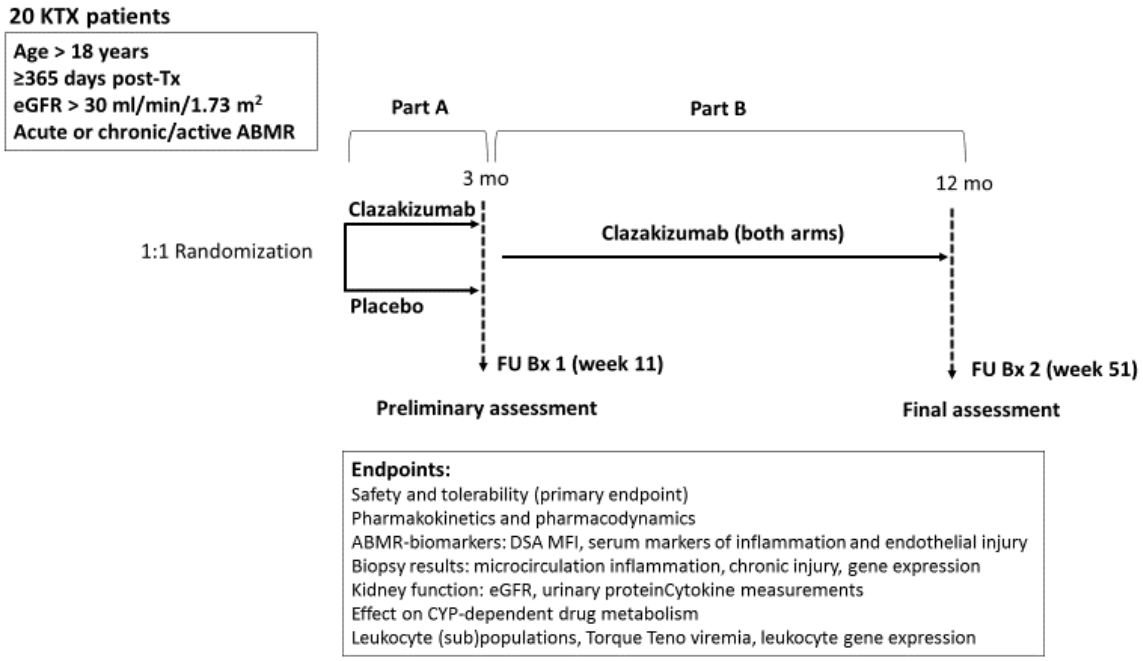
Clinical data to date support that IL-6 blockade is safe and well tolerated, and we hypothesize that clazakizumab will have a similar safety profile in kidney transplant recipients on baseline immunosuppression. Moreover, we hypothesize that repeated administration of clazakizumab is able to counteract tissue inflammation and injury in ongoing ABMR, in particular, inflammation in the microcirculation, HLA antigen-specific B cell alloresponses and, as a consequence, alloantibody-triggered chronic graft injury. The primary objective of this bi-center two-step prospective pilot trial (part A: 12-week double-blind placebo-controlled part of the trial; part B: 40-week open-label part of the trial) is to evaluate the safety and tolerability of clazakizumab in a cohort of 20 kidney transplant recipients diagnosed with late ABMR. Secondary objectives are to evaluate the PK (including measurement of anti-clazakizumab antibodies) and PD of this antibody (subcutaneous administration of 25 mg in 4-weekly intervals) in the specific context of organ transplantation. Moreover, two sequential protocol biopsies (histomorphology, immunohistochemistry, electron microscopy, gene expression patterns), in addition to kidney function, urinary protein monitoring and ABMR-associated blood biomarkers, will allow an in-depth analysis of the anti-inflammatory effect of clazakizumab (early biopsy in part A) and its effect on the progression of antibody-mediated chronic injury (late biopsy in part B). Finally, blockade of the pleiotropic cytokine IL-6 may potentially interfere with cytochrome P450 (CYP) metabolism and thus potentially affect the half-life of CYP-metabolized drugs [24]. We will evaluate the impact of IL-6 blockade on the pharmacokinetics of CYP substrate pantoprazole. The results of this pilot trial will provide a valuable foundation of future systematic long-term trials to assess the efficacy of IL-6 blockade in ABMR.

3. STUDY DESIGN

This bi-center study (MUW, Charité Berlin) is an investigator-driven pilot trial designed to assess the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy (preliminary assessment) of humanized anti-IL-6 monoclonal antibody clazakizumab in kidney transplant recipients with late ABMR. This study, a phase 2 trial, has two subsequent sub-parts, a randomized placebo-controlled trial (part A) of 12 weeks, where recipients are allocated to receive either clazakizumab (n=10) or placebo (n=10), followed by an open-label prospective study, where all 20 study patients will receive clazakizumab for a period of 40

weeks. In this second part, treatment will be offered to all subjects for two major reasons: (i) in a recent uncontrolled preliminary observational study, interference with IL-6/IL-6R blockade in ABMR patients using tocilizumab was reported to be safe and well tolerated, and first results have suggested stabilization of kidney function in many of the treated patients; (ii) two subsequent protocol biopsies planned in our trial, which are necessary for an in-depth analysis of the early and late effects of IL-6 blockade, would not be justified for long-term placebo treatment. After completion of part A, the randomization sequence will be unblinded for a first analysis of data. A simplified flow chart of the trial is shown in Figure 1:

Figure 1. Trial overviw



Part A: Patients will be randomized to receive either clazakizumab (25 mg subcutaneous [SC] administration) or placebo (1:1 randomization) for a period of 12 weeks (administration of clazakizumab/placebo at day 0, and after 4 and 8 weeks). After 12 weeks, patients will be subjected to a first follow-up biopsy. Primary goals of this part of the trial are to assess the safety, pharmacokinetics and pharmacodynamics of a short course of treatment. Moreover, part A will allow for a first preliminary assessment of the impact of clazakizumab on ABMR-associated inflammation detected in peripheral blood and in the rejecting organ allograft, on the pharmacokinetics of pantoprazole as a probe drug to investigate influence of IL-6 blockade on cytochrome P450-dependent drug metabolism, and on the short-term course of DSA MFI and kidney allograft function (eGFR, urinary protein excretion). The randomization

sequence will be unblinded for a first data analysis after the last patient has completed the 12-week follow-up period.

