TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Single Blind, Randomised, Placebo Controlled, Repeat Dose, Dose Escalating Study Investigating Safety, Tolerability pharmacokinetics, Pharmacodynamics and the Beta-Cell Preserving Effect of Otelixizumab in New-Onset, Autoimmune Type 1 Diabetes Mellitus Patients

Compound Number: GSK2136525

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Effective Date: 26-OCT-2017

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Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2011N129686_00	2013-SEP-05	Original
2011N129686_01	2014-FEB-27	Amendment No. 1
Addition of unblinded Pharmacy Monitor to table summarising blinding status of personnel; endpoint in table updated to include insulin measurement for 7 days before all outpatient visits; endpoint of glucose added when performing MMTT and clamp procedures; clarification of time period for collecting information in the screening period; removal of TCR complexes and clarification of CD3 requirements throughout protocol; change of volume required to purge the IV infusion line and total volume filled into syringe, and removal of "micopore" from description; the following changes to the Time and Events Tables: clarification that insulin should be recorded for 7 days before all outpatient visits; addition of Day 6 to footnote 18; clarification that glucose will be collected in addition to C-peptide during the hyperglycaemic clamp procedure (Section 6.2.2); addition of ECGs at 6 hours post start of infusion (Section 6.2.3) clarification of which ECGs will be triplicate or single measures; addition of TCR deep sequencing at 24 months to Biomarker Assay Table; clarification that MMTT will be at least 7 days prior to the first dose of study drug; clarification that c-peptide and glucose samples will be shipped within 3 weeks of collection; clarification that the hyperglycaemic range of 180-240mg/dL during 140 minutes for consistency with blood sampling time points.		
2011N129686_02	2014-APR-02	Amendment No. 2
Hyperglycaemic events is included in the follow up endpoints and the Time and Events table to be consistent with the applicable secondary objective; rephrased "Immuno-Assay for syphilis test" in order to allow for different types of tests; increased the overage volume required to remain in the syringe for infusion; clarified the start of AE recording.		
2011N129686_03	2014-JUN-18	Amendment No. 3
The third medical monitor has changed, therefore contact information for the replacement is included. The eligibility inclusion criterion was changed from two to one positive autoantibody associated with TIDM.		
2011N129686_04	2014-JUL-28	Republishing-Amendment No. 3
Clarified that within each cohort administration of study treatment for the first three patients will be staggered by at least three days across each centre.		
2011N129686_05	2015-FEB-11	Amendment No. 4
To increase flexibility for patients, dosing on Day 4, 5 & 6 may be performed on an out-patient basis if the Investigator is satisfied with the clinical status of the patient; clarification that if the infusion needs to be reduced or temporarily stopped the Investigator should first consult with the Medical Monitor who will consult the Sponsor, unless there is an immediate safety hazard, in this case the Investigator can inform the Medical Monitor afterwards; clarified that insulin use is to be recorded prior to each visit and phone call; clarification that the decision to replace a patient is to be based on the		

reason for withdrawal; inclusion criteria # 3 amended; screen failure data are to be collected; assessments following patient withdrawal clarified; clarified that infusion kits are supplied to sites; assessment of EBV reactivation now conducted at 6 weeks after the first active dose (reduced from 12 weeks); blinding status amended to clarify that only the patient is blinded and not site staff; requirement for pharmacy staff to document that investigational product shipping conditions were 2-8°C included; anti-emetic added as a permitted concomitant medication, window of ± 1 day added to Day 14 and 21 visits and Week 4 telephone call; Section 6.2.2 amended to include a phone call at Week 4 to discuss AEs with patient and addition of assessments at Week 6; endpoints amended to reflect the change to visits at Week 4 and Week 6; Section 6.2.3 amended to include ECG at 3 hours and to clarify that assessments may stop at 3 hours post dose; clarification of cytokine release syndrome adverse events grading system and stopping criteria in Section 7.1.5; clarification on requirements for bilirubin samples included; CRO responsibilities clarified and supply of Ensure powder by CRO/GSK included.		
2011N129686_06	2015-AUG-18	Amendment No. 5
The assay for screening EBV IgG and IgM assessment was clarified in exclusion criterion number 18 and in Table 2 in the Risk Management section; exclusion criterion 18 was split into two exclusion criteria (18 and 19) to clarify EBV IgM, IgG and Viral load requirements for the interpretation of the results: a footnote was added to Table 6 (Stopping Criteria for CRS-Adverse Events) to provide further clarification regarding when individual stopping criteria are met; the dose preparation section was updated to clarify that an additional maximum of 30 minutes is allowed for dose preparation tasks and that if 6 hours is exceeded, the syringe and infusion materials must be replaced; EBV serology samples to assess IgG and IgM included for Day -1 in the Time and Events Table (Table 6.2.2 Dosing and Follow-Up).		
2011N129686_07	2016-SEP-12	Amendment No. 6
Clarifications were made to the exploratory biomarker objectives and endpoints. Significant changes were: the addition of Th17 cells to the objective to assess the effect of otelixizumab on circulating lymphocytes; the addition of viral antigens to the endpoints to assess the effect of otelixizumab on the frequency of cytokine-producing antigen specific T cells; the addition of transcriptomic gene expression changes to the objective to assess the effect of otelixizumab on the clonal repertoire of circulating T cell populations; and clarification that the suppression activity of circulating T lymphocytes may be further evaluated by adapting assay conditions, possibly through adding and/or blocking of stimuli. The Time and Events table was updated to show requirement for telephone calls at Month 36, 48 and 60. Month 24 exploratory biomarkers are now being routinely collected and are not subject to the results of Month 12 biomarker analysis. In addition, it was clarified that Month 24 exploratory biomarker samples will be collected and only analysed after review of safety endpoints from Month 12 and not efficacy endpoints as previously stated. Minor clarifications related to the Month 12 Interim Analyses were included. The name Quest was amended to Q^2 Solutions and Study Procedures Manual was changed to Study Reference Manual.		

2011N129686_08	2017-SEP-11	Amendment No. 7
All details of how the currently used Ensure powder (Abbott) is prepared has been removed from the Mixed Meal Tolerance Test (Appendix 5). This has been amended because the manufacturer (Abbott) has discontinued the currently used powder and the new product has a slightly different formulation. The details for each of the products will now be detailed in the Study Reference Manual.		
2011N129686_09	2017-OCT-26	Amendment No. 8
Data which emerged from an interim analysis carried out in this study showed a prompt regain of immune competence observed in treated subjects and consequent rapid resolution of EBV reactivation, both clinically and virologically. The long term EBV related PTLD risk, as observed in solid organ transplant on a chronic immune suppression therapy, is negligible. Therefore, all references to month 48 and 60 have been removed as no patient currently enrolled in the study has reached month 48 of follow up. For the patients who have yet to complete their 24 month visit, this visit will be treated as a final visit and for those who have gone past month 24, they will be followed up with a final communication or visit (final follow up) upon approval of this protocol amendment. Data from the literature identified a causal relationship between the degree of immunosuppression and an increased incidence of EBV related Post Transplant Lymphoprolerative Disorders (PTLD) and for this reason a long-term follow-up was implemented at the start of the study.		

SPONSOR SIGNATORY

PPD

26th October 2017

Caroline O Savage, FRCP, FMedSci
VP & Head, Experimental Medicine Unit

Date

PPD

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number OTX116505

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
ADA	American Diabetes Association
Anti GAD	Antibody to Glutamic Acid Decarboxylase
Anti IA2	Antibody to Protein Tyrosine Phosphatase-like Protein
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area Under the Curve
BDR	Belgian Diabetes Registry
CMV	Cytomegalovirus
CRO	Contract Research Organisation
CRS	Cytokine Release Syndrome
CTL	Cytotoxic T-Lymphocyte
DM	Diabetes Mellitus
EBNA	Epstein-Barr Nuclear Antigen
EBV	Epstein Barr Virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
h	Hour
IAA	Insulin Antibodies
ICA	Antibody to Islet-Cell Antigen
IB	Investigator Brochure
INS	Insulin
ISR	Insulin Secretion Rate
i.v.	Intravenous
LFT	Liver Function Tests
mAb	Monoclonal Antibody
mg	Microgram
mL	Millilitre
MMTT	Mixed Meal Tolerance test
NOD	Non Obese Diabetes
NOT1DM	New Onset Type 1 Diabetes Mellitus
NSAID	Non Steroidal Anti-Inflammatory Drug
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PTLD	Post-Transplant Lymphoproliferative Disorder
qPCR	Quantitative Polymerase Chain Reaction
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RBC	Red Blood Cells
RT-PCR	Reverse Transcription-Polymerase Chain Reaction

SAE	Serious Adverse Event
SOI	Start of Infusion
SRM	Study Reference Manual
TB	Tuberculosis
TCR	T Cell Receptor
TTEDD	Therapeutic Evaluation of Different Multi-Dose Regimens in Type 1 Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organisation

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1. INTRODUCTION

1.1. Study Rationale

The aim of this Phase I/IIa study is to identify a safe and tolerable dosage regimen of intravenously administered otelixizumab. In addition, the C-peptide decline in new onset type 1 diabetes mellitus (NOT1DM) patients and possible immunological mechanisms will be investigated with a view to identifying trends and early immunological biomarkers which could predict response in halting/slowing β-cell destruction in this patient population.

This exploratory study will explore the safety and tolerability between the well tolerated but non-efficacious cumulative dose of 3.1 mg (in previously completed Phase III studies) and a cumulative dose of 48 mg (in a previously completed Phase II study) at which efficacy based on C-peptide analysis was demonstrated, albeit with evidence of Epstein Barr Virus (EBV) reactivation and Cytokine Release Syndrome (CRS). Exploration of the tolerability dose response is considered a necessary first step to determining the therapeutic index of otelixizumab.

It has been shown that treatment with non-mitogenic anti-CD3 monoclonal antibodies (mAbs) can achieve some degree of immuno-modulation in NOT1DM patients resulting in halting the decline of stimulated C-peptide secretion (a validated surrogate of pancreatic β-cell function) for up to 12 months post-treatment (teplizumab - Herold study [Herold, 2005] and otelixizumab BDR study [Keymeulen, 2005]). This effect translated to a reduction of insulin requirements with no loss of glycaemic control up to 18 months post-treatment [Keymeulen, 2005]. The relatively high dose regimens investigated in these studies, were estimated to have reduced circulating free CD3 levels to less than 10% of pre-treatment levels throughout the dosing period (6 and 14 days, for otelixizumab (cumulative dose 48-64 mg) and teplizumab (cumulative dose 34.9 mg) respectively, see Figure 1). However, infusion reactions typical of CRS were consistently observed following administration of both molecules, and in the case of otelixizumab, reactivation of latent EBV occurred in most subjects, accompanied by symptoms of mononucleosis.

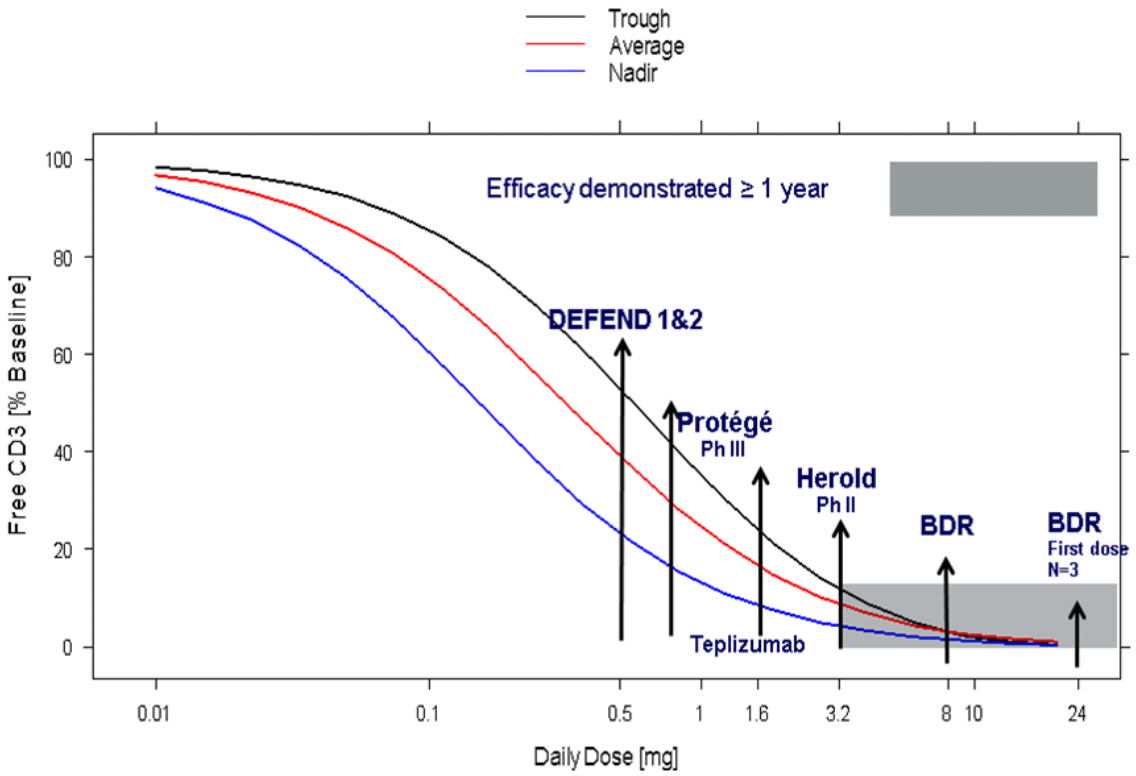
In contrast, in two Phase III trials (DEFEND 1&2, respectively), where a substantially reduced dosage regimen of otelixizumab was investigated (total dose of 3.1 mg vs. 48-64 mg in the BDR proof-of-concept study), no effect on C-peptide or any key secondary or exploratory endpoints were observed. Likewise, in the Phase III trial Protégé, lower doses of teplizumab relative to the proof-of-concept study (0.1, 0.2, 0.4, 0.8, 10 X 1.6 mg per day, 17.5 mg cumulative dose compared to 34.9 mg in the Herold study) failed to demonstrate a statistically significant treatment effect on a range of metabolic endpoints. However, although some trends were observed with respect to C-peptide and insulin requirements, the duration of apparent efficacy was reduced (6 months vs. 12 months). Thus, the relationship between dose, duration of treatment, and magnitude and duration of efficacy has not been fully elucidated with any anti-CD3 antibody. However, the current weight of clinical evidence suggests that a high and sustained degree of blockade of CD3 is required during the dosing period to achieve a clinically relevant and durable response in halting the disease progression of NOT1DM patients.

In addition to dose, several post-hoc analyses (BDR, Herold and Protégé studies [Sherry, 2011; Herold, 2005]) have suggested that time to treat following disease diagnosis and age of the patient are key determinants of treatment response, with teplizumab preserving C-peptide secretion only in T1DM patients treated within 6 weeks from the diagnosis [Sherry, 2011; Herold, 2005].

Therefore, the efficacy measured on the degree of β-cell preservation efficacy seems to be strictly dose and time from diagnosis dependent, with the younger population (<27 years old) being more responsive (BDR and Protégé studies).

It is anticipated that the therapeutic window for anti-CD3 therapy is fairly narrow with the immediate risk of tolerability related to increased severity of cytokine release syndrome (CRS) at higher doses and the longer-term risk related to EBV reactivation. Therefore, the aims of this study are to explore the safety, tolerability, pharmacokinetics, pharmacodynamics, efficacy and immunological profile of escalating repeat doses of intravenously administered otelixizumab in NOT1DM patients. The data obtained from this study will inform the design of subsequent efficacy studies.

Figure 1 **Predicted Dose Response for Human CD3 Antigen Occupancy on CD4+ T cells for Various Clinical Studies in NOT1DM Patients with Anti-CD3 Monoclonal Antibodies**



NB: DEFEND 1 &2 and BDR studies (otelixizumab), Herold and Protégé (teplizumab). Based on *in vitro* characterization and limited clinical data otelixizumab and teplizumab assumed the same potency and pharmacokinetics.

1.2. Brief Background

1.2.1. Tolerance induction by targeting the TCR/CD3 complex

The CD3 complex is a group of cell surface molecules associated with the T-cell antigen receptor, constituting the T Cell Receptor (TCR) complex which, when activated, induces a signalling transduction cascade [Kuhns, 2006]. The CD3 complex is expressed on the surface of thymocytes and mature lymphocytes expressing either alpha-beta or gamma-delta TCR. Multiple effects of anti-CD3 treatment have been demonstrated *in vitro* and *in vivo* including internalization of the TCR-CD3 complex (which renders cells blind to the antigen), stimulation of cytokine release, triggering of apoptosis, induction of T cell anergy, transient lymphopenia/redistribution and eventual expansion of regulatory T cell numbers. In animal models of diabetes [Herold, 1992; Chatenoud, 1994 and Chatenoud, 1997; Belghith, 2003; Li, 2006; Mehta, 2010; Nishio, 2010] autoimmune arthritis [Hughes, 1994; Notley, 2010] and multiple sclerosis [Tran, 2001; Kohm, 2005; Chao, 2009; Belmar, 2009], the collective effects of anti-CD3 treatment appear to modify the immune system to produce "tolerance", leading to sustained remission without continuing anti-CD3 treatment. However, the precise mechanism by which anti-CD3 treatment induces tolerance is not understood. Regulatory/suppressor cells are key to peripheral control of potential autoreactive T lymphocytes which escape thymic deletion [Van Kaer, 2010; Tsai, 2011] and it is assumed that persisting tolerance after anti-CD3 treatment is dependent upon increased regulatory/suppressor activity. Increased numbers of CD4+ and CD8+ regulatory cells have been reported in animals and T1DM patients after anti-CD3 treatment [Nishio, 2010; Waldron-Lynch, 2012; Esplugues, 2011; Bisikirska, 2005].

1.2.2. Type 1 Diabetes Mellitus (T1DM)

Diabetes mellitus (DM) is a metabolic disorder characterised by chronic hyperglycaemia due to deficient production of/or response to insulin. A classification system developed by an international Expert Committee on the Diagnosis and Classification of DM working under the sponsorship of the American Diabetes Association (ADA) recognises four types of diabetes mellitus (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2003)). Type 1 Diabetes Mellitus (T1DM) has been described as diabetes characterized primarily by an absolute deficiency of insulin. Patients with T1DM represent approximately 5% to 10% of all patients with DM.

Type 1 diabetes becomes clinically apparent after a preclinical period of varying length, during which progressive loss of β-cells in the pancreatic islets impairs the ability to maintain blood glucose levels within a physiologic range [Rowe, 2011]. The disease is classified in two subtypes: 1A, which includes the common, immune-mediated forms of the disease; and 1B, which includes non-immune forms [Concannon, 2009]. In autoimmune T1DM, roles for both the innate and adaptive arms of the immune system in the pathogenesis have been postulated, though most recent work has focused on the role of cytotoxic T cells [Coppieters, 2012].

The events triggering the development of an autoimmune attack on the β-cell are unclear. Type 1 diabetes mellitus occurs most often in children, adolescents, and young adults, but

can present at any age. It has been reported that the age of onset is decreasing as cases are doubling for children under five years of age [Patterson, 2009]. Although T1DM aggregates in some families, it does not segregate with any clear mode of inheritance reflecting a complex interaction between environment and inheritance in determining individual risk of developing T1DM. Common viral infections may be a trigger in susceptible individuals [Van Belle, 2011; Coppieters, 2011].

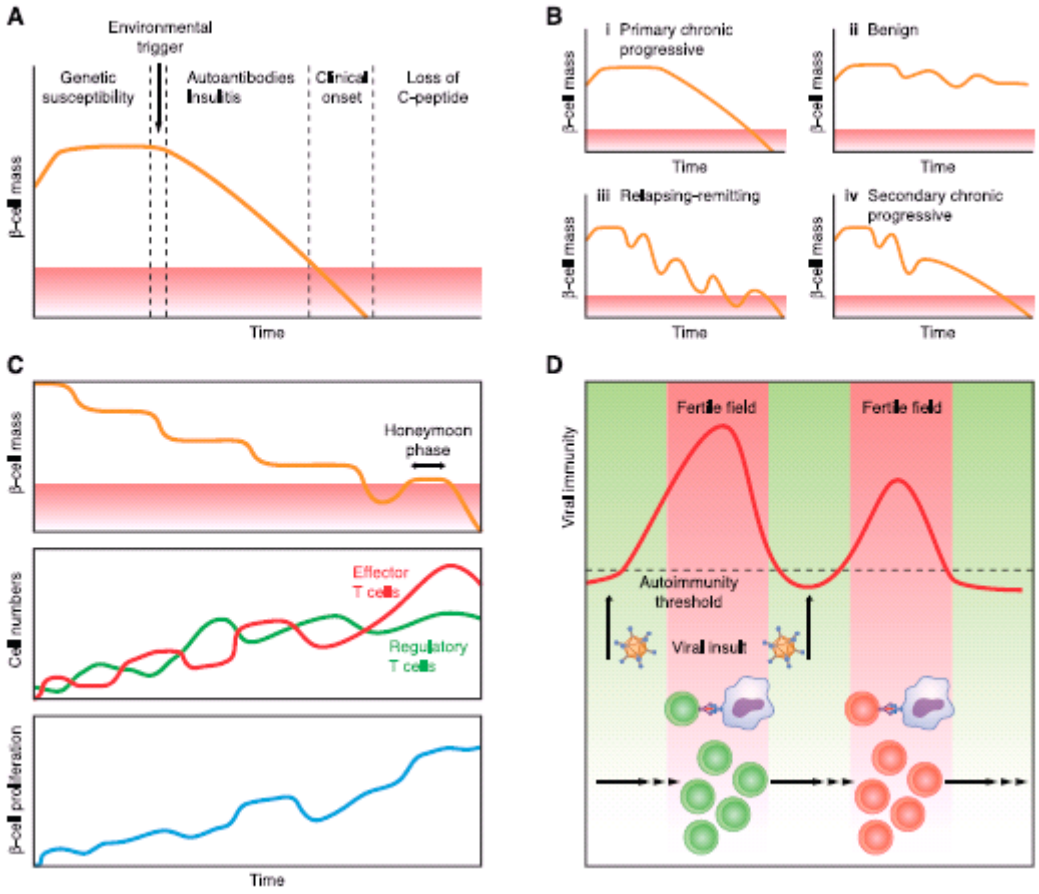
The histological hall mark of the pancreas in T1DM is a loss of β-cells. Analyses of pancreatic islets obtained post-mortem from recent onset T1DM patients suggest a defined sequence of insulitis (with mononuclear inflammatory cell infiltrate around and within islets) accompanied by morphologic changes in β -cells indicative of compensatory mechanism (hypertrophy) to maintain insulin secretion, followed by an absolute loss of β-cells [Rowe, 2011; Willcox, 2009]. In humans, in contrast to rodents, there is limited potential for expansion of β cell numbers in post-neonatal life, either from replication of existing cells or neogenesis from stem cells in the ductal epithelium [Cnop, 2011].

Autoantibodies against GAD, IA 2, IA 2β, and/or insulin are detectable in approximately 85% to 90% of patients with T1DM [Vermeulen, 2011]. Positive serology is a risk factor for progression to T1DM in first degree relatives of affected probands [Alves, 2012; Seidel, 1996]. Autoreactive CD8+ and CD4+ T lymphocytes can be detected in peripheral circulation and are directed to many of the same epitopes [Velthuis, 2010; Unger, 2011]. In diseased islets, cytotoxic CD8+ T cells are the most abundant population of immune cells at all stages of the insulitis. Macrophages (CD68+) are also present during both early and later stages of the insulitis, although in fewer numbers. CD20+ B cells are present in only small numbers in early insulitis and become more numerous as β cell death progresses [Rowe, 2011; Willcox, 2009].

Therefore, the net effect of autoimmune destruction of β cells coupled with little or no regeneration marks a progressive deterioration of glucose homeostasis, culminating in an absolute dependence on exogenous insulin replacement therapy. It is estimated that only 10-20% of β-cells are still functioning at the time of clinical diagnosis [Knip, 2002]. The rate of progression from normo-glycaemia, through pre-clinical impairment of glucose handling to insulin dependence is variable. Indeed, even 1-5 years after diagnosis, about 50% of T1DM show clinically meaningful β-cell function [Palmer, 2009].

The destruction process of β-cells is not a continuous phenomenon and it has been argued that T1DM is a relapsing-remitting disease [Von Herrath, 2007] as longitudinal studies suggested that the decline in β-cell function follows a saw-tooth profile (Figure 2).

Figure 2 Timelines for Type 1 Diabetes



[Van Belle, 2011]

There are currently no curative treatments for T1DM. Current management of T1DM is by lifelong insulin replacement. Clearly safe, well-tolerated strategies to identify and intervene on the autoimmune process involving the destruction of the pancreatic islets represent a major unmet clinical need. Immuno-modulation coupled with other therapeutic strategies such antigen tolerizing approach/regenerative medicine might offer a radical change in the management of new onset T1DM.

1.2.3. Otelixizumab (GSK2136525) is a non-mitogenic, non-depleting anti-CD3 monoclonal antibody (mAb)

Otelixizumab is a humanized, Fc-modified, non-mitogenic anti-CD3 monoclonal antibody (mAb) directed against the ε domain of the human lymphocyte antigen CD3. Otelixizumab has the same amino acid sequence as ChAglyCD3, an anti-human CD3 monoclonal antibody derived from the rat anti-human CD3 mAb YTH12.5. ChAglyCD3 features a mutation of the human IgG1 constant region to remove the only attachment site for N-linked carbohydrate (N297A). This aglycosyl mutation appears to eliminate mitogenicity in the presence of human serum. Studies of the biochemical and biological properties of ChAglyCD3 and otelixizumab have shown that they are analytically comparable and functionally indiscriminate. It has been postulated that otelixizumab may

have a dual mechanism of action. First, activated pathogenic T cells are eliminated or inhibited by redistribution, depletion, or down modulation of the CD3/T cell receptor (TCR) complex. Second, "operational" tolerance is established by the generation and/or expansion of T regulatory cells that actively control the pathogenic autoimmune response.

1.2.4. Previous human experience with GSK2136525 and other anti-CD3 antigen binding therapeutic antibodies

A murine monoclonal IgG2a antibody against CD3ε (Orthoclone, OKT3) has been in clinical use since 1986 for the treatment of acute, glucocorticoid resistant rejection of allogenic renal, heart and liver transplants. OKT3 is associated with infusion reactions and the formation of neutralising auto-drug antibodies which have limited its clinical use and investigation beyond transplantation. The ability of CD3-specific antibodies to induce T-cell proliferation and cytokine production *in vitro* is closely tied to their cross-linking ability to bind to FcRs on monocyte/macrophages and natural killer cells [Nepom, 2011]. A number of second generation anti-CD3 antibodies were developed in an attempt to reduce the immunogenicity and infusion reactions: visilizumab (Hu 291), teplizumab (hOKT31(Ala-Ala)) and otelixizumab (ChAglyCD3) [Kaufman, 2009]. Numerous clinical trials have been conducted with these agents in a variety of autoimmune diseases including ulcerative colitis (visilizumab), [Sandborn, 2010], new onset type 1 diabetes (otelixizumab [Keymeulen, 2005], teplizumab [Herold, 2005; Sherry, 2011], psoriasis [Wiczling, 2010]) and rheumatoid and psoriatic arthritis (otelixizumab and teplizumab) [Utset, 2002].

1.2.5. Anti-CD3 treatment in autoimmune (Type 1) Diabetes Mellitus (T1DM)

1.2.5.1. GSK2136525 (Otelixizumab)

In a randomised placebo-controlled academic-led Phase II proof-of-concept study (BDR study), investigating otelixizumab administered as 6 short daily intravenous infusions of 8 mg per day, the decline in stimulated C-peptide, a validated marker of functioning insulin-producing β -cells in the pancreatic insulae was observed for a period of up to 1 year in NOT1DM patients [Keymeulen, 2005]. In a follow-up, post-hoc analysis, the observed reduction in daily insulin dose in the treated group was maintained for up to 4 years in a subset of patients [Keymeulen, 2010]. However, this regimen was associated with consistent first-dose infusion reactions typical of CRS and EBV reactivation as measured by significant increased viral load (21 out of 22 subjects had evaluable samples) accompanied by clinical symptoms of mononucleosis in 75% of patients dosed with otelixizumab. In contrast, an 8-day intravenous short infusion regimen consisting of much reduced daily doses 0.1, 0.2, 0.3 mg respectively, followed by 5 daily doses of 0.5 mg of otelixizumab, failed to show any efficacy in a similar patient group in the Phase III study DEFEND-1. As a consequence, the replicate Phase III study DEFEND-2 was stopped for futility and terminated. In these latter studies symptoms related to CRS were generally mild and well tolerated and no clinical symptoms of mononucleosis or increases in EBV viral load were observed in either study. In addition, the acute tolerability of various intravenous infusion regimens of otelixizumab in T1DM patients were investigated in the RT4 and Therapeutic Evaluation of Different Multi-Dose

Regimens in Type 1 Diabetes Mellitus (TTEDD) studies. Further details of the individual studies can be found in the Investigators Brochure [GlaxoSmithKline Document Number RM2008/00587/05].

Efficacy in NOT1DM patients has been demonstrated with another therapeutic antibody, teplizumab, (Macrogenics), (hu OKT3y1ala-ala) fully humanised monoclonal Ab also targeting human CD3ε with similar potency. In a randomised, controlled but open-label study investigating a 14-day regimen of teplizumab consisting of nominal (per 70 kg) daily short infusions of 0.1, 0.4, 0.8, and 1.6 mg respectively, followed by 10 daily short infusions of 3.2 mg (cumulative nominal dose of 34.9 mg), the decline in stimulated C-peptide, was similarly halted for a period of up to 1 year in NOT1DM patients. A treatment difference was maintained for up to 2 years, although C-peptide appeared to be declining at the same rate in the treated and placebo group at this time [Herold, 2005]. While consistent, but manageable first dose reactions were observed, no EBV reactivation has been reported. In a subsequent Phase III randomised placebo-controlled study in a similar population, lower dose regimens were investigated. Doses up to a nominal daily dosage regimen of 0.1, 0.2, 0.4, 0.8 mg respectively, followed 10 daily infusions of 1.6 mg (cumulative nominal dose of 17.5 mg), failed to show a statistically significant change in HbA1c, insulin dose, or stimulated C-peptide [Sherry, 2011]. Exploratory post-hoc analysis revealed some trends in slowing C-peptide decline and 5% of patients in the teplizumab treated groups were completely off insulin at one year, compared with none in the placebo group (p=0.03). Furthermore, a greater proportion of those in the highest dose group had better β-cell preservation as measured by an increase in the area under the curve (AUC) for stimulated C-peptide levels compared with placebo (40% versus 28%, P=0.046). β-cell preservation was observed to be improved in patients of age 8-11 years old. Efficacy benefit was also greater for those patients who started on treatment sooner after their diagnosis (within six weeks of the reported date of T1DM diagnosis). CRS symptoms were classified as mild and no EBV reactivation was reported.

2. OBJECTIVES AND ENDPOINTS

Primary Objectives (Safety)	**Primary Endpoints (Safety)**
• To assess the effect of a single course of otelixizumab treatment on the acute and long term safety and tolerability of otelixizumab in NOT1DM patients.	• Incidence of adverse events (AEs) particularly those related to Cytokine release syndrome (CRS). • Epstein-Barr virus (EBV) reactivation over Day 21 to Month24. • Changes in laboratory values, electrocardiograms (ECGs) and vital signs over Day 14 to Month 24.
Secondary Objectives (Pharmacokinetic)	**Secondary Endpoints (Pharmacokinetic)**
• To assess the pharmacokinetics of repeat dose administration of otelixizumab over 14 days in NOT1DM patients.	• Free serum otelixizumab concentrations over Days 1-14 and summary PK parameters.
Secondary Objectives (Efficacy)	**Secondary Endpoints (Efficacy)**
• To assess the effect of a single course of otelixizumab treatment on the rate of decline of pancreatic β-cell function over 24 months in NOT1DM patients.	• Change from baseline in C-peptide and glucose AUC (0-120) after a Mixed Meal Tolerance Test at Month 3, 6, 12, 18 and 24.
• To assess the effect of a single course of otelixizumab treatment on the rate of decline of C-peptide response and insulin sensitivity of β-cell function determined after a hyperglycemic clamp over 24 months in NOT1DM patients.	• Change from baseline in C-Peptide and glucose AUC hyperglycemic phase [H60 to H140 minutes] and insulin sensitivity (IS) index after a hyperglycemic clamp at Months 6 and 24.
• To assess the effect of a single course of otelixizumab treatment on exogenous insulin use for otelixizumab over 24 months in NOT1DM patients.	• Change from baseline in mean daily insulin use over 7 consecutive days during the week preceding all visits and phone calls.
• To assess the effect of a single course of otelixizumab treatment on glycaemic control over 24 months in NOT1DM patients.	• Change from baseline in HbA1c level. • Body weight Day -1, Months 12-24. • Hypoglycemic and hyperglycemic events over Months 1-24.

Secondary Objectives (Pharmacodynamic)	**Secondary Endpoints (Pharmacodynamic)**
• To assess the effect of a single course of otelixizumab treatment on the time course and magnitude of CD4 + and CD8+ cells and CD3 binding and saturation on all these cells during repeat dose administration of otelixizumab over 14 days in NOT1DM patients.	• Relative change from baseline (%) in CD4+ and CD8+ cells, free CD3 and bound otelixizumab on CD4+ and CD8+ cells on Days 1 through 14.
• To assess the effect of a single course of otelixizumab treatment on the immunogenicity of otelixizumab in NOT1DM patients.	• Change from baseline in anti-drug antibody levels at Months 3 and 6.
Exploratory Objectives*	**Exploratory Endpoints***
• To assess the effect of a single course of otelixizumab treatment on circulating lymphocyte populations over 24 months in NOT1DM patients.	• Change from baseline in absolute lymphocyte counts and ratios in some or all, but not limited to subsets (CD3+ CD4+, CD3+ CD8+, and CD19+ cells) and phenotype (eg effector, memory, regulatory T cells, eg CD45RA, CCR7+) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on circulating lymphocytes such as regulatory T cell numbers (as quantified by CD3 and demethylated FoxP3 expression) and Th17 cells over 24 months in NOT1DM patients.	• Change from baseline in cell-type specific methylation marker expression in some or all, but not limited to CD3, FoxP3 and Th17 in whole blood over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on absolute numbers and ratios of circulating antigen specificCD8+ T cells over 24 months in HLA-A2^{+} NOT1DM patients.	• Change from baseline in absolute numbers and ratios of HLA-A2-restricted CD8 T lymphocytes reactive to specific auto-antigens (by multimer) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on frequency of cytokine-producing antigen specific T cells over 24 months in NOT1DM patients.	• Change from baseline in frequency of cytokine producing cells following in vitro stimulation with auto-antigens and viral antigens (by ELISPOT) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on serum auto-antibodies titers and serum analytes associated with treatment or autoimmune pathology over 24 months in NOT1DM patients.	• Change from baseline in auto-antibody titres (using a panel of common auto-antibodies associated with T1DM antigens and possibly other auto-antigens) and serum analytes (such as cytokines/ chemokines) during the first 14 days of treatment and over Week 6 to Month 24.

Exploratory Objectives*	**Exploratory Endpoints***
• To assess the effect of a single course of otelixizumab treatment on clonal repertoire of circulating T cell populations and/or transcriptomic gene expression changes over 24 months in NOT1DM patients.	• Change from baseline in T cell clonal repertoire by TCR deep sequencing over Day 6 to Month 24. • Change from baseline in transcriptomic gene expression profile(s) by micro-array and/or alternative equivalent technologies including RNA sequencing at selected timepoint(s) post dosing.
• To assess the effect of a single course of otelixizumab treatment on β-cell death over 24 months in NOT1DM patients.	• Change from baseline in serum by measuring relative levels of unmethylated *INS* DNA and/or other biomarkers for β-cell death in serum over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on suppression activity of circulating T lymphocytes over 24 months in NOT1DM patients.	• Change from baseline in relative levels of T lymphocyte suppression using micro suppression assay over Week 6 to Month 24. Suppression activity may be further evaluated by adapting assay conditions possibly through adding and/or blocking of stimuli.
Follow up Objectives	**Follow up Endpoints - Data from month 36 (if available) or final follow-up. This will only be applicable for patients past month 24**
• To assess long term safety follow-up with otelixizumab treatment.	• Significant adverse events. • Severe (as per ADA classification, Appendix 7) hypoglycemic events which occurred following Month 24 visit (if available) until final follow-up. • Severe hyperglycemic events which occurred following Month 24 visit (if available) until final follow up. • Mean daily insulin use over 7 consecutive days preceding the call. • HbA1c results around time of the phone call.
*Samples will be collected and only analysed after review of safety endpoints	

3. STUDY DESIGN

3.1. Study Design Detail

The study is a multi-centre, single-blind (see Section 5.4), randomised, placebo-controlled 6 day repeat dose study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, efficacy and immunological profile of intravenously administered otelixizumab in New Onset Type 1 Diabetes Mellitus patients.

Approximately 40 patients will be dosed, in a dose escalation design exploring 4 dose cohorts (4 dose levels and placebo). At each dose cohort 8 patients will be randomised to otelixizumab and 2 patients to placebo.

Screening Period: Patients will be dosed within approximately 28 days of diagnosis (not more than 32 days). Insulin usage will be documented for approximately 7 days prior to Day -1. There will be a 7 - 21-day period from screening to admission to the clinic on Day -2 for the first overnight stay of the in-patient period, this time period will ensure appropriate time to review laboratory results prior to randomisation. During the screening period, total lymphocytes will be quantified on two occasions at least 3 days apart (one of the assessments may be performed on Day -1); lymphocytes must be confirmed as being within normal limits before administration of the first dose. All screening procedures are outlined in the Time and Events Table in Section 6.2.

Pre-Treatment Period: On Day -1 safety assessments will be performed as outlined in the Time and Events Table in Section 6.2. If the investigator is satisfied that the patient still meets the entry criteria they will be randomized to treatment and the hyperglycemic clamp procedure performed.

Treatment Period: Dosing will start on Day 1 and patients will remain in the unit as an in-patient for Days 1, 2 and 3 for intravenous dosing of study treatment.

Patients will be given the following flexible options for dosing on Days 4, 5 and 6:

- Option 1: Receive study treatment on an out-patient basis on any of Days 4, 5 or 6, if the Investigator is satisfied with the clinical condition of the patient. For these patients, safety monitoring will continue up to a minimum of 3 hours post-dose.

- Option 2: Patients will remain in the unit if there are any concerns about their clinical status, or if the patient prefers to remain in the unit for logistical reasons. Patients will be fully discharged from the hospital unit on Day 6 after completion of dosing and all study procedures. If the investigator considers additional safety monitoring is necessary, the patient will be asked to stay in the unit after Day 6 until they are in a satisfactory condition to be discharged.

CRS experienced from dosing to the resolution of symptoms and EBV clinical reactivation will be monitored in all the patients dosed and specific decision criteria will be used for dose escalation based on these assessments.

Within each cohort administration of study treatment for the first three patients will be staggered by at least three days across each centre.

Patients will continue to receive their usual standard of care including insulin while participating in the study.

Figure 3 shows a schematic of the overall study design.

Figure 4 shows a schematic of the study screening, dosing and follow up phases for all study patients.

3.2. Study Schematics

Figure 3 Overall Study Design

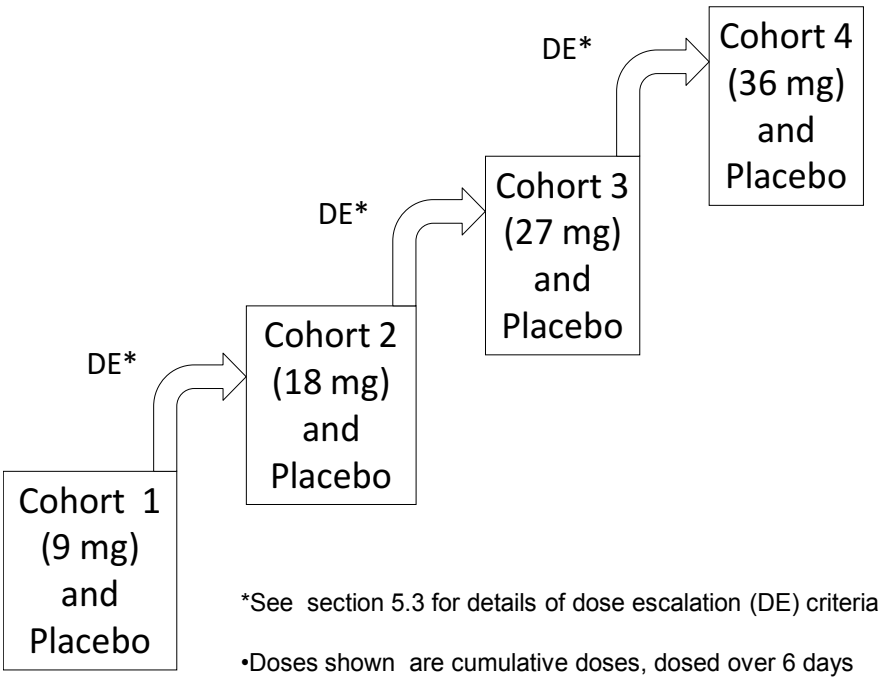
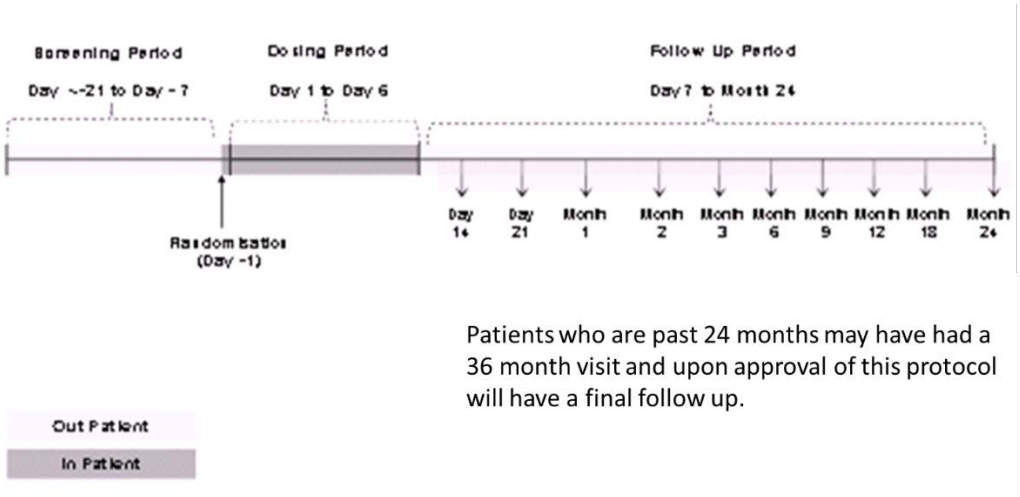


Figure 4 Study Visits Schematic

For study assessments see the Time and Events tables in Section 6.2



Note: Dosing on Days 4-6 inclusive may be performed on an out-patient basis, if judged acceptable on the basis of the clinical condition of the patient by the Investigator.

3.3. Discussion of Study Design

3.3.1. Design Rationale

3.3.1.1. Study Population

The study population is chosen to replicate the demographics of patients who showed least decline in β-cell function based on *post hoc* sub-group analyses in Phase II (BDR) and Phase III (Defend 1 & 2) studies with otelixizumab. See Section 4.2.1 for full inclusion criteria. Patients of paediatric age (16 and 17 years old) will be included as there is a high prevalence of the disease in this age group.

3.3.1.2. Study Duration

Data from the literature at the origin of the study design identified a causal relationship between the degree of immunosuppression and an increased incidence of EBV related Post Transplant Lymphoprolerative Disorders (PTLD) and for this reason a long-term follow-up (60 months) was implemented at the start of the study. The interim analysis data which emerged from this study showed a prompt regain of immune competence observed in treated subjects and consequent rapid resolution of EBV reactivation, both clinically and virologically. The long term EBV related PTLD risk, as observed in solid organ transplant on a chronic immune suppression therapy, is negligible. As a result, the overall study duration for each subject will be 24 months, except for those patients who have already passed the 24 month or 36 month follow up, in which case they will have a final follow up communication (telephone call or visit) as soon as possible following approval of this amendment 08 of the protocol. Further details are provided in the Study Reference Manual (SRM). If further follow up is required, the Investigator will request that the patient visits the site. See Section 9.3 for a description of analysis considerations.

3.3.1.3. Measurement of beta cell mass and function, disease progression and predictive biomarkers

The assessment of the number and function of β-cells *in vivo* is necessarily indirect and based on static or dynamic measures of the concentration of β-cell products in the peripheral circulation. An international D-Cure workshop in 2007 recommended the measurement of stimulated C-peptide under standardised conditions, and particularly the 2-h area under the curve (AUC) during a mixed meal tolerance test (MMTT) as the primary endpoint in interventional trials evaluating therapies aimed at preserving or improving β-cell function in T1DM [Cernea, 2009]. The MMTT test has been validated to assess β-cell function by measuring residual C-peptide secretion as an appropriate outcome for therapeutic trials in early T1D [Greenbaum, 2008]. Validated measures of β-cell function from the MMTT test include fasting and 2-h insulin and C-peptide levels, and the calculated AUC for each analyte during the test. Further parameters are generated by a mathematical model of β-cell function and insulin secretion rate (ISR) calculated by deconvolution analysis of C-peptide levels, and β-cell glucose sensitivity [Mari, 2008]. Both peak C-peptide response and the C-peptide AUC during the MMTT test are highly reproducible and validated against the Glucagon Test [Greenbaum, 2008].

By assessing β-cell function after MMTT, some estimate of the rate of decline of β-cell mass can be made. The majority of the data have been derived from the control/placebo arm of interventional studies and likely reflects disease progression in patients whose insulin therapy has been optimized. Recent studies employing MMTT at baseline, 3, 6, 9 and 12 months post randomization in patients recruited within 3 months of diagnosis report an approximate linear decline in C-peptide AUC over the period from 3-12 months [Herold, 2002, Herold, 2005, Sherry, 2011]. In some of these studies, the initial rate of decline of β-cell loss in these studies (over the period from baseline to 3 months) is reduced in the control patients (or even increased above baseline) and this has been attributed to the effects of tighter glycaemic control reducing the possible toxic effects of hyperglycaemia and dyslipidaemia on β-cell function.

A two-phase glucose-clamp procedure will be also performed at baseline and 6 and 24 months post-treatment (-180 to 0 minutes), when euglycemia (60-90 mg/dl) will be maintained by intravenous insulin infusion to keep low endogenous insulin secretion and during the second phase (0 to 140 minutes), blood glucose levels will be increased and maintained between 180-240 mg/dl in order to test and stimulate the endogenous residual β-cell secretory capacity. This methodology which has been used in previous studies [Keymeulen, 2005] should allow us to characterize the second phase of insulin secretion (+60/+140 min post start of Hyperglycaemic Phase) with a lower degree of intra and inter-individual variability in comparison with the MMTT.

3.3.2. Dose Rationale

The proposed daily and cumulative doses and duration of treatment in this study are supported by the existing clinical safety data obtained in the original proof of concept study in NOT1DM patients (BDR study), where 6 day regimens of short daily infusions of 8 mg, and individual daily doses of up to 24 mg, were investigated (cumulative dose 48-64 mg).

The mechanism of action of anti-CD3 mAb therapy and the degree and duration of pharmacology necessary for clinical benefit is not fully understood. However, the weight of clinical evidence obtained in NOT1DM patients, based on the cumulative experience with otelixizumab and teplizumab (see Section 1.2), suggests a high degree of CD3 target engagement and thus a relatively low level of free CD3 antigen on peripheral blood T-lymphocytes (<10%) during the dosing period may be required to achieve a demonstrable effect on stimulated C-peptide secretion and insulin production. In addition, this level of blockade was required for effective inhibition of a range of human lymphocyte proliferative responses *in vitro* - see the Investigators Brochure. The lowest proposed dosage regimen (9 mg total dose) is anticipated to maintain an average of ~ 10% free CD3 antigen on peripheral blood T-lymphocytes during the dosing interval. Higher doses are anticipated to reduce free CD3 to less than 10% for the entire dosing period. A 6 day dosing regimen, as used in the BDR study where efficacy was demonstrated, was also chosen for this study.