Part B: After 12 weeks, all study patients will enter an open-label part of the study. All 20 subjects will receive clazakizumab (25 mg SC injection) in 4-weekly intervals until the end-of-study (EOS) visit after 52 weeks and will then be subjected to a second protocol biopsy. Major goals of part B are to evaluate the safety and tolerability of a prolonged period of treatment with clazakizumab and the long-term impact of this antibody on the evolution of ABMR, rejection-associated biomarkers and kidney allograft function and survival over a period of 12 months.

We expect a recruitment phase of 18 months, and thus completion of the trial after 30 months.

Inclusion/exclusion criteria

We will include kidney transplant recipients with circulating anti-HLA DSA and biopsy features of ABMR (ABMR according to the Banff 2013 scheme) in an indication biopsy (index biopsy; performed for a positive post-transplant DSA result and/or slow deterioration of allograft function and/or proteinuria. Other key inclusion criteria are a functioning graft at ≥365 days post-transplantation and an eGFR above 30 ml/min/1.73 m^2. This eGFR threshold has been chosen to avoid inclusion of transplants with a high degree of irreversible chronic damage (for patients with very advanced graft injury a sustainable treatment benefit can no longer be expected). Inclusion and exclusion criteria are listed in Table 1.

Table 1. Inclusion and exclusion criteria

INCLUSION CRITERIA
Voluntary written informed consent
Age >18 years
Functioning living or deceased donor allograft after ≥365 days post-transplantation
eGFR >30 ml/min/1.73 m^2
Detection of HLA class I and/or II antigen-specific antibodies (preformed and/or *de novo* DSA).
Acute/active or chronic/active ABMR (±C4d in PTC) according to Banff 2013/2015
Molecular ABMR score (ABMRpm) ≥0.2
EXCLUSION CRITERIA
Patients actively participating in another clinical trial
Age ≤18 years
Female subject is pregnant or lactating
Index biopsy results:
T-cell-mediated rejection classified Banff grade ≥I
De novo or recurrent severe thrombotic microangiopathy
Polyoma virus nephropathy
De novo or recurrent glomerulonephritis
Acute rejection treatment <3 month before screening
Acute deterioration of graft function (eGFR decline within 1-3 months >25%)
Nephrotic range proteinuria >3500 mg/g protein/creatinine ratio
Active viral, bacterial or fungal infection precluding intensified immunosuppression
Active malignant disease precluding intensified immunosuppressive therapy
Abnormal liver function tests (ALT, AST, bilirubin > 1.5 x upper limit of normal)
Other significant liver disease
Latent or active tuberculosis (positive QuantiFERON-TB-Gold test, Chest X-ray)
Administration of a live vaccine within 6 weeks of screening
Neutropenia (<1 G/L) or thrombocytopenia (<100 G/L)
History of gastrointestinal perforation, diverticulitis, or inflammatory bowel disease
Allergy against proton pump inhibitors
History of alcohol or illicit substance abuse
Serious medical or psychiatric illness likely to interfere with participation in the study

Random allocation

For part A of the trial, patients will be centrally randomized by computer assignment between two study arms (part A of the study: clazakizumab versus placebo) using http://www.randomization.com (1:1 randomization). Stratification according to acute/active ABMR and chronic/active ABMR will be used to ensure a balance of patients with these two histological types between the two arms. For each patient, a study ID will be assigned. The participating investigators and the patients will be blinded to group allocation until the completion of part A of the study.

Blinding and unblinding

The first part (A) of the study is designed as a double-blinded trial, in order to minimize bias. Investigational drug (clazakizumab) and placebo (normal 0.9% saline) are prepared by non-blinded pharmacists and formulated to have identical appearance. Neither study participants nor medical staff interacting with patients or data know the assigned treatment (clazakizumab versus placebo). The randomization sequence will be unblinded after the last patient has completed the 12-week follow-up period. Premature unblinding may be necessary in cases of medical emergencies or serious medical conditions, where participants cannot be treated adequately unless the medical staff knows the allocated treatment. Unblinding can, if necessary, be requested by the DSMB.

4. INTERVENTIONS

Treatment with clazakizumab/placebo:
Clazakizumab or placebo will be administered as single SC injection of 1 mL each by blinded qualified study personnel during the double blind phase. All study drug administrations will be documented in the subject's source documents and in the CRF.

Clazakizumab will be supplied in single-dose vials (25 mg/mL) for injection and provided by Vitaeris Inc. The placebo medication will be administered with normal saline for injection (commercially available in country) and will be provided by the Investigator. Prepared syringes may be stored for up to 24 hours in a refrigerator, 2°C to 8°C, and up to 4 hours of the 24 hours may be at room temperature, 15°C to 25°C. The prepared syringes will be protected from light. Prior to administration, clazakizumab/placebo injection must reach room temperature by storing unrefrigerated for 30 to 60 minutes before use.

Storage and Accountability. Clazakizumab will be stored at -20°C or colder, with protection from light. Placebo will be stored at controlled room temperature and should not be frozen. Study product disposition and accountability will be documented on the subject level, whereby all study product dispositions will be listed (drug accountability log). In a stock record, overall bulk study product supplies and accountability will be recorded.

The following medications are prohibited during the study:
Rituximab, eculizumab, proteasome inhibitors, IVIG, plasma exchange or immunoadsorption, other investigational drugs/treatments including commercially available anti-IL-6/sIL-6R monoclonal antibody drugs such as tocilizumab (Actemra®).
The following concomitant medications are permitted during the study:

Calcineurin inhibitors (CNI, tacrolimus or cyclosporine A), mammalian target of rapamycin (mTOR) inhibitor (everolimus or rapamycin), Mycophenolate mofetil (MMF)/mycophenolate sodium; low dose corticosteroids (prednisolne ≤ 5mg/day)

Baseline immunosuppression: Upon diagnosis of ABMR, baseline immunosuppressive treatment will be adjusted according to the standard of the Vienna transplant unit. Upon diagnosis of late ABMR, all recipients (both arms in part A) on therapy with a CNI (tacrolimus or cyclosporine A, CyA) or a mTOR inhibitor (everolimus or rapamycin), without azathioprine or MMF/mycophenolic acid, will receive MMF (initially 2 x 500 mg per day; stepwise increase to 2 x 1000 mg per day if tolerated) to avoid under-immunosuppression. Tacrolimus will be adjusted to achieve target trough levels between 5 and 10 ng/mL, CyA to 80-120 ng/mL. Recipients weaned off steroids will receive low dose prednisolone (5 mg/day).

5. OUTCOME MEASURES

Study endpoints are listed in Table 2.