The majority of all reactions, and all severe infusion-reactions with otelixizumab in the BDR study occurred during the first 3 days of treatment [Keymeulen, 2005]. In the TTEDD study, when the infusion time was reduced from 2 hours to 30 or 15 mins, there was a corresponding increase in both peak serum cytokine levels and the incidence of CRS-related adverse events.

An overview of the regimens proposed for each cohort is presented below in Table 1. The slow infusions for the first three days of treatment are anticipated to improve the tolerability associated with administration of otelixizumab relative to the short infusion regimens investigated in previous studies.

Table 1 Dosage Cohorts

Cohort	Cumulative Dose (mg)	Day 1			Day 2			Day 3			Days 4-6		
		D (mg)	R (mg/h)	T. (h)	D (mg)	R (mg/h)	T. (h)	D (mg)	R (mg/h)	T. (h)	D (mg)	R (mg/h)	T. (h)
1	9	1.5	0.167	9*	1.5	0.25	6	1.5	0.5	3	1.5	1.5	1
2	18	3	0.25	12	3	0.5	6	3	1	3	3	3	1
3	27	4.5	0.375	12	4.5	0.75	6	4.5	1.5	3	4.5	4.5	1
4	36	6	0.5	12	6	1.2	6	6	2	3	6	6	1

NB: D = daily dose, R = rate of infusion, T = infusion time or duration

* The 9mg (Cohort 1) infusion time will be 9 hours on Day 1

If there is any need to reduce the infusion rate or temporarily stop the infusion, the Investigator should first consult with the Medical Monitor who will consult with the Sponsor. However, the Investigator has the flexibility to reduce or temporarily stop the infusion immediately (with no prior consultation with the Medical Monitor), if there are any immediate safety/tolerability concerns. In this case the Investigator must inform the Medical Monitor as soon as possible after reducing or stopping the dosing.

3.4. Risk Management

Table 2 Summary of Key Issues, their Impact and Strategy to Mitigate Risk

Potential Risk	Summary of Data	Impact- Eligibility Criteria	Strategy-Monitoring/Stopping Criteria
Cytokine Release Syndrome (CRS) (chills/rigors, fever, nausea, vomiting, diarrhoea, arthralgia, myalgia, hypotension, headache)	• CRS is a well-known consequence of anti-CD3 therapy when administered via intravenous injection or infusion. • Additionally, with high doses of otelixizumab (e.g. 48-64mg cumulative tested in the BDR study), liver enzyme elevations occurred and were considered to be possibly associated with CRS.	Patients with on-going pyrexial infections and with history of significant systemic infection during the 6 weeks prior to the first dose of study drug will not be enrolled. Only patients with normal liver function will be included, defined as AST or ALT >2.0 ULN	• **Slow infusion;** The infusion of the first dose in each cohort will be conducted over 12 hours. (except for cohort 1 which will last 9 hours). The reduction of the infusion time will be staged. • **Inpatient clinical observation;** at a minimum, patients will be in-house for the first 3 days of the infusion period. Days 4, 5 & 6 may be on an out-patient basis with safety monitoring for at least 3 hours post dose. Patients will be discharged only after Investigator clinical approval. The facilities will be located within a hospital with provision for Intensive Care facilities and with immediate access to resuscitation and emergency care. • **Prophylaxis CRS;** prophylaxis (see Section 5.10.1) will be administered in conjunction with adequate oral hydration prior to and during dosing with otelixizumab • **Withdrawal and stopping criteria;** Individual withdrawal criteria are in place (see Section 5.3). • **Dose Escalation**: dose escalation is based on a strict CRS AE criteria (see Section 5.3)

Potential Risk	Summary of Data	Impact- Eligibility Criteria	Strategy-Monitoring/Stopping Criteria
Allergic hypersensitivity reactions	• Allergic hypersensitivity reactions to biologics are relatively common and in practice may be difficult to differentiate from CRS. • Allergic/hypersensitivity reactions may include the following: flushing, pruritus, rash, hives, bronchospasm, dyspnea, diaphoresis, abdominal cramping. • Angiodema, rash, including urticaria, was seen in otelixizumab studies in patients with T1DM. No anaphylaxis or anaphylactoid reactions have been seen to date.	Patients with prior allergic reaction, including anaphylaxis, to any human, humanised, chimeric, or rodent antibody will not be enrolled.	• An anti-histamine given as part of CRS prophylaxis may decrease the occurrence of rash. • Medical management of more severe allergic reactions as per local clinical guidelines • Individual withdrawal criteria and Study stopping criteria are in place (see Section 5.3)

Potential Risk	Summary of Data	Impact- Eligibility Criteria	Strategy-Monitoring/Stopping Criteria
Epstein-Barr virus (EBV)	• Epstein-Barr virus (EBV) is a widespread human gamma herpes-virus. • Primary infection with EBV usually occurs asymptomatically, where after the virus persists for life in a latent form in B lymphocytes. • The initial expansion and reactivation of these latently infected B lymphocytes is controlled by specific CD8+ major cytotoxic T-lymphocyte (CTL) responses. • EBV reactivation is accompanied by one or more of the following: rash; elevated liver function tests, other signs and symptoms consistent with acute infectious mononucleosis (pharyngo-laryngeal pain, acute tonsillitis, lymphadenopathy, fever). • The most sensitive confirmation of EBV reactivation is by detecting an increase in viral copy number (by RT-PCR). • In patients on chronic immune-suppression persisting EBV reactivation can be detected. Chronic EBV reactivation is thought to be causal for early post-transplant lymphoproliferative disorder (PTLD) which may occur in up to 30-40% of patients chronically maintained on high dose immunosuppression. • In studies with otelixizumab in patients with NOT1DM an increased incidence of transient EBV reactivation with regimens employing higher daily doses has been observed (i.e. 48-64mg cumulative tested in the BDR study). Rapid immune response was evident and full immunity to EBV was restored with no evidence of recurring viremia. Maximum EBV levels occurred around Week 3 and decreased to baseline around Month 3. • As daily dose increases, so the degree of lymphopenia increases and TCR/CD3 surface expression declines, resulting in approximately 90% reduction in surface expression of TCR/CD3 of 90% sustained.	Patients within 3 months of evidence of acute/active EBV infection (e.g) • Symptomatic • Positive EBV capsid Ab IgM in absence of a positive EBV EBNA Ab IgG • EBV viral load of >10,000 copies per 10^6 lymphocytes will not be enrolled in the study.	• Patients with previous history of immunosuppression and/or on active immunosuppressant therapy will be excluded from this study • Patients will be monitored for clinical symptoms of mononucleosis and changes in EBV viral load.

Potential Risk	Summary of Data	Impact- Eligibility Criteria	Strategy-Monitoring/Stopping Criteria
Abnormal Liver Chemistry	• In the Belgian Diabetes Registry study, administration of high cumulative doses of otelixizumab (48-64mg) have been temporally associated with abnormal liver chemistry thought to be due to increased cytokine release. In subsequent dose-finding studies conducted at lower doses, no trends with respect to changes in liver chemistry were observed.	Patients with history of liver diseases and/or persistent AST or ALT >2.0 ULN will not be included	Liver chemistry will be monitored daily for the duration of treatment to detect any unanticipated liver event. Liver chemistry individual withdrawal and study stopping criteria and follow-up are in place (Section 5.3).
Progressive Disease			Intensive monitoring and care will be provided according to current standards of care for patients with type 1 diabetes. Diabetes care will be at the discretion of the investigator and may include consultations with a nutritionist or dietician and/or a diabetes educator according to the local institution's guidelines for NOT1DM. Study centres are expected to work with each subject to optimize glycaemic control as per standard of care, with a target HbA1c less than 7% (53 mmol/mol). HbA1c will not be communicated to the trial centre by BDR unless HbA1c is ≥ 7% . Diabetes management will be directed towards helping each subject reach this target or come as close to it as possible.
Preterm birth	• Preclinically, GLP reproductive toxicity studies have not been completed, however; [Gomez-Lopez N , 2016] reported that pregnant B6 mice dosed with an antimouse CD3 monoclonal antibody (mAb) on Gestation Day 16.5 (late gestation) led to an increased frequency of preterm birth and increased pup mortality thought to be due to T-cell activation, however, no data to demonstrate pharmacology was provided. Clinically, one subject in a GSK clinical trial (RAO112438) was exposed to the investigational product before conception and during the first trimester of pregnancy. One hundred ninety nine (199) days after the last dose of IP, the subject developed Grade 2 or moderate impending parturition prematurus and Grade 2 or moderate hematemesis. The investigator considered that there was no reasonable possibility that the uterine contractions during pregnancy and hematemesis may have been caused by investigational product. After 37 weeks	Eligibility criteria includes contraception requirements for female subjects and male subjects with female partners of child-bearing potential.	Pregnancy will be monitored with serum pregnancy tests at all assessments.

Potential Risk	Summary of Data	Impact- Eligibility Criteria	Strategy-Monitoring/Stopping Criteria
	and six days gestation, the subject gave birth to a female live infant. There were no birth defects.		
Opportunistic Infections	• Mild to severe infections that generally respond to customary treatment have occurred in otelixizumab-treated subjects. There have been no opportunistic infections reported with otelixizumab in subjects with T1DM.	Patients who are immunocompromised (e.g. HIV positive patients) or those on immunosuppressive medications may be at higher risk of infections are excluded from the clinical study with otelixizumab in T1DM.	All safety data will be reviewed by the Safety Review Team per current practices.
JC Virus (JCV)	• JCV reactivation has not been observed with other anti-CD3 MAbs; however, this has been an area of interest with other types of monoclonal antibodies.	Patients with previous history of immunosuppression and/or on active immunosuppressant therapy are excluded from the study.	

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 40 subjects will be enrolled into the study in order to have 10 patients complete dosing on all four cohorts (stopping criteria permitting). Ten (10) subjects will be enrolled in each cohort, 8 on otelixizumab and 2 on placebo (4:1 ratio). Each cohort will comprise a new set of subjects.

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment at the discretion of the Sponsor in consultation with the Investigator.

The decision whether to replace the patient will be based on the reason for premature discontinuation (see Section 4.5 for further information).

Replacement subject numbers will be assigned to the additional subjects.

4.2. Eligibility Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigator Brochure.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male or female aged between 16 and 27 years of age inclusive, at the time of signing the informed consent.

   NOTE: Subjects aged 16 to 17 years must be Tanner Stage ≥2 (see SRM). All subjects must weigh at least 31 kg.

2. Diagnosis of diabetes mellitus according to ADA and WHO criteria and consistent with Type 1a (autoimmune) DM, with an interval of approximately 28 days (not more than 32 days) between the initial diagnosis and the first dose of study drug). Written documentation of the diagnosis of DM, including the date of diagnosis, must be obtained from the diagnosing physician.
3. Currently requires insulin treatment for T1DM and has received insulin therapy for at least 7 days prior to screening.
4. Positive for at least one autoantibody associated with T1DM: antibody to glutamic acid decarboxylase (anti GAD), antibody to protein tyrosine phosphatase-like protein (anti IA 2), antibody to islet-cell antigen (ICA) or ZnT8 Autoantibody.

5. Evidence of residual functioning β cells as measured by mixed meal stimulated C-peptide peak level ≥ 0.2 nmol/L.
6. A female subject is eligible to participate if she has a negative pregnancy test as determined by a serum hCG test at screening or prior to dosing AND
   - Agrees to use one of the contraception methods listed in Section 4.3.1. Female subjects must agree to use contraception for 2 weeks prior to dosing and for 60 days after the last dose of study drug.
   - OR has only same-sex partners (refrains from heterosexual intercourse), when this is her preferred and usual lifestyle.
7. Male subjects with female partners of child-bearing potential must agree to use one of the contraception methods listed in Section 4.3.1. This criterion must be followed from 2 weeks prior to dosing and for 60 days after the last dose of study drug.
8. Willing to follow the procedures outlined in the protocol.
9. AST and ALT <2xULN; alkaline phosphatase and bilirubin ≤1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
10. Subjects eligible for enrolment in the study must meet all of the following criteria:
    - QTc <450msec *or*
    - QTc <480msec for patients with bundle branch block

The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF), or another method, machine or manual overread.

- For subject eligibility and withdrawal, QTcF will be used.
- For purposes of data analysis, QTcF will be used as primary.

The QTc should be based on single or averaged QTc values of triplicate electrocardiograms (ECGs) obtained over a brief recording period.

11. Screening total lymphocyte counts within the normal range in two separate samples taken at least three days apart (eg screening and Day -1).
12. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form. In the case of minors (under 18 years) written informed consent must also be obtained from a parent or Legally Acceptable Representative (LAR).

4.2.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. A positive pre-study Hepatitis B surface antigen or core antibody or positive Hepatitis C antibody result within 3 months of screening.

2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
3. A positive test for HIV 1 and/or 2 antibody.
4. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
5. Exposure to more than four new investigational drugs within 12 months prior to the first dosing day.
6. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or CRO/GSK Medical Monitor, contraindicates their participation.
7. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 3 month period.
8. Lactating females.
9. Subject is mentally or legally incapacitated.
10. History of thrombocytopenia.
11. The subject has received immunization with a vaccine within 4 weeks before the first dose of study drug or requires a vaccine within 30 days after the last dose of study drug
12. The subject has had significant systemic infection during the 6 weeks before the first dose of study drug (e.g., infection requiring hospitalisation, major surgery, or i.v. antibiotics to resolve; other infections, e.g., bronchitis, sinusitis, localised cellulitis, candidiasis, or urinary tract infections, must be assessed on a case-by-case basis by the investigator regarding whether they are serious enough to warrant exclusion).
13. Current or prior malignancy, other than non-melanoma skin cancer.
14. Patient has undergone a splenectomy
15. Radiological evidence of active tuberculosis (TB).
16. Significant and/or active disease in any body system likely to increase the risk to the subject or interfere with the subject’s participation in or completion of the study. Examples of significant diseases include, but are not limited to, coronary artery disease, congestive heart failure, uncontrolled hypertension, renal failure, emphysema, history of bleeding peptic ulcers, history of seizure(s), addiction to illicit drugs, and alcohol abuse.
17. Clinically significant (based on Investigator’s discretion in consultation with the Medical Monitor if second opinion required) abnormal laboratory values during the screening period, other than those due to T1DM. A clinically significant abnormal value will not result in exclusion if, upon retest, the abnormality is resolved or becomes clinically insignificant.
18. Positive EBV capsid Ab IgM in absence of a positive EBV EBNA Ab IgG

19. EBV viral load of >10,000 copies per 10^6 peripheral blood mononuclear cells (PBMCs) as determined by quantitative polymerase chain reaction (qPCR)..
20. IgG negative for EBV.
21. A positive result on a test for syphilis; and if result of the first test is positive, then a confirmatory test using another method will be performed.
22. Have used any atypical antipsychotic drug (e.g., risperidone [Risperdal], quetiapine [Seroquel], or clozapine [Clozaril]) within the 30 days before signing the ICF.
23. Have previously received otelixizumab or any other anti CD3 monoclonal antibody, e.g., OKT3 (muromonab or Orthoclone), ChAglyCD3, or hOKT3γ1 (ala ala), and are not willing to refrain from using any such antibody for the planned duration of study participation (2 years after the last dose of study drug).
24. Previous or current exposure to biologic cell-depleting therapies (e.g. anti-CD11a, anti-CD22, anti-CD20, anti-BLyS/BAFF, anti-CD3, anti-CD5, anti-CD52) including investigational agents, and planning to use any such antibody for the planned duration of study participation (2 years after the last dose of study drug).
25. Predisposition to thromboembolic disease, or thromboembolic event (excluding superficial) in the past 12 months.
26. Is currently receiving corticoid treatment or has received systemic corticoid treatment within a month of screening.
27. History of Graves disease
28. Prior allergic reaction, including anaphylaxis, to any human, humanised, chimeric, or rodent antibody.
29. Have undergone any major surgical procedure within 30 days before the first dose of study drug, and/or planning to undergo any such surgery within 3 months after the last dose of study drug.
30. Any condition or situation that, in the investigator's judgment, is likely to cause the subject to be unable or unwilling to participate in study procedures or to complete all scheduled assessments.

4.3. Lifestyle and/or Dietary Restrictions

4.3.1. Contraception Requirements

4.3.1.1. Female Subjects

Female subjects must not become pregnant for 2 weeks prior to dosing and for 60 days after and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of <1%. Female subjects with same sex partners (when this is their preferred and usual lifestyle) are not required to be abstinent or to use contraception.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of <1%

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of etonogestrel or levonorgestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label
- **Documented** male partner sterilization prior to **the female subject's entry** into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, cream or suppository).

NOTE: These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

4.3.1.2. Male Subjects

Male subjects with female partners of child-bearing potential must use one of the following contraceptive methods for 2 weeks prior to dosing and for 60 days after the last dose of study treatment:

- Condom plus partner use of a highly effective contraceptive (see list in Section 4.3.1.1).
- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

4.3.2. Meals and Dietary Restrictions

4.3.2.1. Alcohol

- During the dosing session, patients will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during the dosing session and around each visit.

4.3.2.2. Activity

Patients will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Patients may participate in light recreational activities during study visits (e.g., watch television, read).

4.3.2.3. Travel

Patients will also be advised to refrain from travelling to countries where there is a high incidence of infectious diseases within the first six months from start of treatment.

4.4. Screen and Baseline Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomized. To ensure transparent reporting of screen failure data (in order to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements), and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including:

- Demography,
- Reason for screen failure,
- Eligibility criteria,
- Serious adverse events.

4.5. Withdrawal Criteria and Procedures

A patient may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. Subjects who withdraw may be replaced to ensure that data on 40 subjects are obtained.

The decision on whether to replace the patient will be based on the reason for premature discontinuation, as described in Table 3.

Table 3 Patient replacement

Patients **will be** replaced if:	• The reason for withdrawal was not treatment related (e.g. patient withdrew consent for personal reasons). • Adverse event judged unrelated to treatment
Patients **will not be** replaced if:	• There is a lack of tolerability to treatment. • Individual or group stopping criteria are met. • Significant changes in any of the safety assessments (e.g. ECG, vital signs, laboratory tests, etc).

Decisions regarding patient replacement will be made in consultation with the Medical Monitor who will discuss with GSK.

Subjects that have received treatment and who withdraw should continue to undergo all safety assessments as per protocol including PK sampling, if possible. However, efficacy (hyperglycaemic clamp and MMTT) pharmacodynamic (PD) assessments may not always be performed. The need to perform PD assessments will be agreed on a case-by-case basis. The date of withdrawal must be recorded in the eCRF. If the patient agrees they will follow the original scheduled visit plan after withdrawal.

Refer to Section 5.3.1 for dose adjustment/stopping criteria.

Liver chemistry threshold stopping criteria have been designed to assure patient safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). See Section 5.3.4 for details.

4.6. Patient Completion

A completed patient is one who has completed Month 24.

The end of the study is defined as the last patient's last visit Month 24 or at final follow-up.

5. STUDY TREATMENT

5.1. Investigational Product and Other Study Treatment

	Study Treatment	
Product name:	GSK2136525: Otelixizumab Concentrated Solution for Infusion, 5 mg/mL	Placebo (0.9% w/v Sodium Chloride)
Dosage form:	Concentrated Solution for Infusion	Solution for Injection
Unit dose strength(s)/Dosage level(s):	Unit dose strength: 5 mg/mL provided as 1 mL solution per vial to be diluted to 0.1 mg/mL in 0.9% sodium chloride Dosage levels: variable	0.9% w/v Sodium Chloride/ Placebo level variable
Route/ Administration/ Duration:	Intravenous infusion via syringe pump; using only the infusion kits supplied by CRO/GSK, administration duration varies	Intravenous infusion via syringe pump; using only the infusion kits supplied by CRO/GSK, administration duration varies
Dosing instructions:	Study medication will be diluted to 0.1 mg/mL in 0.9% w/v sodium chloride to prepare otelixizumab solution for Infusion, 0.1 mg/mL. The 0.1 mg/mL solution is administered by intravenous infusion using a syringe pump and an in-line 0.2 micron filter by study personnel following specified regimens	0.9% w/v sodium chloride administered by intravenous infusion in the same manner as the active by study personnel following specified regimens
Manufacturer/ source of procurement:	Study medication supplied by GSK 0.9% w/v sodium chloride sourced locally by site	0.9% w/v sodium chloride sourced locally by site

5.2. Treatment Assignment

Patients will be assigned to receive either otelixizumab or matching placebo (4:1 ratio), prior to the start of dosing in each cohort by utilizing RAMOS (GSK's Registration and Ordering System). The randomization schedule utilized by RAMOS will be provided by Clinical Statistics (CS), using internal validated software. Once a randomisation number has been assigned it must not be re-assigned.

A description of each regimen is provided in Table 4:

Table 4 Treatment Assignment

Treatment	Cohort	Treatment Description	Daily Dose of Otelixizumab (mg)
A	1	Otelixizumab 9 mg	1.5
B	2	Otelixizumab 18 mg	3
C	3	Otelixizumab 27 mg	4.5
D	4	Otelixizumab 36 mg	6
P	1-4	Placebo	N/A

5.3. Patient Specific and Dose Escalation Stopping Criteria

5.3.1. Cytokine Release Syndrome Stopping Criteria

Cytokine Release Syndrome (CRS) experienced during the 6 days of dosing will be monitored specifically by the investigator according to the grading system presented in Table 5 and Section 7.1.5. In-stream real time data review will be utilised, so as to limit patient exposure unnecessarily, if stopping criteria are met.

Table 5 CRS AE Grading System

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Fever	38.0 - 39.0 degrees C	>39.0 - 40.0 degrees C	>40.0 degrees C for <=24 hrs	>40.0 degrees C for >24 hrs	Death
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs	Life-threatening consequences; urgent intervention indicated	Death
Diarrhoea	Increase of <4 stools per day over baseline.	Increase of 4 - 6 stools per day over baseline.	Increase of >=7 stools per day over baseline; incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Urgent medical intervention indicated	Life-threatening and urgent intervention indicated	Death
Chills	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	-	-
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake.	-	-

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-

ADL= Activities of daily living

Pre-specified CRS individual patient and study dosing stopping criteria are presented in Table 6 and should be followed by the Investigator.

- If individual patient criteria are met: Treatment for that patient will be stopped immediately, will not be restarted, and the patient will be followed up as per protocol.

- If study dosing stopping criteria are met: In addition to the individual patient instruction above, no further patients will be dosed within the cohort currently being investigated and no further dose escalation will occur; patients who have been dosed will be followed up as per protocol.

The symptoms in Table 6 have been classified as objective and subjective endpoints as follows:

Objective Endpoints: Fever, Diarrhoea, Vomiting, Hypotension

Subjective Endpoints: Headache, Chills, Nausea, Arthralgia, Myalgia

Based on the above classification four possible outcomes have been defined where dosing would be stopped, as described in Table 6:

Table 6 Stopping Criteria for CRS-Adverse Events

Scenario	NCI-CTC Scores	Individual Subject Criteria
I	2 objective endpoints ≥ grade 2 OR Fever, vomiting, or diarrhoea ≥ grade 2 persisting >48 hours despite treatment	Stop treatment
II	1 objective endpoint ≥ grade 2 AND • 2 subjective endpoints (except chills) ≥ grade 3 OR • 1 subjective endpoint ≥ grade 3 and Chills ≥ grade 2	Stop treatment
III	Three subjective endpoints ≥ grade 3 (except if one subjective endpoint is Chills, which only needs to be ≥ grade 2)	Stop treatment
IV	1 objective endpoint ≥ grade 4	Stop treatment

Study Dosing Stopping Criteria:

- **If ≥3 subjects on otelixizumab treatment within a cohort meet individual Stopping Criteria I-III detailed above.**

  Or

- **If 1 subject on otelixizumab treatment within a cohort meet individual Stopping Criteria IV.**

Note: in order to meet individual stopping criteria, the reported objective or subjective endpoints must be of different types during one 24 hour dosing period for any of the scenarios involving more than one endpoint.