Primary and secondary outcomes in part A and part B of the trial

PRIMARY OUTCOME
Safety and tolerability
SECONDARY OUTCOMES (PART A AND B)
PK of clazakizumab (every visit; measurement of anti-Claza antibodies included) and of pantoprazole (0, 12, 52 weeks)

PK/PD of clazakizumab (clazakizumab levels and CRP suppression) (every visit)

Cytokines patterns and endothelial activation/injury markers in serum (0, 12, 52 weeks)

Effect on leukocyte subsets in peripheral blood

Effect on IL-6 and IL-6R gene expression in peripheral blood cells

HLA antibody levels (0, 12, 52 weeks)

- Maximum and sum of mean fluorescence intensity (MFI) of DSA
- Number of DSA
- Broadness of sensitization (virtual PRA)

Total Ig classes (IgG, IgA, IgM) and IgG subclasses (IgG1, 2, 3, 4)

Protocol biopsy results at 11 and 51 weeks

- ABMR category
- Microcirculation inflammation (g+ptc score)
- Transplant glomerulopathy (cg) and interstitial fibrosis/tubular atrophy (IFTA) scores
- Molecular ABMR score (molecular microscope, MMDx)
- Archetype analysis of gene expression profiles (molecular microscope, MMDx)

eGFR (every visit)

Protein excretion (protein/creatinine ratio) (every visit)

1-year graft and patient survival

Occurrence of biopsy-proven acute rejection necessitating rejection treatment (52 weeks)

The schedule of events is provided in Table 3.

Table 3. Schedule of events

		Part A							Part B											
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Week	**up to -4**	**0**	**1**	**2**	**3**	**4**	**8**	**11**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**51**	**52**
Informed consent	x																			
Physical examination and medical history	x	x							x											x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test	x					x	x		x	x	x	x	x	x	x	x	x	x		x
Quantiferon test	x																			
Virology	x																			
ECG	x								x											x
Clazakizumab/placebo		x				x	x													
Clazakizumab									x	x	x	x	x	x	x	x	x	x		
Safety																				
AE monitoring		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Safety Lab		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
LDL/HDL cholesterol, triglycerides		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CMV PCR									x		x			x			x			x
Evaluation of PK																				
Clazakizumab concentration and anti-clazakizumab antibodies		x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x		x
Evaluation of PD																				
Ultrasensitive CRP		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Preliminary efficacy assessment																				
Biopsies (incl. MMDx)								x											x	
DSA detection		x							x											x
Ig (sub)classes		x							x											x
Cytokine patterns		x							x											x
Endothelial markers		x							x											x
Leukocyte subpopulations		x							x											x
TTV copy number		x							x											x
eGFR		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Protein/creatinine ratio		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Liver metabolism																				
Pantoprazol i.v.		x							x											x
Pantoprazol concentration		x							x											x
Immunosuppression																				
CNI trough level		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biobanking		x							x											x

Long visits (approx. 6-9 hours) in grey

Primary outcome measures are the safety and tolerability of clazakizumab, evaluated throughout the study period (19 visits until EOS visit at 52 weeks). Secondary endpoints are pharmacokinetics (clazakizumab concentration) and pharmacodynamics (suppression of CRP). For preliminary efficacy assessment, blood-derived biomarkers of ABMR (HLA/DSA antibody levels, cytokines and markers of endothelial injury, patterns of peripheral blood leukocyte subpopulations) and IL-6/IL-6R gene expression will be assessed at day 0, and after 12 and 52 weeks. The study will include two protocol biopsies, an early biopsy after 11 weeks (end of part A) to primarily dissect the effect of IL-6 blockade on microcirculation inflammation in direct comparison to placebo, and a late biopsy after 51 weeks to assess the

effect of clazakizumab on the progression of chronic injury (cg score, IFTA score). All biopsies will in addition be evaluated for ABMR-typical gene expression patterns (ATAGC, Alberta University, Edmonton; major read-out: molecular ABMR score). We will in addition monitor kidney function, protein excretion and graft survival over the whole study period. Finally, we will assess the impact of IL-6 blockade (as compared to placebo) on pharmacokinetics of pantoprazole reflecting CYP-dependent liver metabolism. At day 0, week 12 and week 52, pantoprazole will be administered at a dosage of 20 mg intravenously, and drug levels will be determined every hour over a period of 6 hours. In patients on continuous proton pump inhibitor therapy, oral treatment will be paused for 3 days before pharmacokinetic testing, and re-started one day thereafter.

6. METHODOLOGY

HLA antibody detection. For assessment of the course of DSA levels, serum samples will be evaluated after completion of the study (part A and B). If detailed data on preformed DSA are not available, stored pre-transplant sera will be tested retrospectively for the presence or absence of DSA. Sera will be heat-inactivated to preclude complement-dependent in vitro artifacts (prozone phenomenon) and subjected to single-antigen flow-bead testing (LABscreen Single Antigen assays; One Lambda). Test results will be documented as mean fluorescence intensities, and MFI >1000 will be considered positive. Donor-specificity will be defined according to donor and recipient HLA typing results. Virtual panel-reactive antibody (PRA) levels will be calculated using specific software tools (http://www.eurotransplant.eu).

Transplant biopsies. Biopsies will be performed after exclusion of a coagulation disorder or platelet counts below 80%. Anticoagulants or inhibitors of thrombocyte aggregation will be transiently paused. The biopsy will be performed under local anaesthesia (lidocain) using ultrasound-guided percutaneous techniques (1-2 cores per biopsy, 16 gauge needle). After biopsy, patients will be monitored closely for 5 to 8 hours for any complications (serial blood pressure measurements, monitoring for hematuria, haemoglobin check 4 hours after biopsy). Histomorphology will be evaluated on paraffin-embedded sections applying standard methodology. For immunohistochemical C4d staining, we will use a polyclonal anti-C4d antibody (BI-RC4D, Biomedica; Vienna, Austria), and, following the rules of the Banff scheme [4], minimal immunohistochemical staining (C4d Banff score ≥1) along peritubular capillaries will be considered positive. Biopsies will in addition evaluated by electron microscopy for detection of multilayering of peritubular capillary basement membranes (MLPTC). All biopsies will be analyzed using microarrays, as proposed by the Banff scheme.

For each biopsy, a 3 mm portion of one core will be placed immediately in RNAlater, stored at -20°C and shipped at ambient temperature or dry ice to the Alberta Transplant Applied Genomics Centre (ATAGC, University of Alberta, Edmonton, AB, Canada) for gene array analysis. Thoroughly validated molecular scores based on machine-learning derived lesion-based classifiers related to rejection (ABMRpm, TCMRt, all Rejection) will be generated using the Edmonton reference set of >1200 biopsies. Moreover, gene expression patterns will be evaluated using unbiased archetype analysis. Morphological results will be evaluated by experienced renal transplant pathologists blinded for treatment allocation. For classification of ABMR according to the Banff 2013 scheme, all biopsy results will be analyzed in the context of the molecular results. ABMR categories and morphological single lesions will be defined and scored following the 2013/2015 update of the Banff classification [4]. ABMR will be defined on the basis of both morphological (histomorphology, immunohistochemistry, electron microscopy) and thoroughly validated molecular criteria: (i) evidence of acute or chronic tissue injury, (ii) evidence of current/recent antibody interaction with the vascular endothelium, and (iii) serological evidence of DSA.

Kidney function. eGFR will be assessed using the CKD-EPI formula. Protein excretion will be documented as protein/creatinine ratio.

Pantoprazole pharmacokinetics will be determined by liquid chromatography tandem mass spectrometry.

Cytokine and markers of endothelial activation/injury. Sera collected at week 0, 12 and 52 will be analysed for IL-6, soluble IL-6 receptor, soluble VCAM-1, soluble P-Selectin and DARC in order to document IL-6 decrease in the clazakizumab arm and to monitor endothelial activation and injury. Analysis will be carried out on FlowELISA beads in a multiplex approach (where possible) in a Luminex 200 or ELISA technology (DARC). In parallel, markers of inflammation and endothelial cell activation will be evaluated in urine.

Leukocyte subpopulations. The underlying mechanisms of chronic antibody mediated rejection, especially the role of peripheral T- and B-cell subsets are not fully clarified. Thus, the prospective monitoring of immune phenotype under therapy with clazakizumab is a promising approach to further elucidate the impact on immune-regulatory pathways when IL-6 signal is blocked. For monitoring of leukocyte (sub)populations we will use reproducible immune monitoring (IM) panels for phenotyping. Recently, the international "The ONE study" consortium has designed a standardized panel (DuraClone®) for flow cytometry based immune phenotyping that demonstrated robust results [25] [26]. In the DuraClone IM kits pre-

defined assay tubes contain a layer with the dried-down antibody panel ready to use. Up to 10 different monoclonal antibodies per tube allows the identification of leukocyte (e.g. T cell, B cell, NK cell subsets) subpopulations present in whole blood samples.

Gene expression analysis. For gene expression analysis, 5 mL of blood will be collected in PAXgene Blood RNA tubes and stored at -80°C until retrospective analysis. These tubes are designed for stabilization of RNA in blood during long-term storage at ultra-low temperature. After thawing, RNA will be isolated and transcribed into cDNA. The amount of RNA/cDNA of IL-6 or IL-6R will be determined by quantitative real-time-PCR using the TaqMan assay. Thereby, - on top of a common PCR reaction (amplification of template cDNA between two primer sequences by a DNA polymerase) - IL-6 or IL-6R-specific probes will be placed between the two PCR primers. These probes will be labelled with a fluorochrome which is released upon polymerase action. This released fluorochrome will be measured and compared to another fluorochrome that is released in parallel from a house-keeping gene like G3PDH.

Torque Teno virus (TTV) quantification. TTV DNA will be quantified retrospectively in stored plasma samples obtained at week 0, 12 and 52 using real time PCR.

Collection of biological material (outside routine monitoring). Plasma (10 mL; cytokines, endothelial markers, TTV load), serum (10 mL; HLA antibodies, cytokines, endothelial markers), whole blood (10 mL; flow cytometry, RNA for gene expression analysis) and urine (10 mL) will be collected before study initiation (day 0), after 12 and after 52 weeks (3x25 mL peripheral blood). For pantoprazole kinetics, peripheral blood samples will be collected serially (6 x 5 mL per day) at day 0, week 12 and week 52, respectively. Finally, for measurement of clazakizumab concentrations and anti-clazakizumab reactivity, serum will be obtained at every study visit (5 mL peripheral blood per visit; total of 17 visits). Biological material will be aliquoted and stored for testing (clazakizumab concentration, anti-clazakizumab antibody detection, HLA antibody detection, detection of cytokines and endothelial markers, TTV quantification) at the Department of Clinical Pharmacology.

7. SAMPLE SIZE AND STATISTICAL ANALYSIS

For this pilot study, no exact sample size estimation can be performed, because the effect size is unknown (there is no prior information to base a sample size on). The primary endpoint will be safety and tolerability. A preliminary assessment of efficacy outcomes in 20

kidney transplant recipients with late ABMR will provide first data on the effect of clazakizumab on clinical, morphological, immunological and molecular endpoints. The respective results (e.g. comparison between clazakizumab and placebo with respect to microcirculation inflammation and molecular rejection scores; course of chronic injury from 3 to 12 months), including an assessment of variability, can be expected to provide a valuable foundation of the design of future trials. Analyses will be conducted according to the intention-to-treat principle. Continuous data (e.g. group comparisons in part A for DSA-MFI, g+ptc score, IF/TA score, molecular ABMR score, eGFR and protein/creatinine ratio after 3 months) will be analysed using parametric and non-parametric (independent/dependent data) tests. These include the Mann Whitney U test or the t-test, as appropriate. Nominal data (e.g. occurrence of AEs in the two treatment groups in part A of the study) will be compared using the Fisher's exact test, when appropriate. Transplant and patient survival or AE (SAE)-free survival will be evaluated using Kaplan Meier analysis and the log rank test will be applied for group comparisons. For paired data (e.g. difference in IF/TA score between month 3 and month 12 in the overall cohort - part B), paired t test or Wilcoxon test will be used as appropriate. Analysis of pharmacokinetics of clazakizumab and pantoprazol will include a description of the time evolution of antibody/drug concentration. Elimination half-life, Tmax, Cmax, clearance and volume of distribution will be computed using standard software. For some study endpoints, data on variability and center (median) that can be expected also for the present study, are available from a recent interventional randomized controlled trial performed at our unit, which included a similar cohort of kidney transplant recipients diagnosed with late ABMR (BORTEJECT, NCT01873157; unpublished data; protocol described in: Eskandary et al., Trials. 2014 Apr 3;15:107). The respective data obtained in study groups are listed in the table below:

Table 4. Median and variability of key endpoints – results of the BORTEJECT study