5.3.2. EBV Stopping Criteria

Three parameters as described in Table 7 will be used to assess EBV reactivation at a patient level to determine dose escalation:

Table 7 Parameters used to Assess EBV Reactivation

Parameter	Criteria
Clinical Symptoms of Mononucleosis	Fever, fatigue, malaise, myalgia, pharyngodynia, lymphadenopathy
Change in Viral Load	EBV by PCR more than 10,000 copies per 10^6 peripheral blood mononuclear cells
Change in Serology	Emergence of IgM for EBV on otherwise EBV-IgG positive patients

Table 8 shows the possible combinations of the three EBV parameters that will be used to assess whether the patient has clinical EBV reactivation for the purpose of the stopping criteria. The assessment will be conducted for each subject at approximately 6 weeks post first active dose.

Table 8 Assessment of EBV Reactivation

Clinical Signs of Mononucleosis	Serology	Virology	EBV Reactivation
+	-	-	NO*
+	**+**	**+**	**YES**
+	**+**	**-**	**YES**
+	**-**	**+**	**YES**
-	-	-	NO
-	+	+	NO
-	+	-	NO
-	-	+	NO

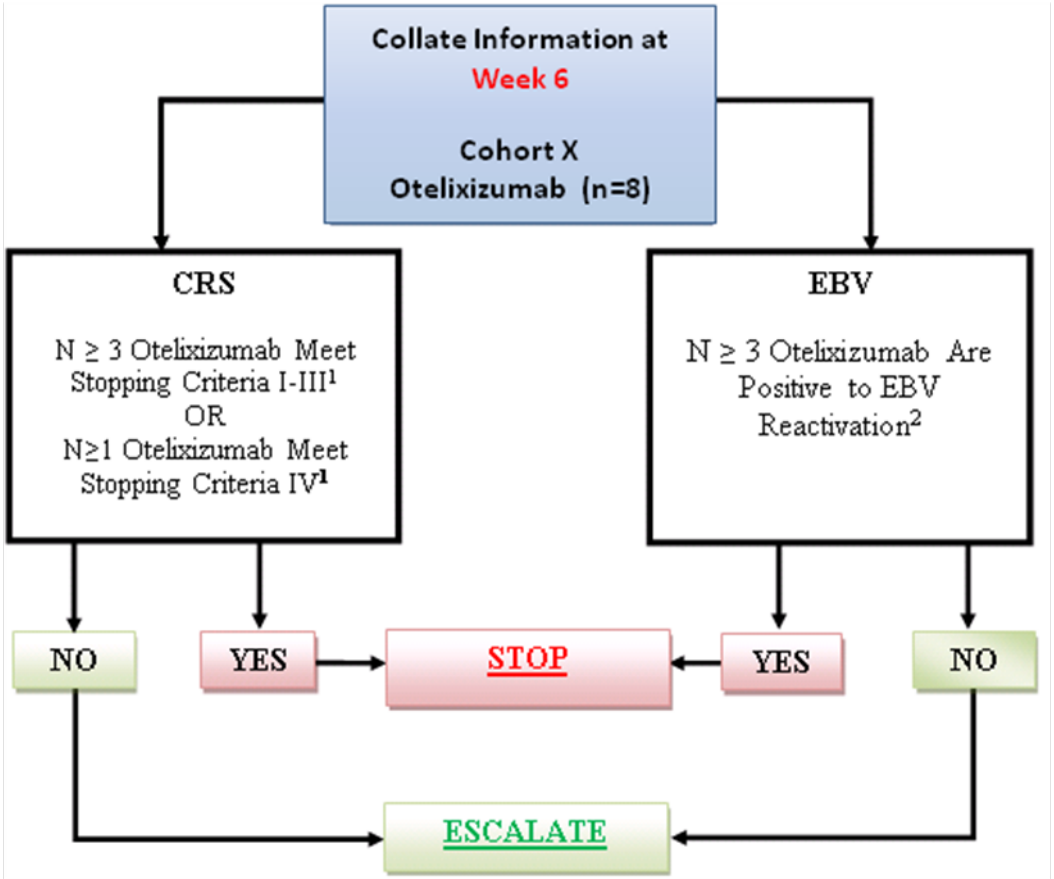
*Other causes of mononucleosis should be checked

There will be ongoing reviews of safety data throughout the trial progression and on completion of each cohort.
If $\geq$ 3/8 patients on active treatment within a cohort develop symptoms of clinical EBV reactivation as described above, the dosing will be stopped and no further dosing will be carried out on any other patients; patients who have been dosed will be followed up as per protocol.
Patient history will be assessed for symptoms of infectious mononucleosis, and spontaneous AE reporting will be implemented for assessing clinical EBV reactivation.

5.3.3. Assessment of Cytokine Release Syndrome & EBV Stopping Criteria

A summary schematic for dose escalation criteria based on CRS & EBV (refer to sub-Sections in Section 5.3 for criteria) are presented in Figure 5:

Figure 5 Dose Escalation Schematic



[1]: As defined in Table 6
[2]: As defined in Table 7

5.3.4. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure patient safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Study treatment will be stopped for a patient if the following liver chemistry stopping criteria is met:

1. ALT ≥ 3xULN and bilirubin ≥ 2xULN
   NOTE: serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).

2. ALT ≥ 5xULN.
3. ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. ALT ≥ 3xULN persists for ≥ 4 weeks.
5. ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks.

Subjects with ALT ≥ 3xULN **and** <5xULN **and** bilirubin <2xULN, who do not exhibit hepatitis symptoms or rash, can continue study treatment as long as they can be monitored weekly for 4 weeks.

NOTE: Refer to Appendix 1, for details of the required assessments if a subject meets any of the above criteria.

5.3.5. QTc Withdrawal Criteria

- A patient that meets any of the criteria below will be withdrawn from the study. The same QT correction formula should be used to determine inclusion and discontinuation for any individual patient throughout the study.
- QTc >500 msec or uncorrected QT >600 msec, or
- Change from baseline: QTc >60 msec

If a patient has underlying bundle branch block the following withdrawal criteria should be used instead.

Baseline QTc value (with underlying bundle branch)	QTc withdrawal criteria
<450 msec	>500 msec
450-480 msec	≥530 msec

Withdrawal of patients is to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period of time and then use the averaged QTc values of the 3 ECGs to determine whether the patient should be discontinued from the study.

5.3.6. Lymphopenia

If a single patient's lymphocyte count does not return to normal 28 days after dosing, the study team will review all available data. The patient will be monitored by bi- monthly blood counts until resolution and clinical assessments will address any evidence of infection.

5.3.7. Hypersensitivity Reaction

If a single patient develops an episode of angioedema or anaphylaxis, or three patients develop the same adverse event of severe urticaria (without angioedema, bronchospasm,

hypotension) the study team will review all available data and determine whether or not to continue the dosing regimen.

5.3.8. Other Stopping Safety Criteria

For **an individual study participant**, other stopping criteria include, but are not limited to:

Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the individual at risk (e.g. ECG, vital signs, laboratory tests, etc), as judged by the Principal Investigator in consultation with the Medical Monitor if necessary.

5.4. Blinding

This will be a single blind study where the patients will not be aware of the treatment they receive. All staff including site personnel, CRO and sponsor team members will be unblinded. However, the randomisation code will be restricted to the pharmacist preparing the infusions.

5.5. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements.

5.6. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of otelixizumab are provided below. Additional details are provided in the SRM.

Study treatment must be dispensed or administered according to procedures described herein:

- Only subjects enrolled in the study may receive study treatment.
- Only authorized site staff may supply or administer study treatment.
- All study treatment must be stored in a secure area with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance. The investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain investigational product accountability records throughout the course of the study. The responsible person(s) will document the amount of study medication received from GSK, document that it was shipped at 2-8°C by checking the temperature monitor, document the amount destroyed at end of study and the amount administered to subjects. The required accountability unit for this study will be vials. Discrepancies are to be

reconciled or resolved. Procedures for final disposition of unused study medication are listed in the SRM.

Study medication is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, medical monitor and/or study manager. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the study medication.

5.6.1. Study Medication Storage and Handling

Otelixizumab Concentrated Solution for Infusion, 5 mg/mL must be stored refrigerated at 2-8ºC, protected from light. Maintenance of a temperature log (manual or automated) is required. All otelixizumab solutions (i.e., drug product and solutions for infusion) must not be frozen. Solutions exposed to temperatures in excess of 25°C must be discarded.

Otelixizumab Solution for Infusion, 0.1 mg/mL must be prepared on the day of administration, as close to dosing as possible, i.e., within 6 hours of dosing, to ensure product quality.

Vigorous shaking of all otelixizumab solutions must be avoided.

5.6.2. Study Medication Preparation

Otelixizumab

Otelixizumab Concentrated Solution for Infusion, 5 mg/mL (1.0 mL vial) must be diluted in Sterile 0.9% Sodium Chloride in an empty 150 mL intravenous bag (Baxter Intravia) to prepare Otelixizumab Solution for Infusion, 0.1 mg/mL.

- Otelixizumab Solution for Infusion, 0.1 mg/mL is prepared by adding 49.0 mL of Sterile 0.9 % Sodium Chloride to the 150 mL empty bag followed by the addition of 1.0 mL of Otelixizumab Concentrated Solution for Infusion, 5 mg/mL (total 50.0 mL).

- Otelixizumab Solution for Infusion, 0.1 mg/mL is stable when stored in the Baxter Intravia bag for 6 hours at up to 25°C.

    - **Important Note:** When drawn into the syringe for administration to the patient it must be administered within 6 hours If needed an additional maximum of 30 minutes is allowed for tasks such as connection of line and filter, pump set up and priming and purging the lines. **However, every attempt should be made not to exceed a total time of 6 hours if possible.**

  - **Important Note:** If the infusion period will exceed 6 hours, then the syringe and infusion materials (IV line, stopcock and PES filter) must be discarded and a new syringe of dose and infusion materials used. Preparation of syringes(s) must be recorded on the Test Article Administration Form.
  - The dose will be drawn from a fresh bag of 0.1 mg/mL Otelixizumab solution.
  - The pharmacist should allow sufficient time to prepare the final solution and must ensure that infusion components are changed at the appropriate times.
  - The temperature must be controlled and should not exceed 25°C.
  - The temperature will be recorded at the pharmacy (when the IV bag is ready to be transferred to the dosing unit) and at the dosing unit (upon receipt).

- The required volume of Otelixizumab Solution for Infusion, 0.1 mg/mL (varies depending on target dose) and includes an excess of approximately 8 mL volume to account for prime/purge (6 mLs – see Section 5.6.3) plus an additional 2 mLs (or more if required) as an overage volume required for the syringe pump to deliver the exact volume to the patient as specified in Table 9 column 7. The additional overage must not be administered to the patient. The required volume must be withdrawn into a suitable size polypropylene syringe as close to the time of the start of the infusion as possible, to ensure product quality.

- For infusion periods that exceed 6 hours or infusion volumes exceeding 55 mL, a second syringe must be prepared and the infusion period divided across two separate syringes.

Placebo

- 0.9 % Sodium Chloride will be administered by intravenous infusion in the same manner as the active by study personnel following specified regimens. The same volume of placebo solution must be withdrawn into the same size polypropylene syringe as the corresponding active regimen.

Table 9 shows dose preparation.

Table 9 Study Medication Dose Preparation

Treat-ment Regimen (cohort)	Cumul-ative Dose (mg)	Dose per day (mg)	Day of Dosing	Period of Dosing (hours)	# of Syringes	Total Dosing Solution Volume to be Infused	Total Vol. Filled into Syringe, Includes Approximately *8 mL Fill Overage (Vol. not Infused)
A (1)	9	1.5	Day 1	9	2	15 mL (7.5 mL x 2 syringes)	15.5 mL x 2 syringes
			Day 2	6	1	15 mL	23 mL
			Day 3	3	1	15 mL	23 mL
			Day 4-6	1	1	15 mL	23 mL
B (2)	18	3	Day 1	12	2	30 mL (15 mL x 2 syringes)	23 mL x 2 syringes
			Day 2	6	1	30 mL	38 mL
			Day 3	3	1	30 mL	38 mL
			Day 4-6	1	1	30 mL	38 mL
C (3)	27	4.5	Day 1	12	2	45 mL (22.5 mL x 2 syringes)	30.5 mL x 2 syringes
			Day 2	6	1	45 mL	53 mL
			Day 3	3	1	45 mL	53 mL
			Day 4-6	1	1	45 mL	53 mL
D (4)	36	6	Day 1	12	2	60 mL (30 mL x 2 syringes)	38 mL x 2 syringes
			Day 2	6	2	60 mL (30 mL x 2 syringes)	38 mL x 2 syringes
			Day 3	3	2	60 mL (30 mL x 2 syringes)	38 mL x 2 syringes
			Day 4-6	1	2	60 mL (30 mL x 2 syringes)	38 mL x 2 syringes
P	0	0	0.9% w/v sodium chloride administered by intravenous infusion in the same manner as the active by study personnel following specified regimens				

*Overage volume may be adjusted to ensure optimal efficiency of syringe pump to deliver the exact dosing volume to be infused. Note the overage volume must NOT be delivered to the patient but remain in the syringe and discarded.

5.6.3. Study Medication Administration

Using the information given in Table 9:

- Withdraw the total required volume of Otelixizumab Solution for Infusion, 0.1 mg/mL or 0.9% Sodium Chloride for the placebo, using the syringe(s) that will be used for administration with the infusion pump (see Section 5.6.2 regarding stability time and time allowed for preparation).

- Connect a polyethylene intravenous line with an in-line 0.2 μm polyethersulfone (PES) filter to the syringe. If a second syringe is needed to provide the dose, a separate infusion line with 0.2 μm PES filter is required.

- The prime volume of the intravenous line and filter must not exceed a total of 3 mL. The approximate 8 mL excess solution in the syringe(s) must be primed/purged (3 mL to waste, about 3 mL fills the IV line); target a priming/purging rate of 1 mL/min or lower. Purging 3 ml to waste is required to account for protein loss due to binding and to ensure that the full dose is administered. The additional 2 mLs (or more if required) should remain as overage in the syringe and must not be administered to the patient.

- After the priming/purging procedure, the syringe(s) contains the volume of Otelixizumab Solution for Infusion, 0.1 mg/mL, or 0.9% Sodium Chloride in the case of placebo, needed to provide the clinical dose and is ready to be connected to the subject for dose delivery.

- Securely connect the infusion line to the patient cannula.

- Set the syringe pump to provide the syringe volume for the duration provided in Table 9 according to Cohort, Day and Dose to be delivered.

- Note that the solution remaining in the IV lines must not be administered to the patient.

If there is any need to reduce the infusion rate or temporarily stop the infusion, the Investigator should first consult with the Medical Monitor who will consult with the Sponsor. However, the Investigator has the flexibility to reduce or temporarily stop the infusion immediately (with no prior consultation with the Medical Monitor), if there are any immediate safety/tolerability concerns. In this case the Investigator must inform the Medical Monitor as soon as possible after reducing or stopping the dosing.

5.7. Assessment of Compliance

Patients will be dosed at the study site and they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

5.8. Treatment of Study Treatment Overdose

In the event of an overdose (defined as administration of more than the protocol-specified dose of otelixizumab, the investigator should:

- Contact the GSK and CRO Medical Monitor immediately
- Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until otelixizumab can no longer be detected systemically (at least 7.5 days) for otelixizumab.
- Additional plasma samples for pharmacokinetic (PK) analysis may be requested by the GSK Medical Monitor within 30 days of the last dose, determined on a case-by-case basis.
- Document the quantity of the excess dose as well as the duration of the overdosing in the electronic case report form (eCRF).
- Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

5.9. Treatment after the End of the Study

Patients will not receive any additional treatment from GSK after completion of the study because other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition.

5.10. Permitted Concomitant Medications and Non-Drug Therapies

All concomitants medications required for the management of the underlying disease will be permitted and must be recorded in the eCRF.

Paracetamol at doses of ≤2grams/day and NSAIDs at the suggested clinical dose are permitted for use from Day 7 onwards. All medications required for the Standard of Care of T1DM will be permitted.

Other concomitant medication will be considered on a case by case basis by the investigator in consultation with the CRO/GSK Medical Monitor.

5.10.1. Prophylaxis and Treatment of Cytokine Release Symptoms

All medications and fluids used as prophylaxis or treatment for cytokine release syndrome (CRS) will be recorded in the eCRF as concomitant medications.

5.10.1.1. Prophylaxis

Prophylaxis for CRS will be administered to each patient on each dosing day. Medications will be administered according to the investigator's clinical judgment; but the following guidelines are recommended:

NSAID Ibuprofen orally as follows: 800 mg 2 hours before start of infusion (SOI), 800 mg 6 hours after SOI, and 400 mg at bedtime for the first 3 days of infusion. The total dose administered as prophylaxis should not exceed 2400 mg in any 24-hour period.

Alternatives to ibuprofen are naproxen and ketoprofen at the recommended clinical dosage as per package dosage inserts.

If the patient is intolerant of ibuprofen or if ibuprofen is contraindicated, paracetamol may be used in place of ibuprofen. Paracetamol doses should be in accordance with current local recommendations for over-the counter dosing and must not exceed 1000 mg per 6 hours or 4000 mg per day during in-patient visit.

To avoid exceeding the maximum daily amount of either ibuprofen or paracetamol, alternance of the two drugs is suggested. Paracetamol doses must be separated by at least 6 hours.

A non-sedating antihistamine (e.g., cetirizine) should be administered approximately 1 hour prior to each infusion of study drug. The recommended initial dose of cetirizine is 5 mg or 10 mg per day orally in adults and children aged 12 years and older. Other antihistamines of this same class (e.g., loratidine) may be substituted as clinically indicated and administered according to manufacturer's instructions.
Isotonic saline solution (ISS) (0.90% w/v of NaCl) administered i.v. if needed to maintain hydration.

Observations from previous studies suggest that inadequate hydration may increase the risk of hypotension in patients receiving otelixizumab, while excessive hydration may increase the risk of some AEs (such as headache) if cytokine release occurs. Subjects should receive adequate oral hydration whenever possible. Investigators should use their clinical judgment to determine whether to administer i.v. ISS, and on the quantity and rate of i.v. ISS infusion. This judgment should be based on the patient's ability to maintain adequate hydration by oral intake and on the patient's volume status, which should be assessed by physical examination and other relevant parameters on each dosing day.

5.10.1.2. Treatment

If cytokine release symptoms persist despite the prophylactic treatment, additional treatment may be given at the discretion of the investigator, including more potent analgesics (e.g., opioids, such as acetaminophen with codeine, and/or triptans, for headache. An anti-emetic such as ondansetron may be given for nausea and/or vomiting). However, use of systemic corticosteroids should be avoided unless such treatment is

medically necessary and alternative treatments are not considered safe or effective. The medical monitor must be notified of the administration of systemic corticosteroids.

NSAID Ibuprofen Additional ibuprofen may be used if, in the Investigator's clinical judgment, this would be appropriate treatment for an AE. The total dose administered as prophylaxis or therapy should not exceed 2400 mg in any 24-hour period.

Antihistamine Additional doses of antihistamine may be administered as clinically indicated and according to manufacturer's instructions.

5.11. Prohibited Concomitant Medications and Non-Drug Therapies

Patients should NOT receive potent immunosuppressive agents (e.g., systemic high-dose corticosteroids on a chronic basis, methotrexate, cyclosporine, anti-TNF agents, *etc.*) during the study. Additionally, patients should not receive such agents within 24 months.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 6.2. Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: PK, safety blood samples, ECG, vital signs, and PD samples.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

The timing and number of planned study assessments, including: safety, pharmacokinetic, pharmacodynamic, biomarker or other assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. The change in timing or addition of time points for any planned study assessments must be approved and documented by GSK, but this will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme.

No more than approximately 500 mL of blood will be collected over the first 3 month period, including any extra assessments that may be required. The volume of blood collected after the first 3 months will be lower, eg less than 200 mL.

6.1. Visit Windows

The following visit windows will be allowed to provide flexibility. Visits completed within the windows will not constitute a protocol deviation:

- A ± 1 day window is permitted for the Day 14 and Day 21 visits and Week 4 telephone call.

- Visits from Week 6 to Month 3 inclusive are permitted a ± 3 day window
- Visits from Month 6 to Month 24 inclusive are permitted a ± 7 day window
- Telephone calls/visits in the follow-up period at Month 36 and final-up are permitted a ±14 day window

6.2. Time and Events Tables

6.2.1. Screening

Medication history
Full physical examination (including height and weight)
Drug/alcohol history
Chest X-ray (to rule out TB)
Serology (EBV, HIV, Hep C, Hep B, Syphillis)
12-lead ECG in triplicate
Vital signs (including temperature, blood pressure and pulse rate (in triplicate) and respiration rate
Urine Pregnancy test (female only)
Haematology (must include total lymphocyte count)
Clinical Chemistry
T1DM Auto antibody (Anti-GAD, anti-IA2, antibody to islet cell antigen (ICA), anti-ZnT8)
EBV Viral Load (PCR)
AE assessment

The following must be performed at least 7 days prior to dosing
Mixed Meal Stimulated C-peptide (MMTT)

*Two Total lymphocyte counts within normal range must be obtained prior to dose administration (counts from screening and Day-1, must be at least 3 days apart)

6.2.2. Dosing and Follow-Up

			Day								Month									
	-2	-1	1	2	3	4	5	6	14	21	Week 4	Week 6	2	3	6	9	12	18	24	36 month (if applicable) and/or final follow up
Patient admitted to unit[1]	X																			
In Patient		X	X	X	X	X[2]	X[2]	X[2]												
Prophylaxis (Section 5.10) then IV Dosing of study treatment			X	X	X	X	X	X												
Patient Discharged[2]								X												
Out Patient#						X	X	X	X	X		X	X	X	X	X	X	X	X	
Telephone call or out-patient visit to collect AEs, hypoglycemic and hyperglycemic events and concomitant medication use											X									X
Brief Physical Examination		X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	X		X	X	X	X	X	X	X	X	
12 lead ECG[4,6]		X	X	X	X	X	X	X	X								X		X	
Vital Signs[5,6]		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Serum Pregnancy Test		X										X	X	X	X	X	X	X	X	
Alcohol & drugs of abuse test		X																		
Haematology[7]		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Clinical Chemistry[7]		X	X	X	X	X	X	X[8]	X			X		X	X	X	X	X	X	
HSV-1 & HSV-2 IgG & IgM[9]		X																		
EBV Viral Load (PCR)[7]		X						X		X		X	X	X	X[10]				X	
EBV Serology - IgG and IgM [7]		X						X		X		X	X	X	X		X		X	

			Day								Month									
	-2	-1	1	2	3	4	5	6	14	21	Week 4	Week 6	2	3	6	9	12	18	24	36 month (if applicable) and/or final follow up
CMV Serology - IgG and IgM[7]		X						X				X	X	X	X		X		X	
PK Blood Sample[6]			X	X	X	X	X	X	X[11]											
CD3 Saturation, free CD3 bound otelixizumab /CD4+/CD8+ Blood Sample[6]			X	X	X	X	X	X	X[11]											
Record insulin usage for 7 days before visit / call		X							X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment			<----------																	---------->
Concomitant Medication Review			<----------																	---------->
Hypoglycaemic / Hyperglycaemic Events			<----------																	---------->
Anti-GAD, anti-IA2, antibody to islet-cell antigen (ICA), anti-ZnT8 & Insulin-antibodies (IAA)		X																		
Anti-otelixizumab antibodies Blood Sample		X												X	X					
Mixed Meal Stimulated C-peptide (MMTT)[12]														X	X[14]		X	X	X[14]	
Beta Cell Function by Hyperglycaemic Clamp[13]		X													X[14]				X[14]	
HbA1c		X													X		X		X	X[15]
Bodyweight		X										X	X	X	X	X	X	X	X	
Various Blood samples for Exploratory Biomarkers		X						X[16]				X		X	X		X		X[17]	
Saliva sample for Pharmacogenetics (PGx)[18]			<----------					---------->												

#Patients will record insulin usage for 7 days prior to out-patient visits (up to Month 24) and before telephone call/visit in Month 36 (if applicable) or final follow up.

Significant AEs including hypoglycaemic (≤3.9 mmol/L; ≤70 mg dL) and hyperglycaemic (>13.9 mmol/L; >250 mg/dL) events will be recorded in a diary whenever they occur, to include start and stop dates.