Endpoints	All patients	n	Placebo (n=23)	Bortezomib (n=21)
HLA DSA after 1 yr				
Immunodominant DSA	3553 (1012-10365; 163-16284)	39	4360 (1080-10226; 778-16284)	2054 (918-10968; 163-14461)
Sum of DSA MFI	4605 (1119-12009; 273-33855)	39	5410 (1354-13612; 778-28828)	3479 (929-12009; 273-33855)
Follow-up biopsy (24 mo)				
g+ptc score	2 (1-5; 0-6)	38	2 (1-5; 0-6)	4 (0-5; 0-6)
IF/TA score	3 (2-5; 0-6)	38	3 (2-4; 0-6)	3 (2-5; 0-6)
Molecular ABMR score	0.61 (0.30-0.89; 0.05-0.99)	37	0.58 (0.24-0.89; 0.08-0.99)	0.77 (0.41-0.90; 0.05-0.97)
Kidney parameters after 1 yr				
eGFR, ml/min/1.73 m2	44 (23-72; 15-95)	43	53 (23-81; 15-95)	42 (25-69; 15-89)
Protein/creatinine ratio, mg/g	201 (86-1249; 0-4863)	44	194 (82-959; 0-4863)	208 (100-1427; 0-2972)

8. INTERIM ANALYSES

This study will be monitored by an independent data and safety monitoring board (DSMB) to assess the safety and data quality. To timely detect major differences between groups in terms of safety aspects, the board members will be instructed to perform interim analyses after 10 and 20 patients have finalized part A of the study. The DSMB will analyze recorded AEs and safety lab results in relation to the randomization sequence. The trial will be terminated prematurely in the following cases: (i) if adverse events occur which are so serious that the risk-benefit ratio is not acceptable, and (ii) if the number of dropouts is so high that proper completion of the trial cannot realistically be expected. For this pilot trial, exact statistical definitions of criteria for premature study termination are not defined.

DSMB - Members

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9. ADVERSE DRUG REACTIONS

Clazakizumab

From previous studies, results obtained in approximately 900 clazakizumab-treated patients/subjects are available for assessment of safety patterns. Overall, adverse events (AEs) reported for clazakizumab treatment are consistent with IL-6 blockade. In previous studies, e.g. in RA and PsA [18,22,23], clazakizumab was administered at doses up to 320 mg, and many patients have received this antibody as an add-on to treatment with methotrexate. However, until now, no data obtained in transplant patients on dual or triple immunosuppression are available, so that safety assessment remains a major objective of this pilot trial. However, preliminary data obtained with the IL-6R antibody tocilizumab in transplant recipients point to a beneficial safety profile of targeting of IL-6/Il-6R also in patients on calcineurin inhibitor (CNI)-based immunosuppression.

Reported AEs caused by clazakizumab are abnormalities in liver function parameters, which are commonly mild to moderate in severity [<3 x upper limit of normal (ULN) in most cases] and were more frequent under concomitant methotrexate treatment. Clinically significant increases in liver function parameters were shown to occur only in a few patients. Clazakizumab was shown to decrease neutrophil counts, whereby the majority of observed cases were mild/moderate in severity, without clinical sequelae. In phase 2 studies evaluating clazakizumab in arthritis, reported infection rates under repeated administration of clazakinumab were low and comparable to patients allocated to control groups [18,22,23]. Nevertheless, intensified immunosuppression, in addition to standard dual or triple baseline

immunosuppression, can be expected to be associated with an increased infection risk. Hence, a careful patient follow-up will include a close monitoring for infectious complications (bacterial, viral and fungal infections). In trials of arthritis, no case of gastrointestinal perforation was reported. However, given the low, but significantly increased risk of gastrointestinal perforation in other large studies evaluating IL-6/IL-6R blockers, patients with a history of gastrointestinal perforation, diverticulitis or inflammatory bowel disease will not be included in the trial. Clazakizumab, as other agents interfering with IL-6/IL-6R, was shown to increase total cholesterol and LDL levels. Moreover, in some patients, a mild decrease in platelet counts was observed. Serious infusion reactions have not been described in any of the published trials, but clazakizumab may cause injection site reactions, apparently in a dose-dependent fashion. Safety results obtained for prolonged treatment with subcutaneous clazakizumab at 25 mg (with or without methotrexate) in two recent phase 2 trials, one in RA [18], the other in PsA [23], are summarized in Table 5 (in both trials also higher doses of clazakizumab were evaluated; some events, such as injection site reactions or liver enzyme elevations, were thereby more frequently observed at higher dosages).

Table 5. Summary of AEs reported for clazakizumab at 25 mg - phase 2 trials in arthritis

Disease entity Author, year	Psoriatic arthritis Mease et al, 2016[23]		Rheumatoid arthritis Weinblatt et al, 2015[18]	
Treatment	**Placebo ±MTX**	**Clazakizumab 25 mg ±MTX**	**Placebo +MTX**	**Clazakizumab 25 mg +MTX**
Patient number	**41**	**41**	**61**	**59**
Deaths	0%	0%	0%	0%
GI perforations	0%	0%	0%	0%
Malignancies	0%	0%	0%	0%
SAEs	4.9%	4.9%	3.3%	8.5%
Discontunation (SAEs)	4.9%	0%	0%	0%
AEs	65.9%	73.2%	60.7%	84.7%
Discontinuation (AEs)	7.3%	2.4%	0%	0%
Infections	48.8%	36.6%	total infection rate not reported	
Liver parameters				
ALT >1-3 x ULN	24.2%	52.6%	21.6%	46%
ALT >3-5 x ULN	0%	5.3%	2%	3.7%
ALT >5-8 x ULN	2.0%	0%	0%	3.7%
AST >1-3 x ULN	13.5%	50%	14.8%	40%
AST >3-5 x ULN	0%	0%	0%	3.6%
AST >5-8 x ULN	0%	2.6%	0%	0%
Total bilirubin				
>1.0-1.5 x ULN	0%	10.8%	0%	8.8%
>1.5-2.0 x ULN	0%	5.4%	0%	1.8%
>2.0-3.0 x ULN	0%	2.7%	0%	0%
Cases of Hy's law	0%	0%	0%	0%
Lipids				
LDL	no details (lipids elevated)		Increase from <130 to ≥130 mg/dL	
			28.3%	61.9%
Neutrophil counts	Mean decrease by about 2 G/L			
0.5-1.0 x 109/liter	no details		0%	1.8%
1.0-1.5 x 109/liter	no details		3.8%	14.3%
Anti-clazakizumab Ab	-	4.9%	-	5.1%
Injection site reaction	-	9.8%	-	13.6%

Adverse drug reactions - specific considerations

Opportunistic Infections and Serious Infections

Physicians should exercise caution when considering the use of clazakizumab in patients with a history of recurring infection or with underlying conditions (eg, diabetes) which may predispose patients to infections. Clazakizumab should not be administered in patients with active infection. The effects of clazakizumab on CRP, neutrophils, and the signs and symptoms of infection should be considered when evaluating a patient for a potential infection.

Vigilance for timely detection of serious infection is recommended for transplant patients receiving biologic agents as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reaction. Patients must be instructed to contact their physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

If a patient develops a serious infection, administration of clazakizumab is to be interrupted until the infection is controlled. The clinician should consider the benefit-risk before resuming treatment with clazakizumab.

Gastrointestinal Perforations

Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticulitis and thus reduce the risk of GI perforations. Therefore, patients should be made aware of the symptomatology potentially indicative of diverticular disease, and they should be instructed to alert their healthcare provider as soon as possible if these symptoms arise. In patients with a history of symptomatic diverticulosis, diverticulitis or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis or other chronic lower GI conditions that might predispose to perforations, the clinician should consider the benefit-risk before using clazakizumab. Discontinuation of clazakizumab is necessary for patients who develop GI perforations.

Hematologic Abnormalities and Bleeding Events

Decreases in neutrophil and platelet counts have been observed following treatment with clazakizumab in combination with MTX. In addition, there may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist. For patients with concomitant medications associated with hematologic toxicity, the reduction or interruption of the suspected medication is recommended prior to modifying clazakizumab. Dosing guidance for neutropenia and thrombocytopenia are described in Tables 6 and 7.

Table 6. Neutropenia risk mitigation

ANC (cells/mm^3)	Action
> 1000	Maintain dose.
500 – 1000	Interrupt clazakizumab dosing. When ANC increases to > 1000, resume clazakizumab 25mg SQ monthly
< 500	Discontinue clazakizumab.
ANC = absolute neutrophil count	

Table 7. Thrombocytopenia risk mitigation

Platelet count (cells/mm^3)	Action
> 100,000	Maintain dose.
50,000 – 100,000	Interrupt clazakizumab dosing. When platelet count increases to > 100,000, resume Clazakizumab at 25mg SQ monthly
< 50,000	Discontinue clazakizumab.

Dosing recommendations for events of elevated liver enzymes are described in Table 8.

Elevated Liver Enzymes and Hepatic Events

Elevations in ALT and AST have been observed during treatment with the study medications

Table 8. Elevated liver enzymes – risk mitigation

Lab Value	Action
> 1 to 3x ULN	Dose modify concomitant transplant immunosuppressive drugs if appropriate For persistent increases in this range, interrupt clazakizumab until ALT/AST have normalized Restart with 25mg SC monthly as clinically appropriate
> 3 to 5x ULN (confirmed by repeat testing)	Interrupt clazakizumab dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN, discontinue clazakizumab Discontinue clazakizumab if total bilirubin >2 x ULN
> 5x ULN	Discontinue clazakizumab

Cardiovascular Events and Elevated Lipids

Kidney transplant recipients may have an increased risk for cardiovascular disorders, therefore, risk factors for cardiovascular disease (eg, hypertension, hyperlipidemia) should be managed as part of their standard of care. See section on Drug Interactions.

For patients with LDL cholesterol ≥160 mg/dL, it is strongly recommended that investigators advise therapeutic lifestyle changes that may include initiation lipid-lowering agents. Lipid-lowering agents should also be considered for patients with lower LDL cholesterol levels as part of their therapeutic lifestyle changes depending on their overall risk as defined in NCEP ATP III or other national guidelines.

Malignancies

The impact of immunosuppression on the development of malignancies is not known, however an increased rate of some malignancies, notably lymphoma, has been observed in RA patients. Although no imbalance of malignancies was observed in clinical trials of Clazakizumab, malignancies have been identified as a concern for other biologics. It is recognized that identification of such events in clazakizumab-treated patients may require a longer period of surveillance. Clazakizumab should be discontinued in patients with malignancies (with the exception of local basal or squamous cell carcinoma of the skin that is completely excised with free margins).

Demyelinating Disorders

The impact of treatment with clazakizumab on demyelinating disorders is not known; events were rarely reported. Patients should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders. Physicians should exercise caution in considering the use of clazakizumab in patients with pre-existing or recent onset demyelinating disorders. Treatment with clazakizumab should be interrupted during

assessment of a potential demyelination event and only resumed if the benefit of continuing study drug is favorable.

Hypersensitivity or Anaphylaxis

An infusion/dose reaction is defined as an adverse event occurring during and within 24 hours after the infusion or SC injection of clazakizumab. This may include hypersensitivity reactions or anaphylactic reactions.

Signs of a possible hypersensitivity reaction include but are not limited to:

- fever, chills, pruritus, urticaria, angioedema, and skin rash.
- cardiopulmonary reactions, including chest pain, dyspnea, hypotension or hypertension.

Healthcare professionals administering clazakizumab should be trained in the appropriate administrative procedures, be able to recognize the symptoms associated with potential anaphylactic or hypersensitivity reactions, and have the appropriate medication available for immediate use in case of anaphylaxis or hypersensitivity reaction during or after administration of clazakizumab. Healthcare professionals should also instruct patients to seek medical attention if they experience symptoms of a hypersensitivity reaction outside of the clinic.

If a patient has symptoms of anaphylaxis or serious hypersensitivity, or requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity, administration of clazakizumab must be discontinued permanently. The patient should be treated according to the standard of care for management of the hypersensitivity reaction. A blood sample for the presence of anti-clazakizumab antibodies should be obtained.

Clazakizumab should not be administered to subjects who have had any previous allergic reactions to monoclonal antibodies. To date, no infusion reactions have been associated with clazakizumab administered by IV infusion. Injection site reactions have been reported with SC administration. Reactions have been mild or moderate and have resolved without treatment. Both allergic reactions and injection site reactions should be treated with standard of care. Subjects who have developed significant allergic reaction to study drugs should not be re-challenged.

Viral Reactivation

Though rarely reported within the clazakizumab program due to exclusion criteria at study entry, reactivation of viral and other serious infections (e.g. EBV or TB) has been observed with biologic therapies.