1. Patient admitted evening of Day -2
2. Discharged on Day 6 if health considered satisfactory by the investigator. Dosing Day 4-6 may be performed on out-patient basis (see Section 3.1)
3. Physical exam performed to monitor for changes in clinical status
4. ECG pre-dose (in triplicate), at the end of the infusion and 6 hours post start infusion (if infusion <6 hours)
5. Vital signs include temperature, blood pressure and pulse rate (in triplicate), and respiration rate
6. See Section 6.2.3 for timings
7. Pre-dose on dosing days
8. If LFTs have shown an upward trend continue to monitor daily after day 6
9. HSV-1 & HSV-2 IgG & IgM will be measured at Day -1 and during the study if clinically indicated
10. If still positive at 6 months EBV viral load will be monitored every 3 months until month 24
11. One sample during visit
12. Blood samples for C-peptide and glucose levels collected at -10, 0, 15, 30, 60, 90 and 120 minutes
13. Plasma C-peptide and glucose levels will be measured during the hyperglycaemic clamp procedure at the following time points: L150, L165 and L180 minutes [during the euglycaemic (L)ow phase], H0, H60, H90, H120 and H140 minutes [during the hyperglycaemic (H)igh phase]
14. Mixed Meal and Glucose Clamp must be separated by at least 4 days
15. Patients will be asked to report verbally their HbA1c at Month 36 (if applicable) and/or final follow-up; followed eventually (if available) by a printed result via regular mail (or scan electronically).
16. Limited biomarkers on Day 6 pre-dose
17. Blood samples for exploratory biomarkers will only be analysed at Month 24 if indicated based on Month 12 results
18. One PGx (DNA) saliva sample taken between Day 1 and 6

6.2.3. Detail for Vitals, ECG and Pharmacokinetic and Pharmacodynamic Monitoring over the Infusion Period (Cohorts 1-4)

Day	Cohort	Assessment	Pre Dose	0 H	30 M	1 H	2 H	3 H	4 H	5 H	6 H	7 H	8 H	9 H	10 H	11 H	12 H	13 H	14 H	15 H	16 H
1	C1	Dosing																			
		VItals[1,2]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X
		ECG	X								X			X							
		PK/CD3 Saturation	X		X	X	X		X		X		X	X							X
	C2-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		ECG	X								X						X				
		PK/CD3 Saturation	X		X	X	X		X		X		X				X				X
2	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X	X	X	X	X	X	X	X		X				X
		ECG	X								X										
		PK/CD3 Saturation	X																		
3	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X	X	X	X	X	X				X				X
		ECG	X					X			X										
		PK/CD3 Saturation	X																		

Day	Cohort	Assessment	Pre Dose	0 H	30 M	1 H	2 H	3 H	4 H	5 H	6 H	7 H	8 H	9 H	10 H	11 H	12 H	13 H	14 H	15 H	16 H
4	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X[3]													
		ECG	X			X		X[3]													
		PK/CD3 Saturation	X																		
5	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X[3]													
		ECG	X			X		X[3]													
		PK/CD3 Saturation	X																		
6	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X[3]													
		ECG	X			X		X[3]													
		PK/CD3 Saturation	X			X															

1. Blood pressure to be taken in triplicate at Pre-dose
2. Vitals to be repeated at 30 min intervals should there be any safety concern
3. If patients are dosed on an out-patient basis on Day 4, 5 and 6, vital signs and ECGs will stop after the 3 hour post dose time point (if the Investigator is satisfied with the clinical status of the patient), if there are any concerns then vital signs and ECGs may be continued as judged necessary by the investigator until the investigator is satisfied

Day	Cohort	Assessment	Preferably within first hour of visit, time to be recorded in eCRF
14	C1-C4	PK/CD3 Saturation	X

6.3. Demographic/Medical History Assessments

The following demographic parameters will be captured: year of birth, gender, race and ethnicity.

Medical/medication/drug and alcohol history will be assessed as related to the eligibility criteria listed in Section 4.2. Cardiovascular medical history/risk factors including height, weight, blood pressure, smoking history, medical conditions will also be assessed at baseline.

6.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 6.2). Additional time points for safety tests such as vital signs, physical exams and laboratory tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

6.4.1. Physical Exams

- A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.
- A brief physical examination will include assessments of the skin, lungs, cardiovascular system, extremities and abdomen (liver and spleen).

6.4.2. Vital Signs

Vital sign measurements will be measured in a semi-supine position after 5 minutes rest (before the first measurement) and will include systolic and diastolic blood pressure and pulse rate (triplicate measures, the average will be recorded in the eCRF), respiratory rate and temperature.

6.4.3. Electrocardiogram (ECG)

12-lead ECGs will be obtained in the semi-supine position after the subject has been resting in the semi-supine position for at least 5 minutes at each time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTc intervals (QTcB and F). At screening, baseline (Day -1) and pre-dose on dosing days, ECG assessments will be performed in triplicate (5 minutes apart) to obtain an average, single ECGs will be performed at other timepoints. Refer to Section 5.3.5 for QTc withdrawal criteria, which requires triplicate ECGs to assess QTc.

6.4.4. Clinical Laboratory Assessments

Haematology, clinical chemistry, and additional parameters to be tested are listed below. Details for the preparation and shipment of samples will be provided by the testing laboratory. Reference ranges for all safety parameters will be provided to the site by the laboratory.

If additional non-protocol specified laboratory assessments are performed at the site's local laboratory and result in a change in patient management, or are considered clinically significant by the investigator (for example SAE or AE or dose modification) the results must be captured in the eCRF and the Medical Monitor notified.

6.4.4.1. Haematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes (see Section 6.6)
Reticulocyte Count	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

6.4.4.2. Clinical Chemistry

BUN	Potassium	AST (SGOT)	Total and direct bilirubin*
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose, fasting	Total CO_2	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
To include CRP (Day -1 only)			

- It is not mandatory to measure fractionated bilirubin if total bilirubin is not above the normal range.

NOTE: Details of Liver Chemistry Stopping Criteria and Follow-Up Procedures are given in Section 5.3.4

Other

Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).
Pregnancy (Serum test)

6.4.4.3. Serology

Serology tests for the following will be performed at the time points indicated in the Time and Events Table

- Hepatitis B surface antigen and for antibodies to Hepatitis B core antigen, Hepatitis C, HIV I and II, IgG and IgM antibodies to EBV and cytomegalovirus (CMV). In addition, IgG and IgM antibodies to HSV-1 and HSV-2 will be measured on Day -1 and during the study if clinically indicated.

6.4.5. Tuberculosis

All patients will have a chest x-ray at the screening visit to rule out active tuberculosis.

6.4.6. EBV Viral Load Detection (PCR)

Blood samples will be drawn for EBV viral load detection by PCR at the timepoints indicated in the Time and Events Table.

6.5. Pharmacokinetics

6.5.1. Blood Sample Collection

Blood samples of approximately 2.5 mL for pharmacokinetic analysis of serum free otelixizumab will be collected at the time points indicated in Section 6.2, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. This will not constitute a protocol amendment

The total volume will not exceed approximately 500 mL during the first 3 months then approximately 200 mL or less at each visit until month 24 inclusive. Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

6.5.2. Sample Analysis

Serum analysis will be performed by or under the auspices of Bioanalytical Science and Toxicokinetics, DMPK, GlaxoSmithKline. Concentrations of free otelixizumab will be determined in serum using the currently approved bioanalytical methodology. Raw data will be stored in the GLP Archives.

6.6. Biomarker(s)/Pharmacodynamic Markers

6.6.1. Anti-Otelixizumab Antibodies

Blood samples will be taken at the time points specified in the Time and Events Table (Section 6.2) to assess the immunogenicity of otelixizumab.

Samples will be analyzed for the presence of anti-otelixizumab antibodies using a validated immunoelectrochemiluminescent (ECL) assay. Samples testing positive for anti-otelixizumab binding may be further characterized.

Details of blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

6.6.2. TIDM Auto-antibodies

Tests for antibodies associated with TIDM will be performed at screening and baseline (Day -1). At screening tests for anti-GAD, anti-IA2, antibody to islet cell antigen (ICA) and anti-ZnT8will be performed. The same tests will be performed at Day -1 together with a test for insulin antibodies (IAA).

6.6.3. CD4+, CD8+ Levels and CD3. Free CD3 and bound otelixizumab on CD4 and CD8+ Cells

Whole blood samples will be drawn, as detailed on the Time and Events Table, for determining CD4+ and CD8+ levels, together with CD3, free CD3 and bound otelixizumab on CD4 and CD8+ cells, respectively. The samples will be analysed by flow cytometry.

6.6.4. Exploratory Biomarkers

Blood samples for exploratory biomarkers will be collected at the time points indicated in the Time and Event Table (Section 6.2). Exploratory samples will only be analysed after review of safety endpoints. Month 24 blood samples for exploratory biomarkers will only be analysed if indicated based on results from Month 12 biomarker analyses. Full details on sample collection, processing and shipment will be provided in the SRM/Q^2 Solutions manual. Below is a table with details on the exploratory biomarker assays under consideration to address the exploratory objectives and endpoints as outlined in Section 2. As new data emerge, it may also be possible to probe novel aspects of the biology of T1D, as well as the biological and clinical responses to otelixizumab. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events.

Biomarker Assay	Sample Type	D -1	D6	M1.5	M3	M6	M12	M24*
CD8+ Multimer analysis	PBMC	X		X	X	X	X	X
Whole Blood Absolute Lymphocyte Count + CD3+ CD4+, CD3+ CD8+, CD19+	BCT CytoChex	X		X	X	X	X	X
Antigen-specific ex vivo ELISPOT responses	PBMC	X		X	X	X	X	X
Demethylated FoxP3/CD3/Th17 analysis	BD Vacutainer Plus 2mL lavender/EDTA with Hemogard – part number 368841	X		X	X	X	X	X
Exploratory Lymphocyte Sub-set phenotyping of CD3+ T (eg effector, memory, regulatory T cells using cell surface markers such as CD45RA, CCR7) and CD19+ B cells	PBMC	X		X	X	X	X	X
Auto-antibody (+ serum analytes) analysis	Serum	X		X	X	X	X	X
TCR deep sequencing[2]	PAXgene Blood RNA Tube	X	X[1]	X	X	X	X	X
Beta cell death biomarker analysis	Serum	X		X	X	X	X	X
T lymphocyte suppression assay	PBMC	X		X	X	X	X	X

[1]Sample taken pre-dose
[2] Similar additional transcriptomics analysis may be performed using micro-array and/or alternative equivalent technologies including RNA sequencing
* Blood samples for exploratory biomarkers will only be analysed at Month 24 if indicated based on Month 12 results

6.7. Efficacy

6.7.1. Mixed Meal Tolerance Test, (C-Peptide Unstimulated, Serum Stimulated C-Peptide Peak Levels and C-Peptide AUC)

The Mixed Meal Stimulated C-peptide and C-peptide unstimulated will be performed using the MMTT as shown in Section 6.2 Time and Events Table. See Appendix 5 for the procedure that must be followed for the MMTT. Glucose will also be measured with C-Peptide at all timepoints.

An MMTT test will be performed in the screening period, at least 7 days before the first dose of study medication is given.

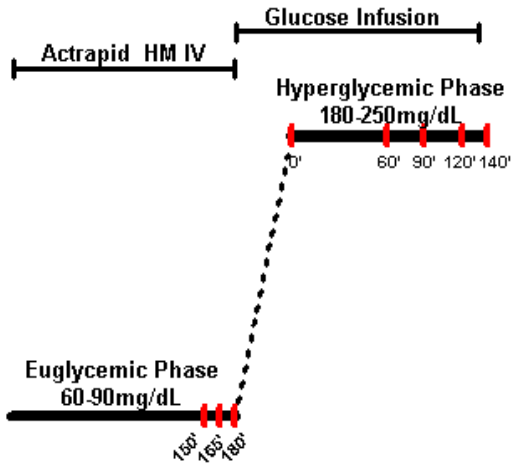
Levels of glucose and C-peptide will be assessed from blood samples taken 10 minutes before and immediately before Time 0 and at 15, 30, 60, 90, and 120 minutes after Time 0. See Appendix 5.

Mixed meal-stimulated C-peptide AUC will be the area under the C-peptide/time curve from Time 0 to 120 minutes, calculated using the trapezoidal rule. This AUC will be normalised for time interval by dividing it by the number of minutes over which it was determined (expected to be 120 minutes, but may vary in some cases). This normalised AUC will be calculated for each patient at baseline (screening) and Months 3, 6, 12, 18 and 24.

6.7.2. Hyperglycaemic Clamp Serum Stimulated C-Peptide Levels and C-Peptide AUC

Plasma C-peptide and glucose levels will be measured during the hyperglycaemic clamp procedure at the following time points: L150, L165 and L180 minutes [during the euglycaemic (L)ow phase], H0, H60, H90, H120 and H140 minutes [during the hyperglycaemic (H)igh phase]. C-peptide AUC will be the area under the C-peptide/time curve from Time H60 to H140 minutes (Figure 6). AUC will be expressed as value per minute for each period. This value will be calculated at baseline, 6 and 24 months.

Figure 6 Schematic showing the Euglycaemic and Hyperglycaemic phases of the Clamp Procedure



See Appendix 6 for the procedure that must be followed for the hyperglycaemic clamp test.

NB. The MMTT and hyperglycemic clamp test must be separated by at least 4 days

6.7.3. Daily Insulin Use

Patients will be asked to record their daily insulin usage thoroughly and accurately for 7 consecutive days in a diary during the week before all outpatient visits or phone calls, ie, at Baseline, Day 14 and 21, Week 4 and 6 and Months 2, 3, 6, 9, 12, 18, 24, 36 (if applicable) and final follow up (if applicable). Information on insulin usage will be transcribed from diaries into the eCRF.

Mean daily insulin use over the 7 consecutive days (in units of IU per kg body weight per day) will be calculated for each patient at the timepoints described above.

Long acting and short acting insulin should be reported separately. The delivery device will also be recorded.

6.7.4. Glycosylated Haemoglobin, HbA1c

HbA1c will be recorded at visits as shown in the Time and Events Table. Patients will be asked to report verbally their HbA1c (if available) around the time of month 36 (if applicable) and/or final follow-up; followed eventually by a printed result via regular mail (or scan electronically) if available. HbA1c values will be captured in the eCRF.

HbA1c up to Month 24 will be analysed by BDR.

6.8. Pharmacogenetics

A saliva sample will be collected for pharmacogenetic (DNA) analysis on Day – 1 (after randomisation) or any other visit up to month 24.

Information regarding pharmacogenetic (PGx) research is included in Appendix 2. The IRB/IEC and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site.

7. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND PREGNANCY

7.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The investigator or site staff are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.1.1. Time Period for Collecting AE and SAE Information

AEs will be collected from signing the Informed Consent Form until the follow-up contact, approximately 2 years post last dose.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a patient consents to participate in the study up to and including any follow-up contact. All SAEs will be recorded and reported to the Medical Monitor and GSK within 24 hours, as indicated in Appendix 4.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator would promptly notify the Medical Monitor and GSK.

NOTE: The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to the Medical Monitor and GSK are provided in Appendix 4.

7.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.1.3. Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE **include**:

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

- The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

7.1.4. Definition of Serious Adverse Events

If an event is not an AE per Section 7.1.3, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Is associated with liver injury **and** impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to patients receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

7.1.5. Cytokine Release Syndrome Adverse Events

CRS is a well-known consequence of anti-CD3 therapy when administered via intravenous injection or infusion and therefore any CRS AEs experienced during the dosing period will be assessed against the grading system shown in Table 5. This grading system has been developed using NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 (Table 5) by selecting AEs that are specifically thought to be associated with cytokine release syndrome. Pre-specified CRS individual patient and study dosing stopping criteria are shown in Table 6. The symptoms in Table 6 have been classified as objective and subjective endpoints as follows:

- **Objective Endpoints**: Fever, Diarrhoea, Vomiting, Hypotension
- **Subjective Endpoints:** Headache, Chills, Nausea, Arthralgia, Myalgia

7.1.6. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thrombosis
- Deep Venous Thrombosis
- Revascularization

This information should be recorded within one week of when the AE/SAE(s) are first reported.

7.1.7. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non- cardiovascular death.

This information should be recorded within one week of when the death is first reported.

7.1.8. Prompt Reporting of SAEs to GSK

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to the Medical Monitor and GSK within 24 hours. Any follow-up information on a previously reported SAE will also be reported to the Medical Monitor and GSK within 24 hours.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the Medical Monitor and GSK of the event and completing the appropriate data collection tool. The investigator will always provide an assessment of causality at the time of the initial report as described in Appendix 4.

7.1.9. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. CRO/GSK will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.2. Pregnancy

7.2.1. Time Period for Collecting Pregnancy Information

All pregnancy information in female subjects and/or female partners of male subjects will be collected after the start of dosing until 24 months after the last dose of study drug.

7.2.2. Action to be taken if pregnancy occurs

Patients must not receive study drug until a negative pregnancy result has been obtained. If a female patient becomes pregnant during the follow-up period (up to 24 months post dose), the investigator will record pregnancy information on the appropriate form and submit it to CRO (who will notify GSK) within 2 weeks of learning of a patient's pregnancy. The subject will be asked to remain in the study and attend all scheduled visits for collection of safety data; no MMTT (or other PD or efficacy assessments) will be performed if the patient is pregnant. The patient will be followed to learn the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. The investigator will notify the CRO/Sponsor if the pregnancy is terminated. If the subject gives birth, information on the health status of the mother and child will be forwarded to the CRO/Sponsor. At visits that take place after the birth, information on the health status of the child will be recorded. Three months after the birth, the subject will be asked to resume her regular schedule of MMTTs and other PD and efficacy assessments.

If a male subject's partner becomes pregnant, she will be asked to consent to collection of data on her health status and the outcome of the pregnancy. If she consents, she will be followed to learn the outcome of the pregnancy. The investigator will notify the CRO/Sponsor if the pregnancy is terminated. If the subject's partner gives birth, information on the health status of the mother and child will be forwarded to the CRO/Sponsor. Pregnancy, childbirth, and elective termination of pregnancy are not necessarily considered AEs. Complications of pregnancy or childbirth, spontaneous abortions, and termination of pregnancy for medical reasons are AEs; they will be considered serious if they meet the definition of an SAE in Section 7.1.4. A spontaneous abortion will be considered an SAE if required by the regulations of the country in which it occurs.

7.2.3. Action to be taken if pregnancy occurs in a female partner of a male study patient

The investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study. This applies only to patients who are randomised to receive study medication. After obtaining the necessary written informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the CRO within 2 weeks of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the CRO. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

8. DATA MANAGEMENT

For this study patient data will be entered into GSK approved electronic case report forms (eCRFs), combined with data provided from other sources in a validated data system and transmitted electronically to the CRO.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Patient's PII (Personal identifiable information) including a full date of birth and initials will not be collected or transmitted to CRO/GSK according to CRO/GSK policy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Hypotheses and Treatment Comparisons

As the primary objective is to assess the safety, tolerability and maximum tolerated dose of Otelixizumab in subjects with NOT1DM patients, there are no formal hypotheses being tested in the study, instead an estimation and inference approach will be adopted to evaluate the objectives.

If data permits, a model-based approach will be used to characterise and assess any evidence of dose response relationships with endpoints of interest.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

There are no formal calculations of power or sample size for this study. The sample sizes have been chosen based on feasibility, to primarily allow characterization of safety and tolerability of ascending doses of otelixizumab, in T1DM patients.

A total of 40 patients will be recruited into the study and for each cohort, 8 patients will be randomized to otelixizumab and 2 patients to placebo.

The primary objective of the study is based on safety and tolerability, where safety events are of interest, particularly those related to CRS and EBV reactivation which have associated defined stopping criteria. From a expected benefit : risk perspective it would be unacceptable to continue dosing patients within a cohort or subsequent cohorts, if ≥ 3 subjects met the defined CRS or EBV stopping criteria described in Section 5.3 Patient Specific and Dose Escalation Stopping Criteria.

Assuming we were to observe a number of events out of the 8, then in Table 10, the following are estimated for various numbers of observed responders:

[1] 95% credible intervals for proportion of responders
[2] Probability of response rate >0.375, derived within a Bayesian framework with a non informative conjugate prior distribution, Beta (1, 1), for the response rate.

Table 10 Estimated 95% Credible Intervals for Proportion of Responders & Probability of Response Rate >0.375

Total No. of Subjects Per Cohort	Observed No. of Responders	95% Credible Interval for Proportion of Responders, Given Observed Data	Probability of Response Rate >0.375 (3/8), Given Observed Data
8	0	(0.00 , 0.34)	0.01
8	1	(0.03 , 0.48)	0.09
8	2	(0.07 , 0.60)	0.28
8	3	(0.14 , 0.70)	0.55
8	4	(0.21, 0.79)	0.78
8	5	(0.30 , 0.86)	0.93
8	6	(0.40, 0.93)	0.98
8	7	(0.52 , 0.97)	0.99
8	8	(0.66 , 1.00)	1.00

If we were to observe 0 out of 8 subjects with a given CRS or EBV event, the estimated 95% credible interval for the proportion of responders is (0.00, 0.34) and there would be a very low probability (0.01) of the true response rate being greater than 0.375.

However, if we were to observe 3 out of 8 subjects with a given CRS or EBV event, the estimated 95% credible interval for the proportion of responders is (0.14, 0.70) and there would be a 0.55 probability of the true response rate being greater than 0.375.

In the above scenario where 3 out 8 subjects have a given CRS or EBV event:

- Treatment for individual patients will be stopped immediately, will not be restarted, and the patients will be followed up as per protocol.
- No further patients will be dosed within the cohort currently being investigated and no further dose escalation will occur.

9.2.2. Sample Size Sensitivity

A sensitivity analyses was conducted on the primary endpoint based on safety events of interest, particularly those related to CRS and EBV reactivation. Table 11, provides further estimates of the 95% credible interval for the proportion of responders based on various accumulated number of subjects within a cohort.

Table 11 Estimated 95% Credible Intervals for Proportion of Responders

Total No. of Subjects	Observed No. of Responders	95% Credible Interval for Proportion of Responders, Given Observed Data
1	0	(0.01, 0.84)
	1	(0.16, 0.99)
2	0	(0.01, 0.71)
	1	(0.09, 0.91)
	2	(0.23, 0.99)
3	0	(0.01, 0.60)
	1	(0.07, 0.81)
	2	(0.19, 0.93)
	3	(0.40, 0.99)

If we were to observe 2 out of 2 subjects with a given CRS or EBV event, the estimated 95% credible interval for the proportion of responders is (0.23, 0.99).

9.2.3. Sample Size Re-estimation

No sample size re-estimation will be performed.

No sample size re-estimation is currently planned for this study. However, if during the course of the study, new information becomes available about safety events, clinically meaningful differences or variability estimates, a sample size re-estimation may be conducted. Full details of the procedure used would be specified in the analysis and reporting plan (RAP), and any subsequent change to the target sample size would be documented in a protocol amendment.

9.3. Data Analysis Considerations

9.3.1. Interim Analyses

9.3.1.1. During the Study

There will be ongoing data reviews conducted by the study team of the unblinded safety and efficacy data, and any available pharmacokinetic and pharmacodynamic data throughout the trial progression.

9.3.1.2. Dose Escalation

Further unblinded data reviews of safety data will be performed to support whether to dose escalate to the next cohort. If deemed appropriate, the review may also include supportive pharmacokinetic, biomarker or pharmacodynamic data if available. Details are provided below:

- Data will be reviewed after 10 patients have been dosed in cohort 1 (8 patients on otelixizumab 9 mg and 2 patients on placebo) and have completed approximately 6 weeks of the study after the first active dose, and required data is available.
- If required, data reviews prior to 6 weeks may also be conducted to facilitate dose escalation to the next cohort.
- It is not expected that this review will occur on a fully cleaned data.
- Further data reviews based on criteria provided for cohort 1, will be performed for subsequent cohorts, including an overall review of accumulated data across the cohorts.
- Core members of the dose escalation review team will include the Principal Investigator, Medical Monitor, GCSP, Clinical Pharmacologist and Statistician. Other GSK/CRO study team members may also be included as required.

9.3.1.3. Interim Analyses (12 Months)

Formal unblinded interim analyses are also planned:

- The first interim will occur when all patients in cohorts 1 and 2 have completed 12 months study duration, but may also include any available data from subsequent cohorts 3 and 4 as appropriate.
- The second interim analysis will occur when all patients from the last fully enrolled cohort (i.e. not stopped due to safety / tolerability) have completed 12 months study duration.
- The purpose of these interim analyses is to provide the project team and GSK stakeholders with key data to inform internal decision making, in order to plan future studies within the clinical development for the asset.
- There are no planned implications for the conduct of the study.

- Appropriate data summaries will be at the treatment group level for key endpoints of interest and the circulation of results will be restricted to selected members of the project team and key GSK stakeholders. Results or discussions will not be circulated to staff involved in the conduct of the study at the sites.
- Full details of planned interim analyses will be included in the reporting and analysis plan (RAP).

9.3.2. Final Analyses

Data will be summarized and analysed according to the GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

9.3.2.1. Final Analyses (24 Months)

The final analysis will occur when the last planned cohort (i.e. based on the dose escalation criteria) have completed 24 months study duration or have had a final follow-up for subjects who, at the time of the implementation of Amendment 08 of the protocol, will have already reached months 24.

9.3.3. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

Further details, regarding specific analyses of safety endpoints (e.g. Cytokine Release Syndrome and Epstein-Barr Virus) will be further detailed and included in the RAP.

9.3.4. Pharmacokinetic Analyses

All free serum otelixizumab concentration data will be graphically represented, descriptively summarised and listed appropriately.

Free serum otelixizumab concentration time data will be analyzed by non-compartmental methods with WinNonlin Version 6.1 or higher. Calculations will be based on the nominal sampling times recorded during the study. From the serum concentration-time data, the following pharmacokinetic parameters may be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t) and AUC(0- τ], and apparent terminal phase half-life (t1/2). Additional parameters may be included as required.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

9.3.5. Efficacy Analyses

Descriptive statistics of both raw and change from baseline data, where appropriate, (i.e. n, arithmetic mean, standard deviation, minimum, median and maximum) will be calculated for efficacy endpoints and summarized across cohorts. Graphical displays will be produced over time if deemed appropriate. All data will be listed.

If data permits, formal statistical analyses of efficacy endpoints may be conducted, if deemed appropriate and full details will be provided in the RAP. Based on the specified statistical analyses, estimates of the differences between doses of otelixizumab and placebo will be calculated and appropriate statistical inferences based on these results will be made. Distributional assumptions underlying the analyses will be assessed as appropriate. If these assumptions are strongly violated, appropriate transformations will be investigated and if required alternative statistical analyses considered.

9.3.6. Pharmacodynamic/Biomarker Analyses

Descriptive statistics of both raw and change from baseline data, where appropriate, (i.e. n, arithmetic mean, standard deviation, minimum, median and maximum) will be calculated for pharmacodynamic/biomarker endpoints and summarized across cohorts. Graphical displays will be produced over time if deemed appropriate. All data will be listed.

If data permits, formal statistical analyses of efficacy endpoints may be conducted, if deemed appropriate and full details will be provided in the RAP. Based on the specified statistical analyses, estimates of the differences between doses of otelixizumab and placebo will be calculated and appropriate statistical inferences based on these results will be made. Distributional assumptions underlying the analyses will be assessed as appropriate. If these assumptions are strongly violated, appropriate transformations will be investigated and if required alternative statistical analyses considered.

9.3.7. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between dose, free serum otelixizumab concentration and pharmacodynamic endpoints including free CD3 or bound otelixizumab on CD4+ and CD8+ cells may be investigated first by exploratory graphical analysis and then by non-linear mixed effects modelling. Further details of model terms and possible covariates will be included in the RAP.

9.3.8. Exploratory Biomarker(s) Analyses

The results of these exploratory biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the exploratory biomarker.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of patients begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent (and any amendments) to be obtained for each patient before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

Written informed consent must be obtained from each patient prior to participation in the study.

10.2.1. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the study treatment, and this new event is likely to affect the safety of patients the Sponsor and the investigator will take appropriate urgent safety measures to protect patients against any immediate hazard.

The sponsor or designee will work with the investigator to ensure the IEC/IRB is notified.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, GSK or CRO monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the

discussion will also include identification, agreement and documentation of data items for which the CRF or eCRF will serve as the source document.

GSK or the CRO will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of patients are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK procedures.

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites. If GSK determines such action is needed, CRO/GSK will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action. When feasible, CRO/GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

If the study is suspended or prematurely discontinued for safety reasons, CRO/GSK will promptly inform investigators or the head of the medical institution (where applicable) and the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The CRO on behalf of GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the CRO of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator leaves the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study patients, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal

for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

The results summary for an approved GSK medicinal product will be posted to the Clinical Study Register no later than 12 months after the last subject's last visit (LSLV) or sooner if required by legal agreement, local law or regulation. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of LSLV. When manuscript publication in a peer reviewed journal is not feasible, further study information is posted to the GSK Clinical Study Register to supplement the results summary.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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12. APPENDICES

12.1. Appendix 1: Liver Safety Process

The procedures listed below are to be followed if a patient meets any of the liver chemistry stopping criteria defined in Section 5.3.4

- Immediately withdraw the patient from study treatment if the 6 day treatment period has not been completed. Patients will continue to be monitored for safety as per protocol
- Notify the GSK medical monitor within 24 hours of learning of the abnormality to confirm the patient's study treatment cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 7.1.4), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up withdraw the patient from the study unless further safety follow up is required.
- Do not re-challenge with investigational product

Safety Follow-Up Procedures for patients with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct); or ALT ≥3xULN and INR[1] >1.5 [Stopping Criteria #1]:

- This event is considered an SAE (see Section 7.1.4). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have the patients return to the clinic (within 24 hours) for repeat liver chemistries, additional testing and to be monitored closely (with specialist or hepatology consultation recommended).
- Monitor patients twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for patients with ALT ≥5xULN or ALT ≥3xULN who have hepatitis symptoms or rash, can't be monitored for 4 weeks or have elevations that persist ≥4 weeks [Stopping Criteria #2 - #5]:

- Make every reasonable attempt to have the patient return to the clinic within 24-72 hrs for repeat liver chemistries and additional testing.

[1] INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants.

- Monitor patients weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for patients with ALT ≥ 3xULN and <5xULN and bilirubin <2xULN, who do not exhibit hepatitis symptoms or rash:

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss patient safety.
- Patient can continue study treatment if liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) can be monitored weekly for up to 4 weeks.
- If at any point these patients meet the liver chemistry stopping criteria (outlined in Section 5.3.4), immediately withdraw study treatment, perform additional testing and continue safety follow-up until liver chemistries resolve, stabilize or return to baseline values.
- After 4 weeks of monitoring, if ALT <3xULN and bilirubin <2xULN, patients must be monitored twice monthly until liver chemistries normalize or return to within baseline values.

Additional Follow-Up Procedures for patients who meet *any* of the stopping criteria:

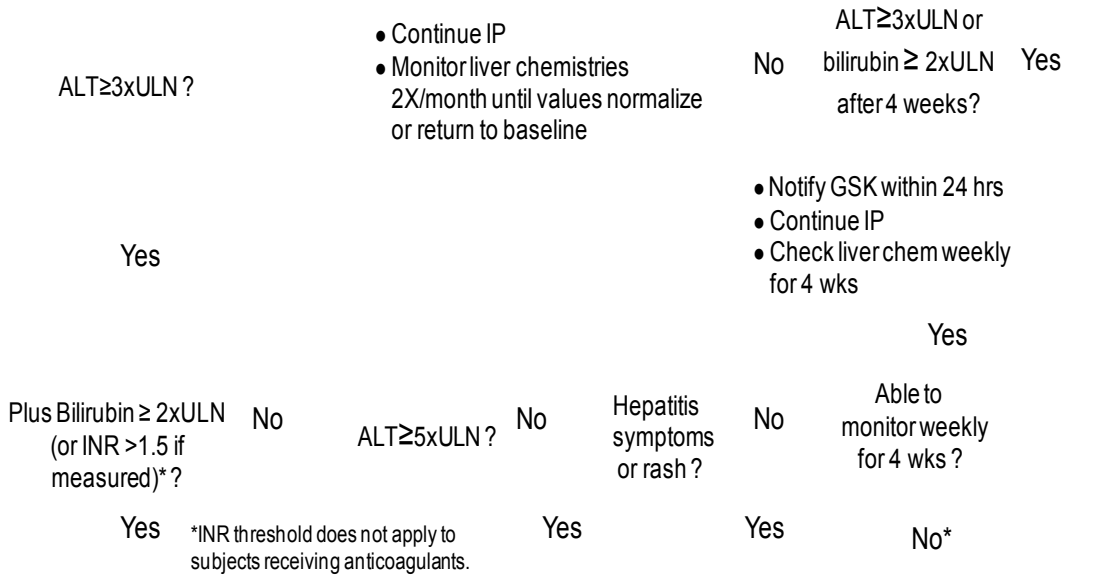
- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody.
- Blood sample for pharmacokinetic (PK) analysis, obtained within 7 days of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the patients's best approximation. If the date/time of the last dose can not be approximated OR a PK sample can not be collected in the time period indicated above, **do not obtain a PK sample**. Instructions for sample handling and shipping are included in the SRM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥ 2xULN.
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) as relevant on the AE eCRF

- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications eCRF.
- Record alcohol use on the Liver Events eCRF.

The following are required for patients with ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in patients with definite or likely acetaminophen use in the preceding week [James, 2009]).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- The Liver Imaging and/or Liver Biopsy eCRFs are also to be completed if these tests are performed.

Refer to the diagram below for a visual presentation of the procedures listed above.



- Instruct subject to stop investigational product (IP)
- Notify GSK and arrange clinical followup within 24 hrs
- Perform liver event f/u assessments (serology, PK, etc)
- Report as an SAE (exc. hepatic impairment or cirrhosis studies); complete SAE & liver event CRF + liver imaging and biopsy CRFs (if tests performed).
- Obtain twice weekly liver chemistries until resolved, stabilized or returned to baseline values
- Consultation with hepatologist/specialist recommended
- **Withdraw subject from study after liver chemistry monitoring complete + do not re-challenge with IP**

- Instruct subject to stop IP
- Notify GSK + arrange clinical followup within 24-72h
- Obtain weekly liver chemistries (*if possible) until resolved, stabilized or returned to baseline values
- Perform liver event follow up assessments (serology, PK sample, etc as in protocol)
- Complete liver event CRF & if appropriate liver imaging and biopsy CRFs (if these tests performed)
- **Withdraw subject from study after liver chemistry monitoring complete + do not rechallenge with study medication**

12.2. Appendix 2: Pharmacogenetic research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	*HLA-B* 57:01 (Human Leukocyte Antigen B)*	Carriage of the *HLA-B*57:01* variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective *HLA-B*57:01* screening and exclusion of *HLA-B*57:01* positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective *HLA-B*57:01* screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. *HLA-B*57:01* screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	*HLA-B*15:02*	Independent studies indicated that patients of East Asian ancestry who carry *HLA-B*15:02* are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of *HLA-B*15:02* prior to initiating treatment with carbamazepine.

Drug	Disease	Gene Variant	Outcome
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	*UGT1A1*28*	Variations in the *UGT1A1* gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular *UGT1A1* gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the *UGT1A1*28* variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples or saliva samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to otelixizumab.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to otelixizumab. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with otelixizumab, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Pharmacokinetics and/or pharmacodynamics of study treatment
- Safety and/or tolerability
- Efficacy

Study Population

Any subject who is enrolled in the clinical study, can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Saliva samples will be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

Saliva (2mL) is collected into the DNA self-collection kit. A single sample will be taken but can be duplicated if the first sample is unusable. It is recommended that the saliva sample be collected between Day 1 and 6.

- The PGx sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The saliva sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the saliva sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of otelixizumab has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to otelixizumab.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the PGx sample, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

Pharmacogenetics Analyses

Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to otelixizumab. The genes that may code for these proteins may also be studied.

Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any saliva being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarize the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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12.3. Appendix 3: Country Specific Requirements

There are no country specific requirements.

12.4. Appendix 4: Procedures for Detection, Evaluation, Follow-Up and Reporting of Adverse Events

Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the appropriate data collection tool.

It is not acceptable for the investigator to send photocopies of the patients's medical records to GSK in lieu of completion of the GSK, AE/SAE data collection tool. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all patient identifiers, with the exception of the patient number, will be blinded on the copies of the medical records prior to submission of to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

Evaluating AEs and SAEs

Assessment of Intensity

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

Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the

study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to the CRO Medical Monitor and GSK.** The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed data collection tool. The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Reporting of SAEs to GSK

Electronic Facsimile and/or e-mail transmission of the paper SAE data collection form is the preferred method to transmit this information to the CRO and GSK Medical Monitors. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the paper SAE data collection form within the designated reporting time frames.

CRO and GSK contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Mixed Meal Tolerance Test (MMTT)

The Mixed Meal Stimulated C-peptide and C-peptide unstimulated will be performed as shown in the protocol Section 6.2 Time and Events Table

On the evening before the C-peptide analysis, subjects should eat a full, standard meal. They must fast from 12 PM the evening before the test until the test is completed. They should remain hydrated and may consume water, black coffee, or black tea (with no sugar or artificial sweeteners) during the fast and test.

Subjects will start the C-peptide analysis in the morning. The time at which the test is started should be kept as consistent as possible. Before the test is started, blood glucose will be measured using a finger-stick test. The Mixed Meal Stimulated C-peptide may be performed only if the blood glucose level is above **70 mg/dL** and no higher than **200 mg/dL**. Documentation that the glucose is in this range will be required. If the glucose is outside this range, this test must be rescheduled.

On the morning of the test, subjects will modify their insulin regimen as follows:

- For subjects who do not use an insulin pump: withhold the morning dose of long- or intermediate-acting insulin. No regular insulin for at least 6 hours before the test; no very short-acting insulin for at least 2 hours before the test.
- For subjects who use an insulin pump: continue the basal insulin rate until the start of the test, then stop the pump. No regular insulin boluses for at least 6 hours before the test; no short-acting insulin boluses for at least 2 hours before the test.

When both unstimulated and Mixed Meal stimulated C-peptide analysis should be done, each subject will consume a standardized amount of Ensure Powder (Abbott) drink supplied by the CRO/GSK. Further details on this product are provided in the study reference manual.

The time when the subject starts drinking the Ensure will be defined as Time 0. The subject will drink the Ensure powder solution within 5 minutes or less. Blood samples will be taken 10 minutes before and immediately before the subject starts drinking the Ensure drink at Time 0. These 2 blood samplings belong to the unstimulated C-peptide analysis. For the Mixed Meal stimulated C-peptide analysis, blood sampling will be done at 15, 30, 60, 90, and 120 minutes after Time 0. The subject may consume water or unsweetened black coffee or tea during this period.

If only the unstimulated C-peptide analysis should be performed (Protocol Section 6.2 Time and Events Table), 1 blood sample is sufficient.

A snack appropriate for a subject with diabetes will be available immediately after the 120-minute blood draw. Glucose will be measured by finger stick; insulin and/or a snack will be given as indicated. As soon as feasible after completing the C-peptide analysis test, subjects will resume their usual insulin and diet regimens.

The tubes with the blood samples will be kept on ice during collection, until centrifuged for 15 min at 1530 x g and 4°C. The plasma will be harvested into 2 green cap transfer vials 2.0 mL and stored at <-15°C until shipment (within 3 weeks of collection). The tubes must be shipped on dry ice and remain frozen until analysis. Further details will be provided in the SRM.

12.6. Appendix 6: Hyperglycaemic Clamp Procedure

1. The evening before the clamp procedure:

AIM: Keep blood glucose (BG) between 80-120mg/dl

- 8pm+: Sc long acting insulin (if basal-bolus therapy) or sc rapid insulin (if sc insulin pump) are replaced by intravenous Actrapid with pump. Blood Glucose measurements every 2h and adapt Actrapid IV treatment as described in the SOP of the hospital, with aim of BG ≈ 90mg/dL at 8am on day of clamp, and without episodes of hypoglycaemia during the night before.

2. Day of clamp procedure:

A. Euglycemic Phase:

AIM: Keep blood glucose between 60-90mg/dl during 180 minutes.

Start Euglycemic phase only when BG 60-90mg/dL

Measure blood glucose every 15 minutes and adapt according to Table A

Table A:

Blood Glucose (BG)	**Actrapid HM Pump IV**	**Infusion 100ml/hr**
Start = t0		
80-90 mg/dL	Daily dose/24/hr	NaCl 0.9%
50-80 mg/dL	0.5IU/hr	NaCl 0.9%
<50mg/dL	STOP TEST*	Glucose 5%
Adaptation of insulin pump during test:		
Adapt Actrapid IV if BG >60mg/dL		
Increase >10mg/dL	+0.5IU/hr	NaCl 0.9%
Decrease >10mg/dL	- 0.5 IU/h	NaCl 0.9%

Blood Glucose (BG)	Actrapid HM Pump IV	Infusion 100ml/hr
Adapt Actrapid IV if BG 50 - 60mg/dL		
	0.5IU/h	NaCl 0.9%
Never stop insulin Pump during the test unless BG <50mg/dL = STOP TEST*		

***: Stop test + REPEAT Clamp 1 day later**

Take blood samples for C-Peptide (Trasylol-EDTA on ice) and glycaemia (NaF) at:

Time	Sample Name
Time 0 + 150 min	L150
Time 0 + 165 min	L165
Time 0 + 180 min**	L180

B. <u>Let blood glucose increase till 180mg/dL</u>

AIM: increase BG till 180mg/dL in a period of 30 minutes.

At Time 0 + 180 min**: **STOP Actrapid IV** and **START glucose 10%** at 50 mL/hr during 15 minutes.

Measure blood glucose every 15 minutes and adapt according to Table B. Blood glucose should increase to minimally 180 mg/dL with help of glucose infusion.

Table B:

	Blood Glucose (BG)	Actrapid HM Pump IV	Glucose Infusion
Adaptation of glucose infusion till BG 180mg:dl:			
15’	<180 mg/dL	STOP	Increase Glucose 10% to 100ml/h
15’	<180 mg/dL	STOP	Replace Glucose 10% by Glucose 20% at 100ml/h (same rate)
15'	<180 mg/dL	STOP	Keep Glucose 20% infusion at 100ml/h (same rate)
180-240mg/dL: START Test =Time 0* **			

C. Hyperglycemic Phase start BG 180-240mg/dL

AIM: keep hyperglycaemia (range 180-240mg/dL) during 140 minutes.

When blood glucose >180 mg/dL = Time 0***

Take blood samples for C-Peptide (Trasylol-EDTA on ice) and glycemia (NaF) at:

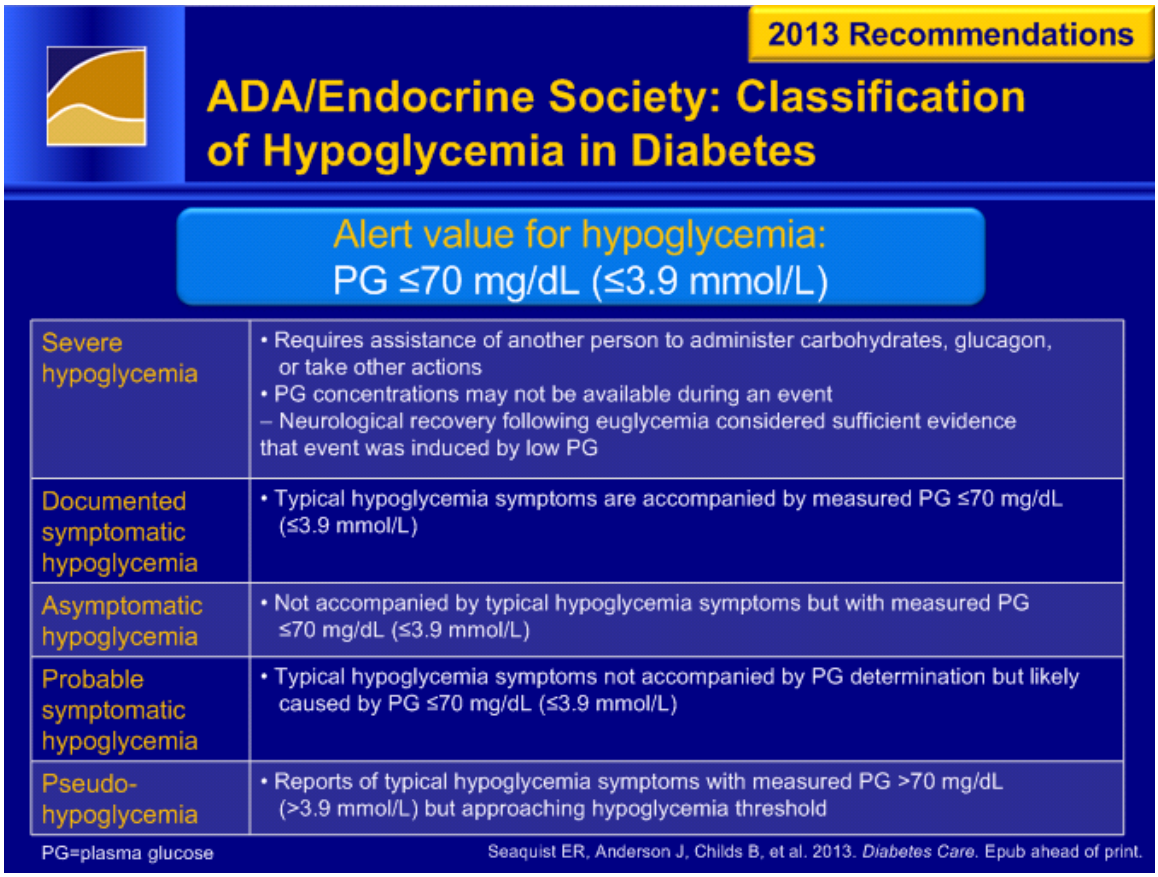
Time	Sample Name
Time 0***	H0
Time 0 + 60 min	H60
Time 0 + 90 min	H90
Time 0 + 120 min	H120
Time 0 + 140 min	H140

Measure BG at least every 15 min and adapt according to Table C.

Table C:

	Blood Glucose (BG)	**Actrapid HM Pump IV**	**Infusion**
	180-240mg/dL	STOP	Keep glucose infusion
Adaptation of glucose infusion if BG >240mg/dl:			
15’	>240 mg/dL	STOP	Glucose 10% 100ml/h
15’	>240 mg/dL	STOP	Glucose 10% 50ml/h
15’	>240 mg/dL	STOP	NaCl 0.9% 50ml/h
Adaptation of glucose infusion if BG <200mg/dl:			
15’	<200 mg/dL	STOP	Glucose 10% 50ml/h
15’	<200 mg/dL	STOP	Glucose 10% 100ml/h
15’	<200 mg/dL	STOP	Glucose 20% 100ml/h

12.7. Appendix 7: ADA Classification



Alert Value for Hyperglycemia: >13.9 mmol/L; >250 mg/dL

12.8. Appendix 8: Protocol Amendment Changes

2011N129686_00	2013-SEP-05	Original
2011N129686_01	2014-FEB-27	Amendment No. 1
2011N129686_02	2014-APR-02	Amendment No. 2
2011N129686_03	2014-JUN-18	Amendment No. 3
2011N129686_04	2014-JUL-28	Republishing-Amendment No. 3
2011N129686_05	2015-FEB-11	Amendment No. 4
2011N129686_06	2015-AUG-18	Amendment No. 5
2011N129686_07	2016-SEP-12	Amendment No. 6
2011N129686_08	2017-SEP-11	Amendment No. 7
2011N129686_09	2017-OCT-26	Amendment No. 8

Protocol Changes for Amendment 8 (26-OCT-2017) from Protocol Amendment 7 (11-Sep-2017)

Where the Amendment Applies

All sites

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

Data which emerged from an interim analysis carried out in this study showed a prompt regain of immune competence observed in treated subjects and consequent rapid resolution of EBV reactivation, both clinically and virologically. The long term EBV related PTLD risk, as observed in solid organ transplant on a chronic immune suppression therapy, is negligible.

Therefore, all references to month 48 and 60 have been removed as no patient currently enrolled in the study has reached month 48 of follow up. For the patients who have yet to complete their 24 month visit, this visit will be treated as a final visit and for those who have gone past month 24, they will be followed up with a final communication or visit (final follow up) upon approval of this protocol amendment.