Drug Interaction

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (eg, IL-6) during chronic inflammation. Therefore, it is expected that for molecules that antagonize cytokine activity, such as clazakizumab, the formation of CYP450 enzymes could be normalized. When starting or stopping therapy with clazakizumab, patients taking medications which are individually dose-adjusted and metabolized via CYP450, 3A4, 1A2, or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine, or benzodiazepines) should be monitored as doses may need to be adjusted to maintain their therapeutic effect. Given its long elimination half-life (t1/2), the effect of clazakizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Pregnancies and Women of Child Bearing Potential

There are no adequate well-controlled studies in pregnant or lactating women. In nonclinical studies, an increase in the number of monkeys with retention of the placenta at parturition was observed at clazakizumab doses corresponding to 22 and 220 times the planned human dose of 25 mg. In 3 of the 5 monkeys with retained placentas, the resulting excessive uterine hemorrhage led to moribund status in the mothers.

Three pregnancies have been reported to date in subjects taking clazakizumab. The outcomes included one spontaneous abortion (outcome unknown for the other 2 pregnancies).

All subjects of child bearing potential being treated with clazakizumab (and their partners) must be informed of this risk, and use highly effective birth control, as defined in the study protocol. Administration of clazakizumab may decrease the efficacy of hormonal oral contraceptive.

Under no circumstances shall clazakizumab injection be administered to women known to be pregnant or lactating. All pregnancies must be reported to Vitaeris within 24 hours and in accordance with SAE reporting procedures.

Pantoprazole

The most common reported **side effects of pantoprazole** are headache, diarrhea and injection site thrombophlebitis. Other common side effects are rash, tiredness, flu-like symptoms, nausea, vomiting, abdominal pain/discomfort, constipation, dry mouth, loose stools, and flatulence. While some patients show increases in liver enzymes, hepatic failure is very rare. Rare events are fever, taste disorders, gynecomastia, agranulocytosis, thrombocytopenia, severe skin reactions or allergic reactions. Occurrence of interstitial nephritis is very rare.

10. SAFETY ASSESSMENT AND REPORTING

Definition of adverse events

An AE is any untoward adverse change from the subject's baseline condition, i.e., any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease which is considered to be clinically relevant by the physician that occurs during the course of the study, whether or not considered related to the study drug.

Adverse events include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Events considered by the investigator to be related to study-mandated procedures.
- Abnormal assessments, e.g., ECG and physical examination findings, must be reported as AEs if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study.
- Laboratory test abnormalities must be reported as AEs if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug.

Adverse events do not include:

- Pre-planned interventions or occurrence of endpoints specified in the study protocol are not considered AE´s, if not defined otherwise (eg.as a result of overdose)
- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure will be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Overdose of either study drug or concomitant medication without any signs or symptoms. However, overdose must be mentioned in the Study Drug Log.

Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) will be defined by the International Conference on Harmonization (ICH) guidelines and WHO GCP guidelines as any AE fulfilling at least one of the following criteria:

- Results in deaths.
- Life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring subject's hospitalization or prolongation of existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Resulting in persistent or significant disability or incapacity (i.e., a substantial disruption of a person’s ability to conduct normal life functions).
- Congenital anomaly or birth defect.
- Is medically significant or requires intervention to prevent at least one of the outcomes listed above.

Life-threatening refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

Hospitalization – Prolongation of existing hospitalization

Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room. An additional overnight stay defines a prolongation of existing hospitalization.

The following is not considered an SAE and will be reported as an AE only:

- Treatment on an emergency or outsubject basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.

The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:

- Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for chemotherapy for cancer, elective hip replacement for arthritis.

SAEs related to study-mandated procedures

Such SAEs are defined as SAEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of study drug) such as discontinuation of subject's previous treatment during a washout period, or complication of a mandated invasive procedure (e.g., blood sampling, heart catheterization), or car accident on the way to the hospital for a study visit, etc.

Suspected unexpected serious adverse reactions (SUSARs)

SUSARs are all serious adverse reactions with suspect causal relationship to the study drug that is unexpected (not previously described in the Investigator’s brochure) and serious.

Pregnancy

Pregnancy itself is not an AE/SAE; the outcome of a pregnancy can be a SAE. Any pregnancy that occurs during study participation will be reported to the investigator/sponsor. To ensure subject safety, each pregnancy will be reported to the investigator/sponsor immediately. The pregnancy will be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons will be reported as an AE or SAE. Spontaneous abortions will be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator’s attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, will be promptly reported to the principal investigator/sponsor. In addition, the investigator will attempt to collect pregnancy

information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information will be reported to the investigator/sponsor as described above.

Severity of adverse events

The severity of clinical AEs will be graded on a three-point scale: mild, moderate, severe, and reported on specific AE pages of the CRF. If the severity of an AE worsens during study drug administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required. If an AE occurs during a washout or placebo run-in phase and afterwards worsens during the treatment phase, a new AE page will be filled in with the intensity observed during study drug administration.

Mild: Event may be noticeable to subject; does not influence daily activities; the AE resolves spontaneously or may require minimal therapeutic intervention;

Moderate: Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed; the AE produces no sequelae.

Severe: Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; the AE produces sequelae, which require prolonged therapeutic intervention.

A mild, moderate or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

Relationship to study drug

For all AEs, the investigator will assess the causal relationship between the study drug and the AE using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the AE:

Unrelated

- May or may not follow a reasonable temporal sequence from administration of the study product

- Is biologically implausible and does not follow known response pattern to the suspect study drug (if response pattern is previously known).
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
- Unlikely
- May or may not follow a reasonable temporal sequence from administration of the study product
- Is biologically not very plausible
- May be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Possible related

- Follows a reasonable temporal sequence form administration of the study drug.
- May follow a known response pattern to the study drug (if response pattern is previously known).
- Could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, if applicable.
- Probable
- Follows a reasonable temporal sequence form administration of the study drug.
- Follows a known response pattern to the study drug (if response pattern is previously known).
- other causes for the event are unlikely

Definitely related

- Follows a reasonable temporal sequence form administration of the study drug.
- Follows a known response pattern to the study drug (if response pattern is previously known).
- No other reasonable cause is present.

Reporting procedures

A special section is designated to adverse events in the case report form. The following details must thereby be entered:

- Type of adverse event
- Start (date and time)
- End (date and time)
- Severity (mild, moderate, severe)

- Serious (no / yes)
- Unexpected (no / yes)
- Outcome (resolved, ongoing, ongoing – improved, ongoing – worsening)
- Relation to study drug (unrelated, possibly related, definitely related)

Adverse events are to be documented in the case report form in accordance with the above mentioned criteria.