Data from the literature identified a causal relationship between the degree of immunosuppression and an increased incidence of EBV related Post Transplant Lymphoprolerative Disorders (PTLD) and for this reason a long-term follow-up was implemented at the start of the study.

LIST OF SPECIFIC CHANGES

Section 2. Objectives and Endpoints

PREVIOUS TEXT

Follow up Objectives	**Follow up Endpoints (Data Collected at Month 36, 48 & 60 if Available)**
• To assess long term safety follow-up with otelixizumab treatment.	• Significant adverse events. • Severe (as per ADA classification, Appendix 7) hypoglycemic events which occurred between Months 24 up to 60. • Severe hyperglycemic events which occurred between Months 24 up to 60. • Mean daily insulin use over 7 consecutive days preceding the call. • HbA1c results around time of the phone call.

REVISED TEXT

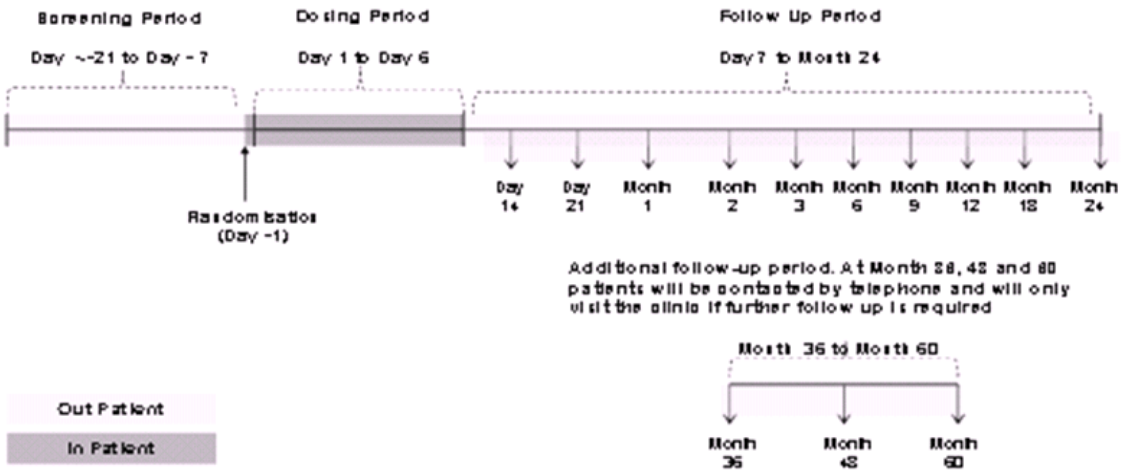
Follow up Objectives	**Follow up Endpoints - Data ~~Collected at Month 36, 48 & 60 if Available~~ <u>from month 36 (if available) or final follow-up. This will only be applicable for patients past month 24</u>**
• To assess long term safety follow-up with otelixizumab treatment.	• Significant adverse events. • Severe (as per ADA classification, Appendix 7) hypoglycemic events which occurred <u>**following**</u> Month 24 <u>**visit**</u> ~~up to 60~~ <u>**(if available) until final follow-up**</u>. • Severe hyperglycemic events which occurred <u>**following**</u> Months 24 <u>**visit**</u> ~~up to 60~~ <u>**(if available) until final follow-up**</u>. • Mean daily insulin use over 7 consecutive days preceding the call. • HbA1c results around time of the phone call.

Section 3.2. Study Schematics

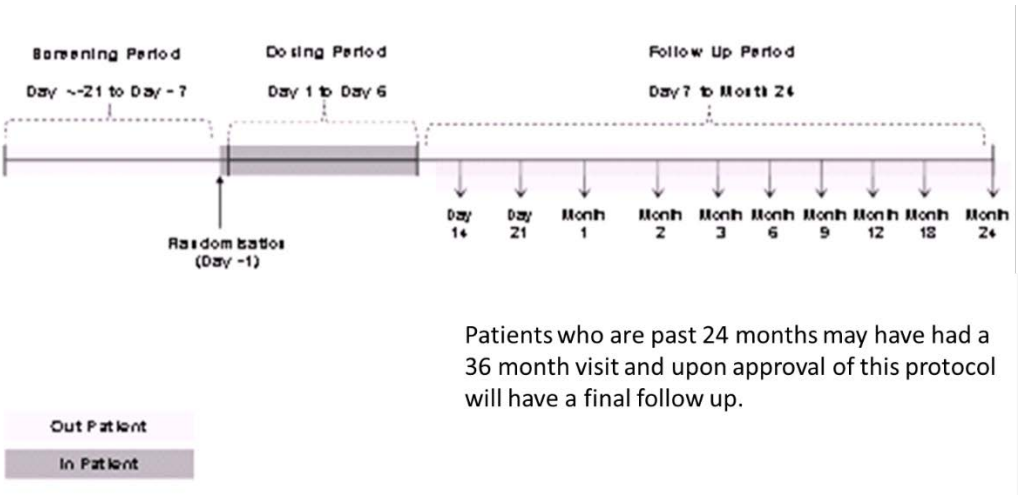
PREVIOUS TEXT

Figure 4 Study Visits Schematic

For study assessments see the Time and Events tables in Section 6.2



REVISED TEXT



Section 3.3.1.2. Study Duration

PREVIOUS TEXT

The overall study duration for each subject is 60 months (up to 61 months including the screening period). Primary study completion for each subject will be at 24 months when all available data will be analysed. Patients will then complete a further 36 month period to enable long-term safety follow-up. The Investigator will contact patients by telephone to discuss their clinical status at Months 36, 48 and 60. Further details are provided in the Study Reference Manual (SRM). If further follow up is required the Investigator will

request that the patient visits the site. See Section 9.3 for a description of analysis considerations.

REVISED TEXT

Data from the literature at the origin of the study design identified a causal relationship between the degree of immunosuppression and an increased incidence of EBV related Post Transplant Lymphoprolerative Disorders (PTLD) and for this reason a long-term follow-up (60 months) was implemented at the start of the study. The interim analysis data which emerged from this study showed a prompt regain of immune competence observed in treated subjects and consequent rapid resolution of EBV reactivation, both clinically and virologically. The long term EBV related PTLD risk, as observed in solid organ transplant on a chronic immune suppression therapy, is negligible. As a result, ~~T~~the overall study duration for each subject ~~is 60 months (up to 61 months including the screening period). Primary study completion for each subject will be at 24 months when all available data will be analysed. Patients will then complete a further 36 month period to enable long-term safety follow-up. The Investigator will contact patients by telephone to discuss their clinical status at Months 36, 48 and 60.~~ **will be 24 months, except for those patients who have already reached the 24 or 36 month follow up in which case they will have a final follow up communication (telephone call or visit) as soon as possible following approval of this amendment 08 of the protocol.** Further details are provided in the Study Reference Manual (SRM). If further follow up is required the Investigator will request that the patient visits the site. See Section 9.3 for a description of analysis considerations.

Section 3.4 Risk Management

PREVIOUS TEXT

Abnormal Liver Chemistry	• In the Belgian Diabetes Registry study, administration of high cumulative doses of otelixizumab (48-64mg) have been temporally associated with abnormal liver chemistry thought to be due to increased cytokine release. In subsequent dose-finding studies conducted at lower doses, no trends with respect to changes in liver chemistry were observed.	Patients with history of liver diseases and/or persistent AST or ALT >2.0 ULN will not be included	Liver chemistry will be monitored daily for the duration of treatment to detect any unanticipated liver event. Liver chemistry individual withdrawal and study stopping criteria and follow-up are in place (Section 5.3).
Progressive Disease			Intensive monitoring and care will be provided according to current standards of care for patients with type 1 diabetes. Diabetes care will be at the discretion of the investigator and may include consultations with a nutritionist or dietician and/or a diabetes educator according to the local institution's guidelines for NOT1DM. Study centres are expected to work with each subject to optimize glycaemic control as per standard of care, with a target HbA1c less than 7% (53 mmol/mol). HbA1c will not be communicated to the trial centre by BDR unless HbA1c is ≥ 7% . Diabetes management will be directed towards helping each subject reach this target or come as close to it as possible.

REVISED TEXT

Abnormal Liver Chemistry	• In the Belgian Diabetes Registry study, administration of high cumulative doses of otelixizumab (48-64mg) have been temporally associated with abnormal liver chemistry thought to be due to increased cytokine release. In subsequent dose-finding studies conducted at lower doses, no trends with respect to changes in liver chemistry were observed.	Patients with history of liver diseases and/or persistent AST or ALT >2.0 ULN will not be included	Liver chemistry will be monitored daily for the duration of treatment to detect any unanticipated liver event. Liver chemistry individual withdrawal and study stopping criteria and follow-up are in place (Section 5.3).
Progressive Disease			Intensive monitoring and care will be provided according to current standards of care for patients with type 1 diabetes. Diabetes care will be at the discretion of the investigator and may include consultations with a nutritionist or dietician and/or a diabetes educator according to the local institution's guidelines for NOT1DM. Study centres are expected to work with each subject to optimize glycaemic control as per standard of care, with a target HbA1c less than 7% (53 mmol/mol). HbA1c will not be communicated to the trial centre by BDR unless HbA1c is ≥ 7% . Diabetes management will be directed towards helping each subject reach this target or come as close to it as possible.
Preterm birth	• **Preclinically, GLP reproductive toxicity studies have not been completed, however; [Gomez-Lopez N, 2016] reported that pregnant B6 mice dosed with an antimouse CD3 monoclonal antibody (mAb) on Gestation Day 16.5 (late gestation) led to an increased frequency of preterm birth and increased pup mortality thought to be due to T-cell activation, however, no data to demonstrate pharmacology was provided.** • **Clinically, one subject in a GDSK**	**Eligibility criteria includes contraception requirements for female subjects and male subjects with female partners of child-bearing potential.**	**Pregnancy will be monitored with serum pregnancy tests at all assessments.**

	clinical trial (RAO112438) was exposed to the investigational product before conception and during the first trimester of pregnancy. One hundred ninety nine (199) days after the last dose of IP, the subject developed Grade 2 or moderate impending parturition prematurus and Grade 2 or moderate hematemesis. The investigator considered that there was no reasonable possibility that the uterine contractions during pregnancy and hematemesis may have been caused by investigational product. After 37 weeks and six days gestation, the subject gave birth to a female live infant. There were no birth defects.		
Opportunistic Infections	**Mild to severe infections that generally respond to customary treatment have occurred in otelixizumab-treated subjects. There have been no opportunistic infections reported with otelixizumab in subjects with T1DM.**	**Patients who are immunocompromised (e.g. HIV positive patients) or those on immunosuppressive medications may be at higher risk of infections are excluded from the clinical study with otelixizumab in T1DM.**	**All safety data will be reviewed by the Safety Review Team per current practices.**
JC Virus (JCV)	**JCV reactivation has not been observed with other anti-CD3 MAbs; however, this has been an area of interest with other types of monoclonal antibodies.**	**Patients with previous history of immunosuppression and/or on active immunosuppressant therapy are excluded from the study.**	

Section 4.2.1 Inclusion Criteria 2

PREVIOUS TEXT

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male or female aged between 16 and 27 years of age inclusive, at the time of signing the informed consent.

   NOTE: Subjects aged 16 to 17 years must be Tanner Stage ≥2 (see SRM). All subjects must weigh at least 31 kg.

2. Diagnosis of diabetes mellitus according to ADA and WHO criteria and consistent with Type 1a (autoimmune) DM, with an interval of approximately 28 days (not more than 32 days) between the initial diagnosis and the first dose of study drug). Written documentation of the diagnosis of DM, including the date of diagnosis, must be obtained from the diagnosing physician.
3. Currently requires insulin treatment for T1DM and has received insulin therapy for at least 7 days prior to screening.
4. Positive for at least one autoantibody associated with T1DM: antibody to glutamic acid decarboxylase (anti GAD), antibody to protein tyrosine phosphatase-like protein (anti IA 2), antibody to islet-cell antigen (ICA) or ZnT8 Autoantibody.
5. Evidence of residual functioning β cells as measured by mixed meal stimulated C-peptide peak level ≥ 0.2 nmol/L.
6. A female subject is eligible to participate if she has a negative pregnancy test as determined by a urine hCG test at screening or prior to dosing AND
    - Agrees to use one of the contraception methods listed in Section 4.3.1. Female subjects must agree to use contraception for 2 weeks prior to dosing and for 60 days after the last dose of study drug.
    - OR has only same-sex partners (refrains from heterosexual intercourse), when this is her preferred and usual lifestyle.
7. Male subjects with female partners of child-bearing potential must agree to use one of the contraception methods listed in Section 4.3.1. This criterion must be followed from 2 weeks prior to dosing and for 60 days after the last dose of study drug.
8. Willing to follow the procedures outlined in the protocol.
9. AST and ALT <2xULN; alkaline phosphatase and bilirubin ≤1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
10. Subjects eligible for enrolment in the study must meet all of the following criteria:
    - QTc <450msec *or*
    - QTc <480msec for patients with bundle branch block

The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF), or another method, machine or manual overread.

- For subject eligibility and withdrawal, QTcF will be used.
- For purposes of data analysis, QTcF will be used as primary.

The QTc should be based on single or averaged QTc values of triplicate electrocardiograms (ECGs) obtained over a brief recording period.

11. Screening total lymphocyte counts within the normal range in two separate samples taken at least three days apart (eg screening and Day -1).

12. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form. In the case of minors (under 18 years) written informed consent must also be obtained from a parent or Legally Acceptable Representative (LAR).

REVISED TEXT

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male or female aged between 16 and 27 years of age inclusive, at the time of signing the informed consent.

   NOTE: Subjects aged 16 to 17 years must be Tanner Stage ≥2 (see SRM). All subjects must weigh at least 31 kg.

2. Diagnosis of diabetes mellitus according to ADA and WHO criteria and consistent with Type 1a (autoimmune) DM, with an interval of approximately 28 days (not more than 32 days) between the initial diagnosis and the first dose of study drug). Written documentation of the diagnosis of DM, including the date of diagnosis, must be obtained from the diagnosing physician.
3. Currently requires insulin treatment for T1DM and has received insulin therapy for at least 7 days prior to screening.
4. Positive for at least one autoantibody associated with T1DM: antibody to glutamic acid decarboxylase (anti GAD), antibody to protein tyrosine phosphatase-like protein (anti IA 2), antibody to islet-cell antigen (ICA) or ZnT8 Autoantibody.
5. Evidence of residual functioning β cells as measured by mixed meal stimulated C-peptide peak level ≥ 0.2 nmol/L.
6. A female subject is eligible to participate if she has a negative pregnancy test as determined by a ~~urine~~ **serum** hCG test at screening or prior to dosing AND
   - Agrees to use one of the contraception methods listed in Section 4.3.1. Female subjects must agree to use contraception for 2 weeks prior to dosing and for 60 days after the last dose of study drug.
   - OR has only same-sex partners (refrains from heterosexual intercourse), when this is her preferred and usual lifestyle.
7. Male subjects with female partners of child-bearing potential must agree to use one of the contraception methods listed in Section 4.3.1. This criterion must be followed from 2 weeks prior to dosing and for 60 days after the last dose of study drug.
8. Willing to follow the procedures outlined in the protocol.
9. AST and ALT <2xULN; alkaline phosphatase and bilirubin ≤1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
10. Subjects eligible for enrolment in the study must meet all of the following criteria:
    - QTc <450msec *or*

- QTc <480msec for patients with bundle branch block

The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF), or another method, machine or manual overread.

- For subject eligibility and withdrawal, QTcF will be used.
- For purposes of data analysis, QTcF will be used as primary.

The QTc should be based on single or averaged QTc values of triplicate electrocardiograms (ECGs) obtained over a brief recording period.

11. Screening total lymphocyte counts within the normal range in two separate samples taken at least three days apart (eg screening and Day -1).
12. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form. In the case of minors (under 18 years) written informed consent must also be obtained from a parent or Legally Acceptable Representative (LAR).

Section 4.6 Patient Completion

PREVIOUS TEXT

A completed patient is one who has completed Month 24.

The end of the study is defined as the last patient's last visit at Month 60.

REVISED TEXT

A completed patient is one who has completed Month 24.

The end of the study is defined as the last patient's last visit at ~~Month 60~~ **Month 24 or at final follow-up.**

Section 6.1 Visit Windows

PREVIOUS TEXT

The following visit windows will be allowed to provide flexibility. Visits completed within the windows will not constitute a protocol deviation:

- A ± 1 day window is permitted for the Day 14 and Day 21 visits and Week 4 telephone call.
- Visits from Week 6 to Month 3 inclusive are permitted a ± 3 day window
- Visits from Month 6 to Month 24 inclusive are permitted a ± 7 day window

- Telephone calls in the follow-up period at Month 36, 48 and 60 are permitted a ±14 day window

REVISED TEXT

The following visit windows will be allowed to provide flexibility. Visits completed within the windows will not constitute a protocol deviation:

- A ± 1 day window is permitted for the Day 14 and Day 21 visits and Week 4 telephone call.
- Visits from Week 6 to Month 3 inclusive are permitted a ± 3 day window
- Visits from Month 6 to Month 24 inclusive are permitted a ± 7 day window
- Telephone calls**/visits** in the follow-up period at Month 36~~, 48 and 60~~ **and final-up** are permitted a ±14 day window

Section 6.2.2 Dosing and follow-up

PREVIOUS TEXT

			Day								Month									
	-2	-1	1	2	3	4	5	6	14	21	Week 4	Week 6	2	3	6	9	12	18	24	36, 48 & 60#
Patient admitted to unit[1]	X																			
In Patient		X	X	X	X	X[2]	X[2]	X[2]												
Prophylaxis (Section 5.10) then IV Dosing of study treatment			X	X	X	X	X	X												
Patient Discharged[2]								X												
Out Patient#						X	X	X	X	X		X	X	X	X	X	X	X	X	
Telephone call to collect AEs, hypoglycemic and hyperglycemic events and concomitant medication use											X									X
Brief Physical Examination		X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	X		X	X	X	X	X	X	X	X	
12 lead ECG[4,6]		X	X	X	X	X	X	X	X								X		X	
Vital Signs[5,6]		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Urine Pregnancy Test		X										X	X	X	X	X	X	X	X	
Alcohol & drugs of abuse test		X																		
Haematology[7]		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	

			Day								Month									
	-2	-1	1	2	3	4	5	6	14	21	Week 4	Week 6	2	3	6	9	12	18	24	36, 48 & 60#
Clinical Chemistry[7]		X	X	X	X	X	X	X[8]	X			X		X	X	X	X	X	X	
HSV-1 & HSV-2 IgG & IgM[9]		X																		
EBV Viral Load (PCR)[7]		X						X		X		X	X	X	X[10]				X	
EBV Serology - IgG and IgM [7]		X						X		X		X	X	X	X		X		X	
CMV Serology - IgG and IgM[7]		X						X				X	X	X	X		X		X	
PK Blood Sample[6]			X	X	X	X	X	X	X[11]											
CD3 Saturation, free CD3 bound otelixizumab /CD4+/CD8+ Blood Sample[6]			X	X	X	X	X	X	X[11]											
Record insulin usage for 7 days before visit / call		X							X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment			<----------																	
Concomitant Medication Review			<----------																	
Hypoglycaemic / Hyperglycaemic Events			<----------																	
Anti-GAD, anti-IA2, antibody to islet-cell antigen (ICA), anti-ZnT8 & Insulin-antibodies (IAA)		X																		
Anti-otelixizumab antibodies Blood Sample		X												X	X					
Mixed Meal Stimulated C-peptide (MMTT)[12]														X	X[14]		X	X	X[14]	
Beta Cell Function by Hyperglycaemic Clamp[13]		X													X[14]				X[14]	
HbA1c		X													X		X		X	X[15]
Bodyweight		X										X	X	X	X	X	X	X	X	
Various Blood samples for Exploratory Biomarkers		X						X[16]				X		X	X		X		X[17]	
Saliva sample for Pharmacogenetics (PGx)[18]			<----------																	

#Patients will record insulin usage for 7 days prior to out-patient visits (up to Month 24) and before telephone calls in Month 36, 48 and 60. Significant AEs including hypoglycaemic (≤3.9 mmol/L; ≤70 mg dL) and hyperglycaemic (>13.9 mmol/L; >250 mg/dL) events will be recorded in a diary whenever they occur, to include start and stop dates.

1. Patient admitted evening of Day -2
2. Discharged on Day 6 if health considered satisfactory by the investigator. Dosing Day 4-6 may be performed on out-patient basis (see Section 3.1)
3. Physical exam performed to monitor for changes in clinical status
4. ECG pre-dose (in triplicate), at the end of the infusion and 6 hours post start infusion (if infusion <6 hours)
5. Vital signs include temperature, blood pressure and pulse rate (in triplicate), and respiration rate
6. See Section 6.2.3 for timings
7. Pre-dose on dosing days
8. If LFTs have shown an upward trend continue to monitor daily after day 6

9. HSV-1 & HSV-2 IgG & IgM will be measured at Day -1 and during the study if clinically indicated
10. If still positive at 6 months EBV viral load will be monitored every 3 months until month 24
11. One sample during visit
12. Blood samples for C-peptide and glucose levels collected at -10, 0, 15, 30, 60, 90 and 120 minutes
13. Plasma C-peptide and glucose levels will be measured during the hyperglycaemic clamp procedure at the following time points: L150, L165 and L180 minutes [during the euglycaemic (L)ow phase], H0, H60, H90, H120 and H140 minutes [during the hyperglycaemic (H)igh phase]
14. Mixed Meal and Glucose Clamp must be separated by at least 4 days
15. Patients will be asked to report verbally their HbA1c at Month 36, 48 & 60 followed eventually (if available) by a printed result via regular mail (or scan electronically).
16. Limited biomarkers on Day 6 pre-dose
17. Blood samples for exploratory biomarkers will only be analysed at Month 24 if indicated based on Month 12 results
18. One PGx (DNA) saliva sample taken between Day 1 and 6

REVISED TEXT

			Day								Month									
	-2	-1	1	2	3	4	5	6	14	21	Week 4	Week 6	2	3	6	9	12	18	24	~~36, 48 & 60#~~36 month (if applicable) and/or final follow up
Patient admitted to unit[1]	X																			
In Patient		X	X	X	X	X[2]	X[2]	X[2]												
Prophylaxis (Section 5.10) then IV Dosing of study treatment			X	X	X	X	X	X												
Patient Discharged[2]								X												
Out Patient#						X	X	X	X	X		X	X	X	X	X	X	X	X	
Telephone call or out-patient visit to collect AEs, hypoglycemic and hyperglycemic events and concomitant medication use											X									X
Brief Physical Examination		X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	X		X	X	X	X	X	X	X	X	
12 lead ECG[4,6]		X	X	X	X	X	X	X	X								X		X	
Vital Signs[5,6]		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	

			Day								Month									
	-2	-1	1	2	3	4	5	6	14	21	Week 4	Week 6	2	3	6	9	12	18	24	~~36, 48 & 60#~~36 month (if applicable) and/or final follow up
Serum Pregnancy Test		X										X	X	X	X	X	X	X	X	
Alcohol & drugs of abuse test		X																		
Haematology[7]		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Clinical Chemistry[7]		X	X	X	X	X	X	X[8]	X			X		X	X	X	X	X	X	
HSV-1 & HSV-2 IgG & IgM[9]		X																		
EBV Viral Load (PCR)[7]		X						X		X		X	X	X	X[10]				X	
EBV Serology - IgG and IgM [7]		X						X		X		X	X	X	X		X		X	
CMV Serology - IgG and IgM[7]		X						X				X	X	X	X		X		X	
PK Blood Sample[6]			X	X	X	X	X	X	X[11]											
CD3 Saturation, free CD3 bound otelixizumab /CD4+/CD8+ Blood Sample[6]			X	X	X	X	X	X	X[11]											
Record insulin usage for 7 days before visit / call		X							X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment			<----------																	
Concomitant Medication Review			<----------																	
Hypoglycaemic / Hyperglycaemic Events			<----------																	
Anti-GAD, anti-IA2, antibody to islet-cell antigen (ICA), anti-ZnT8 & Insulin-antibodies (IAA)		X																		
Anti-otelixizumab antibodies Blood Sample		X												X	X					
Mixed Meal Stimulated C-peptide (MMTT)[12]														X	X[14]		X	X	X[14]	
Beta Cell Function by Hyperglycaemic Clamp[13]		X													X[14]				X[14]	
HbA1c		X													X		X		X	X[15]
Bodyweight		X										X	X	X	X	X	X	X	X	
Various Blood samples for Exploratory Biomarkers		X						X[16]				X		X	X		X		X[17]	
Saliva sample for Pharmacogenetics (PGx)[18]			<----------																	

#Patients will record insulin usage for 7 days prior to out-patient visits (up to Month 24) and before telephone call/visit in Month 36 (if applicable) or final follow up. Significant AEs including hypoglycaemic (≤3.9 mmol/L; ≤70 mg dL) and hyperglycaemic (>13.9 mmol/L; >250 mg/dL) events will be recorded in a diary whenever they occur, to include start and stop dates

1. Patient admitted evening of Day -2
2. Discharged on Day 6 if health considered satisfactory by the investigator. Dosing Day 4-6 may be performed on out-patient basis (see Section 3.1)
3. Physical exam performed to monitor for changes in clinical status
4. ECG pre-dose (in triplicate), at the end of the infusion and 6 hours post start infusion (if infusion <6 hours)
5. Vital signs include temperature, blood pressure and pulse rate (in triplicate), and respiration rate
6. See Section 6.2.3 for timings
7. Pre-dose on dosing days
8. If LFTs have shown an upward trend continue to monitor daily after day 6
9. HSV-1 & HSV-2 IgG & IgM will be measured at Day -1 and during the study if clinically indicated
10. If still positive at 6 months EBV viral load will be monitored every 3 months until month 24
11. One sample during visit
12. Blood samples for C-peptide and glucose levels collected at -10, 0, 15, 30, 60, 90 and 120 minutes
13. Plasma C-peptide and glucose levels will be measured during the hyperglycaemic clamp procedure at the following time points: L150, L165 and L180 minutes [during the euglycaemic (L)ow phase], H0, H60, H90, H120 and H140 minutes [during the hyperglycaemic (H)igh phase]
14. Mixed Meal and Glucose Clamp must be separated by at least 4 days
15. Patients will be asked to report verbally their HbA1c at Month 36 ~~48 & 60~~ **(if applicable) and/or final follow-up;** followed eventually (if available) by a printed result via regular mail (or scan electronically).
16. Limited biomarkers on Day 6 pre-dose
17. Blood samples for exploratory biomarkers will only be analysed at Month 24 if indicated based on Month 12 results
18. One PGx (DNA) saliva sample taken between Day 1 and 6

Section 6.4.4. 2 Clinical Chemistry

PREVIOUS TEXT

BUN	Potassium	AST (SGOT)	Total and direct bilirubin*
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose, fasting	Total CO_2	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
To include CRP (Day -1 only)			

- It is not mandatory to measure fractionated bilirubin if total bilirubin is not above the normal range.