Reporting procedures for SAEs

In the event of serious, the investigator has to use all supportive measures for best patient treatment. A written report is also to be prepared and made available to the clinical investigator immediately. The following details should at least be available:

- Patient initials and number
- Patient: date of birth, sex, ethical origin
- The suspected investigational medical product (IMP)
- The adverse event assessed as serious
- Short description of the event and outcome

If applicable, the initial report should be followed by the Follow up report, indicating the outcome of the SAE.

All SAEs for which there is a reasonable possibility the experience may have been caused by clazakizumab (this applies to both expected and unexpected events) will be recorded on a CIOMS Form and submitted to:

SAE Reporting	**Contact Information**
Vitaeris Drug Safety: Dr Edward Chong This must be reported to Vitaeris within 24 hours.	Tel: 604 638 1582 (0ffice), 250 216 6371 (cell) email: eddie.chong@vitaerisbio.com For submission of SAE report information: By email: safety@vitaerisbio.com or Fax: 800-518-5253

Reporting procedures for SUSARs

It must be remembered that the regulatory authorities, and in case of SUSARs which could possibly concern the safety of the study participants, also the Institutional Review Board / Independent Ethics Committee (IRB / IEC) are to be informed. Such reports shall be made by the study management and the following details should be at least available:

- Patient initials and number
- Patient: date of birth, sex, ethical origin
- Name of investigator and investigating site
- Period of administration
- The suspected investigational medical product (IMP)
- The adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship to the IMP
- Concomitant disease and medication
- Short description of the event:
    - Description
    - Onset and if applicable, end
    - Therapeutic intervention
    - Causal relationship
    - Hospitalization of prolongation of hospitalization
    - Death, life-threatening, persistent or significant disability or incapacity

Electronic reporting should be the expected method for reporting of SUSARs to the competent authority.

The Development Safety Update Report (DSUR)

The DSUR will be provided by the principal investigator at least once a year.

This report will also be presented annually to the Independent Ethics (IEC) and to the competent authorities by the sponsor.

11. STUDY TERMINATION, WITHDRAWAL AND REPLACEMENT OF SUBJECTS

Criteria for withdrawal

Subjects may prematurely discontinue from the study at any time. Premature discontinuation from the study is to be understood when the subject did not undergo EOS examination and / or all pivotal assessments during the study.

Subjects will be withdrawn under the following circumstances:

- at their own request
- if the investigator feels it would not be in the best interest of the subject to continue

- if the subject violates conditions laid out in the consent form / information sheet or disregards instructions by the study personal

In all cases, the reason why subjects are withdrawn will be recorded in detail in the CRF and in the subject's medical records. Should the study be discontinued prematurely, all study materials (complete, partially completed and empty CRFs) will be retained.

Follow-up of patients withdrawn from the study
In case of premature discontinuation after study drug intake, the investigations scheduled for the EOS visit will be performed 7 days after study drug discontinuation. The subjects will be advised that participation in these investigations is voluntary. Furthermore, they may request that from the time point of withdrawal no more data will be recorded and that all biological samples collected in the course of the study will be destroyed.

Premature termination of the study
The sponsor has the right to close this study at any time. The IEC and the competent regulatory authority must be informed within 15 days of early termination.
The trial or single dose steps will be terminated prematurely in the following cases:

- If adverse events occur which are so serious that the risk-benefit ratio is not acceptable.
- If the number of dropouts is so high that proper completion of the trial cannot realistically be expected.

12. ETHICAL ISSUES

The study will be conducted in accordance with the principles of the Declaration of Helsinki 2008. Ethical committee approval will be obtained for all aspects of the study. All study participants will be asked to sign the informed consent to participate in the study (patient insurance included).

13. REGULATORY REQUIREMENTS

We will adhere to all the trial-related requirements, Good Clinical Practice (GCP) requirements (ICH GCP), Good Laboratory Practice (GLP) and the applicable regulatory requirements.

14. PERIODIC MONITORING

The designated monitor (Dr. Peter Matzneller, Department of Clinical Pharmacology, Medical University Vienna; Tel. 01 40400 29810) will contact and visit the investigator regularly and will be allowed to have access to all source documents needed to verify the entries in the CRFs and other protocol-related documents provided that subject confidentiality is maintained in agreement with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals according to the monitoring plan throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of the main efficacy, safety, and tolerability endpoints. The monitor will be working according to SOPs and will provide a monitoring report after each visit. The investigator will resolve discrepancies of data. Source data will be checked by the monitor (which means 100% SDV).

15. AUDIT AND INSPECTIONS

Upon request, the investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the sponsor or to competent authority inspectors. The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for assessment of safety and efficacy of the investigational product have appropriately been reported to the sponsor.

16. INVESTIGATOR TRAINING

All investigators and their study personnel will receive training regarding the study procedures and GCP/regulations specific to the conduct of clinical trials. This training will be documented and will take place prior to enrollment and throughout the study as necessary.

17. RECORD RETENTION

Essential documents will be retained as required by the applicable regulatory requirements or by an agreement with Vitaeris.

18. STUDY REGISTRATION

The study is planned to be approved by the Austrian regulatory authority (Federal Office for Safety in Health Care, Austrian Agency for Health and Food Safety) and German regulatory authority (The Paul-Ehrlich-Institut, PEI). We plan to register the study to the European Clinical Trials Database (EUDRACT) and a public clinical trial database (http://clinicaltrial.gov). The study protocol will be submitted for publication to *Trials* (http://www.trialsjournal.com/).

19. MODIFICATIONS TO THE PROTOCOL

Protocol Amendments

Protocol amendments, except where necessary to eliminate an immediate hazard to patients, will be made with the prior approval of Vitaeris. Each applicable Regulatory Authority/IRB/EC/IEC will review and approve amendments prior to their implementation. Regulatory Authority/IRB/EC/IEC approval need not be obtained prior to removal of an immediate hazard to patients.

Protocol Violations and Deviations

Protocol waivers will not be permitted except where necessary to eliminate an immediate hazard to patients. The Principal Investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IEC and agreed to by the Principal Investigator. Protocol violations and deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal Investigator will be notified of violations and/or deviations in writing by the monitor. The IEC will be notified of all protocol violations and deviations according to IEC reporting requirements.

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