NOTE: Details of Liver Chemistry Stopping Criteria and Follow-Up Procedures are given in Section 5.3.4

Other

Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).
Pregnancy (Urine test)

REVISED TEXT

BUN	Potassium	AST (SGOT)	Total and direct bilirubin*
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose, fasting	Total CO_2	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
To include CRP (Day -1 only)			

- It is not mandatory to measure fractionated bilirubin if total bilirubin is not above the normal range.

NOTE: Details of Liver Chemistry Stopping Criteria and Follow-Up Procedures are given in Section 5.3.4

Other

Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).
Pregnancy (~~Urine~~ **Serum** test)

Section 6.7.3 Daily Insulin Use

PREVIOUS TEXT

Patients will be asked to record their daily insulin usage thoroughly and accurately for 7 consecutive days in a diary during the week before all outpatient visits or phone calls, ie, at Baseline, Day 14 and 21, Week 4 and 6 and Months 2, 3, 6, 9, 12, 18, and 24, and before each telephone call in the long term follow-up period (Month 36, 48 and 60). Information on insulin usage will be transcribed from diaries into the eCRF.

REVISED TEXT

Patients will be asked to record their daily insulin usage thoroughly and accurately for 7 consecutive days in a diary during the week before all outpatient visits or phone calls, ie, at Baseline, Day 14 and 21, Week 4 and 6 and Months 2, 3, 6, 9, 12, 18, ~~and~~ 24~~, and before each telephone call in the long term follow-up period (Month 36, 48 and 60).~~ **36 (if applicable) and final follow up (if applicable)**. Information on insulin usage will be transcribed from diaries into the eCRF.

Section 6.7.4 Glycosylated Haemoglobin, HbA1c

PREVIOUS TEXT

HbA1c will be recorded at visits as shown in the Time and Events Table. Patients will be asked to report verbally their HbA1c (if available) around the time of month 36, 48 and 60 followed eventually by a printed result via regular mail (or scan electronically) if available. HbA1c values will be captured in the eCRF.

REVISED TEXT

HbA1c will be recorded at visits as shown in the Time and Events Table. Patients will be asked to report verbally their HbA1c (if available) around the time of month 36~~, 48 and 60~~ **(if applicable) and/or final follow-up;** followed eventually by a printed result via regular mail (or scan electronically) if available. HbA1c values will be captured in the eCRF.

Section 7.1.1 Time Period for Collecting AE and SAE Information

PREVIOUS TEXT

AEs will be collected from signing the Informed Consent Form until the follow-up contact, approximately 5 years post last dose.

REVISED TEXT

AEs will be collected from signing the Informed Consent Form until the follow-up contact, approximately ~~5~~ **2** years post last dose.

Section 9.3.2.1 Final Analyses (24 Months)

PREVIOUS TEXT

The final primary analysis will occur when the last planned cohort (i.e. based on the dose escalation criteria) have completed 24 months study duration.

REVISED TEXT

The final analysis will occur when the last planned cohort (i.e. based on the dose escalation criteria) have completed 24 months study duration **or have had a final follow-up for subjects who, at the time of the implementation of Amendment 08 of the protocol, will have already reached months 24.**

Section 9.3.2.2 Final Analyses (60 Months)

PREVIOUS TEXT

The final analysis will occur when the last planned cohort (i.e. based on the dose escalation criteria) has completed 60 months study duration and last subject last visit has been achieved.

REVISED TEXT

~~The final analysis will occur when the last planned cohort (i.e. based on the dose escalation criteria) has completed 60 months study duration and last subject last visit has been achieved.~~

AMENDMENT 7

11-SEP-2016

Where the Amendment Applies

All sites

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

All details of how the currently used Ensure powder (Abbott) is prepared has been removed from the Mixed Meal Tolerance Test (Appendix 5). This has been amended because the manufacturer (Abbott) has discontinued the currently used powder and the new product has a slightly different formulation. The details for each of the products will now be detailed in the Study Reference Manual.

LIST OF SPECIFIC CHANGES

Section 12.5 Appendix 5: Mixed Meal Tolerance Test (MMTT)

PREVIOUS TEXT

When both unstimulated and Mixed Meal stimulated C-peptide analysis should be done, each subject will consume a standardized amount of Ensure Powder (Abbott) drink supplied by the CRO/GSK. This drink will be prepared by dissolving 9 cups (± 81g) into 210 ml cold water. This mixture results in a 300 ml drink containing 375 kcal. The volume of dissolved Ensure Powder will contain 6 kcal per kg body weight up to a maximum of 300 ml with 375 kcal.

Weight	**Volume Ensure Powder Drink (375 kcal/300 ml)**
45 kg	216 ml
50 kg	240 ml
55 kg	264 ml
60 kg	288 ml
>60 kg	300 ml

Please see the SRM for further details regarding volumes

REVISED TEXT

When both unstimulated and Mixed Meal stimulated C-peptide analysis should be done, each subject will consume a standardized amount of Ensure Powder (Abbott) drink supplied by the CRO/GSK. **Further details on this product are provided in the study reference manual.** ~~This drink will be prepared by dissolving 9 cups (≈ 81g) into 210 ml cold water. This mixture results in a 300ml drink containing 375 kcal. The volume of dissolved Ensure Powder will contain 6 kcal per kg body weight up to a maximum of 300ml with 375 kcal.~~

~~**Weight**~~	~~**Volume Ensure Powder Drink (375 kcal/300 ml)**~~
~~45 kg~~	~~216 ml~~
~~50 kg~~	~~240 ml~~
~~55 kg~~	~~264 ml~~
~~60 kg~~	~~288 ml~~
~~>60 kg~~	~~300 ml~~

~~Please see the SRM for further details regarding volumes~~

AMENDMENT 6

Where the Amendment Applies

All sites

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

The exploratory objectives and endpoints were amended to allow greater flexibility in biomarker assays to evaluate efficacy following treatment with otelixizumab and to probe novel aspects of the biology of T1D. Previously it was stated that Month 24 blood samples for exploratory biomarker analysis would only be collected if indicated based on results from Month 12 biomarker analysis, however, this is no longer correct as Month 24 samples are being collected routinely. In addition, it was previously stated that exploratory biomarker samples would be collected and only analysed after review of efficacy endpoints, however, this is incorrect and has been clarified as after review of safety endpoints. The Time and Events table was updated to show requirement for telephone calls to patients at Month 36, 48 and 60. Minor changes were made to the 12 Month Interim Analysis, mainly to clarify that a second interim analysis will occur when all patients have completed 12 months study duration. The section header “novel biomarker analyses” was changed to “Exploratory biomarker analyses” for consistency. The name Quest was amended to Q2 Solutions following a company name change, and Study Procedures Manual was changed to Study Reference Manual in line with recent renaming by GSK.

LIST OF SPECIFIC CHANGES

Section 2 OBJECTIVES AND ENDPOINTS, Exploratory Objectives and Exploratory Endpoints

PREVIOUS TEXT

Exploratory Objectives*	**Exploratory Endpoints***
• To assess the effect of a single course of otelixizumab treatment on circulating lymphocyte populations over 24 months in NOT1DM patients.	• Change from baseline in absolute lymphocyte counts and subsets (CD3+ CD4+, CD3+ CD8+, and CD19+ cells) and phenotype (eg effector, memory, regulatory T cells, eg CD45RA, CCR7+) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on circulating regulatory T cell numbers (as quantified by demethylated FoxP3 expression) over 24 months in NOT1DM patients.	• Change from baseline in demethylated FoxP3 expression in whole blood over Week 6 to Month 24.

Exploratory Objectives*	**Exploratory Endpoints***
• To assess the effect of a single course of otelixizumab treatment on absolute numbers of circulating antigen specificCD8+ T cells over 24 months in HLA-A2^{+} NOT1DM patients.	• Change from baseline in absolute numbers of HLA-A2-restricted CD8 T lymphocytes reactive to specific auto-antigens (by multimer) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on frequency of cytokine-producing antigen specific T cells over 24 months in NOT1DM patients.	• Change from baseline in frequency of cytokine producing cells following in vitro stimulation with auto-antigens (by ELISPOT) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on serum auto-antibodies titers and serum analytes associated with treatment or autoimmune pathology over 24 months in NOT1DM patients.	• Change from baseline in auto-antibody titres (using a panel of common auto-antibodies associated with T1DM antigens and possibly other auto-antigens) and serum analytes (such as cytokines/ chemokines) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on clonal repertoire of circulating T cell populations over 24 months in NOT1DM patients.	• Change from baseline in T cell clonal repertoire by TCR deep sequencing over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on β-cell death over 24 months in NOT1DM patients.	• Change from baseline in serum by measuring relative levels of unmethylated *INS* DNA and/or other biomarkers for β-cell death in serum over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on suppression activity of circulating T lymphocytes over 24 months in NOT1DM patients.	• Change from baseline in relative levels of T lymphocyte suppression using micro suppression assay over Week 6 to Month 24.

REVISED TEXT

Exploratory Objectives*	**Exploratory Endpoints***
• To assess the effect of a single course of otelixizumab treatment on circulating lymphocyte populations over 24 months in NOT1DM patients.	• Change from baseline in absolute lymphocyte counts **and ratios in some or all, but not limited to** ~~and~~ subsets (CD3+ CD4+, CD3+ CD8+, and CD19+ cells) and phenotype (eg effector, memory, regulatory T cells, eg CD45RA, CCR7+) over Week 6 to Month 24.

Exploratory Objectives*	**Exploratory Endpoints***
• To assess the effect of a single course of otelixizumab treatment on circulating **lymphocytes such as** regulatory T cell numbers (as quantified by **CD3 and** demethylated FoxP3 expression) **and Th17 cells** over 24 months in NOT1DM patients.	• Change from baseline in **cell-type specific methylation marker** ~~demethylated FoxP3~~ expression **in some or all, but not limited to CD3, FoxP3 and Th17** in whole blood over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on absolute numbers **and ratios** of circulating antigen specificCD8+ T cells over 24 months in HLA-A2^{+} NOT1DM patients.	• Change from baseline in absolute numbers **and ratios** of HLA-A2-restricted CD8 T lymphocytes reactive to specific auto-antigens (by multimer) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on frequency of cytokine-producing antigen specific T cells over 24 months in NOT1DM patients.	• Change from baseline in frequency of cytokine producing cells following in vitro stimulation with auto-antigens **and viral antigens** (by ELISPOT) over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on serum auto-antibodies titers and serum analytes associated with treatment or autoimmune pathology over 24 months in NOT1DM patients.	• Change from baseline in auto-antibody titres (using a panel of common auto-antibodies associated with T1DM antigens and possibly other auto-antigens) and serum analytes (such as cytokines/ chemokines) **during the first 14 days of treatment and** over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on clonal repertoire of circulating T cell populations **and/or trancriptomic gene expression changes** over 24 months in NOT1DM patients.	• Change from baseline in T cell clonal repertoire by TCR deep sequencing over ~~Week~~ **Day** 6 to Month 24. • **Change from baseline in transcriptomic gene expression profile(s) by micro-array and/or alternative equivalent technologies including RNA sequencing at selected timepoint(s) post dosing**.
• To assess the effect of a single course of otelixizumab treatment on β-cell death over 24 months in NOT1DM patients.	• Change from baseline in serum by measuring relative levels of unmethylated *INS* DNA and/or other biomarkers for β-cell death in serum over Week 6 to Month 24.
• To assess the effect of a single course of otelixizumab treatment on suppression activity of circulating T lymphocytes over 24 months in NOT1DM patients.	• Change from baseline in relative levels of T lymphocyte suppression using micro suppression assay over Week 6 to Month 24. **Suppression activity may be further evaluated by adapting assay conditions possibly through adding and/or blocking of stimuli.**

Section 2 OBJECTIVES ANS ENDPOINTS, Change to last row in table (footnote)

PREVIOUS TEXT

*Samples will be collected and only analysed after review of efficacy endpoints

REVISED TEXT

*Samples will be collected and only analysed after review of ~~efficacy~~ **safety** endpoints

Section 6.2 Time and Events Tables (6.2.2 Dosing and Follow-Up), row 6 amended

PREVIOUS TEXT

Telephone call to collect AEs, hypoglycemic and hyperglycemic events and concomitant medication use										X								

REVISED TEXT

Telephone call to collect AEs, hypoglycemic and hyperglycemic events and concomitant medication use										X								**X**

Section 6.2 Time and Events Tables (6.2.2 Dosing and Follow-Up), footnote 17 amended

PREVIOUS TEXT

Blood samples for exploratory biomarkers will only be collected at Month 24 if indicated based on Month 12 results

REVISED TEXT

Blood samples for exploratory biomarkers will only be ~~collected~~ **analysed** at Month 24 if indicated based on Month 12 results

Section 6.6.4 Exploratory Biomarkers

PREVIOUS TEXT

Blood samples for exploratory biomarkers will be collected at the time points indicated in the Time and Event Table (Section 6.2). Blood will be collected and processed for the following biomarkers and sample types. Exploratory samples will be collected and only analysed after review of efficacy endpoints. Month 24 blood samples for exploratory biomarkers will only be collected if indicated based on results from Month 12 biomarker analysis. Full details on sample collection, processing and shipment will be provided in the SPM/Quest manual

Biomarker Assay	Sample Type	D -1	D6	M1.5	M3	M6	M12	M24*
CD8+ Multimer analysis	PBMC	X		X	X	X	X	X
Whole Blood Absolute Lymphocyte Count + CD3+ CD4+, CD3+ CD8+, CD19+	BCT CytoChex	X		X	X	X	X	X
Antigen-specific ex vivo ELISPOT responses	PBMC	X		X	X	X	X	X
Demethylated FoxP3/CD3 analysis	BD Vacutainer Plus 2mL lavender/EDTA with Hemogard – part number 368841	X		X	X	X	X	X
Exploratory Lymphocyte Sub-set phenotyping of CD3+ T (eg effector, memory, regulatory T cells using cell surface markers such as CD45RA, CCR7) and CD19+ B cells	PBMC	X		X	X	X	X	X
Auto-antibody (serum analyte) analysis	Serum	X		X	X	X	X	X
TCR deep sequencing	PAXgene Blood RNA Tube	X	X[1]	X	X	X	X	X
Beta cell death biomarker analysis	Serum	X		X	X	X	X	X
T lymphocyte suppression assay	PBMC	X		X	X	X	X	X

[1]Sample taken pre-dose * Blood samples for exploratory biomarkers will only be collected at Month 24 if indicated based on Month 12 results

REVISED TEXT

Blood samples for exploratory biomarkers will be collected at the time points indicated in the Time and Event Table (Section 6.2). ~~Blood will be collected and processed for the following biomarkers and sample types.~~ Exploratory samples will ~~be collected and~~ only **be analysed** after review of ~~efficacy~~ **safety** endpoints. Month 24 blood samples for exploratory biomarkers will only be ~~collected~~ **analysed** if indicated based on results from Month 12 biomarker analyses. Full details on sample collection, processing and shipment will be provided in the S**R**~~P~~M/**Q^2 Solutions** ~~Quest~~ manual **Below is a table with details**

on the exploratory biomarker assays under consideration to address the exploratory objectives and endpoints as outlined in Section 2. As new data emerge, it may also be possible to probe novel aspects of the biology of T1D, as well as the biological and clinical responses to otelixizumab. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events.

Biomarker Assay	Sample Type	D -1	D6	M1.5	M3	M6	M12	M24*
CD8+ Multimer analysis	PBMC	X		X	X	X	X	X
Whole Blood Absolute Lymphocyte Count + CD3+ CD4+, CD3+ CD8+, CD19+	BCT CytoChex	X		X	X	X	X	X
Antigen-specific ex vivo ELISPOT responses	PBMC	X		X	X	X	X	X
Demethylated FoxP3/CD3/**Th17** analysis	BD Vacutainer Plus 2mL lavender/EDTA with Hemogard – part number 368841	X		X	X	X	X	X
Exploratory Lymphocyte Sub-set phenotyping of CD3+ T (eg effector, memory, regulatory T cells using cell surface markers such as CD45RA, CCR7) and CD19+ B cells	PBMC	X		X	X	X	X	X
Auto-antibody (±serum analyte**s**) analysis	Serum	X		X	X	X	X	X
TCR deep sequencing[2]	PAXgene Blood RNA Tube	X	X[1]	X	X	X	X	X
Beta cell death biomarker analysis	Serum	X		X	X	X	X	X
T lymphocyte suppression assay	PBMC	X		X	X	X	X	X

[1]Sample taken pre-dose

[2] Similar additional transcriptomics analysis may be performed using micro-array and/or alternative equivalent technologies including RNA sequencing

* Blood samples for exploratory biomarkers will only be ~~collected~~ **analysed** at Month 24 if indicated based on Month 12 results

9.3.1.3. Interim Analysis (12 Months)

PREVIOUS TEXT

A formal unblinded interim analysis is also planned to occur:

- When all patients have completed 12 months study duration for cohorts 1 and 2, but may also include available data from subsequent cohorts 3 and 4 as appropriate.
- The purpose of this interim analysis is to provide the project team and GSK stakeholders with key data to inform internal decision making, in order to plan future studies within the clinical development for the asset.
- There are no planned implications for the conduct of the study.

- Appropriate data summaries will be at the treatment group level for key endpoints of interest and the circulation of results will be restricted to selected members of the project team and key GSK stakeholders. Results or discussions will not be circulated to staff involved in the conduct of the study at the sites.
- Full details of planned interim analysis will be included in the reporting and analysis plan (RAP).

REVISED TEXT

9.3.1.3. Interim Analysi~~e~~s (12 Months)

~~A f~~**F**ormal unblinded interim analysi~~e~~s is**are** also planned: ~~to occur:~~

- **The first interim** will occur ~~W~~**w**hen all patients **in cohorts 1 and 2** have completed 12 months study duration ~~for cohorts 1 and 2~~, but may also include **any** available data from subsequent cohorts 3 and 4 as appropriate.
- **The second interim will occur when all patients from the last fully enrolled cohort (i.e. not stopped due to safety / tolerability) have completed 12 months study duration.**
- The purpose of ~~this~~ **these** interim ~~analysis~~ **analyses** is to provide the project team and GSK stakeholders with key data to inform internal decision making, in order to plan future studies within the clinical development for the asset.
- There are no planned implications for the conduct of the study.
- Appropriate data summaries will be at the treatment group level for key endpoints of interest and the circulation of results will be restricted to selected members of the project team and key GSK stakeholders. Results or discussions will not be circulated to staff involved in the conduct of the study at the sites.
- Full details of planned interim ~~analysis~~ **analyses** will be included in the reporting and analysis plan (RAP).

9.3.8. Novel Biomarker(s) Analyses

PREVIOUS TEXT

The results of these biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the novel biomarker

REVISED TEXT

9.3.8. ~~Novel~~ Exploratory Biomarker(s) Analyses

The results of these **exploratory** biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the ~~novel~~ **exploratory** biomarker.

AMENDMENT 5

Where the Amendment Applies

All sites

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

Further clarification around the assay for assessing screening EBV IgG and IgM was included to ensure patients are not excluded unnecessarily. The risk management table was also updated to reflect the changes. Exclusion criterion number 18 was split into two exclusion criteria (18 and 19) to clarify that a patient will not be eligible if they have a positive EBV capsid Ab IgM in absence of a positive EBV EBNA Ab IgG (exclusion criterion 18), EBV viral load of >10,000 copies per 10^6 peripheral blood mononuclear cells (PBMCs) as determined by quantitative polymerase chain reaction (qPCR) (exlusion criterion 19). A footnote was added to Table 6 (Stopping Criteria for CRS-Adverse Events) to add further clarification on individual dosing stopping criteria, i.e., to clarify that objective or subjective endpoints must be of different types during one 24 hour dosing period for any of the scenarios involving more than one endpoint. The dose preparation section was updated to clarify that an additional maximum of 30 minutes is allowed for dose preparation tasks such as connection of line and filter, pump set up and priming and purging the lines and that if 6 hours is exceeded, then the syringe and infusion materials (IV line, stopcock and PES filter) must be discarded and a new syringe of dose and infusion materials used. This is to ensure that the stability period is not exceeded. EBV serology to assess IgG and IgM was included at Day -1 in Table 6.2.2 of the Time and Event Tables (Dosing and Follow-Up) to provide a baseline against which follow up results may be compared.

LIST OF SPECIFIC CHANGES

Section 3.4 Risk Management.Table 2 Summary of Key Issues, their Impact and Strategy to Mitigate Risk. Potential Risk column on Epstein-Barr virus (EBV), 3rd column Impact-Eligibility Criteria

PREVIOUS TEXT

Patients within 3 months of evidence of acute/active EBV infection (e.g Symptomatic, positive EBV IgM or EBV viral load of >10,000 copies per 10^6 lymphocytes) will not be enrolled in the study.

REVISED TEXT

Patients within 3 months of evidence of acute/active EBV infection (e.g)

- Symptomatic
- Positive **EBV capsid Ab IgM in absence of a positive EBV EBNA Ab IgG**
- EBV viral load of >10,000 copies per 10^6 lymphocytes

will not be enrolled in the study

Section 4.2.2 Exclusion Criterion number 18 amended and split into exclusion criteria 18 and 19

PREVIOUS TEXT

18. Positive EBV IgM or EBV viral load of >10,000 copies per 10^6 peripheral blood mononuclear cells (PBMCs) as determined by quantitative polymerase chain reaction (qPCR).

REVISED TEXT

18. Positive **EBV capsid Ab IgM in absence of a positive EBV EBNA Ab IgG**
19. EBV viral load of >10,000 copies per 10^6 peripheral blood mononuclear cells (PBMCs) as determined by quantitative polymerase chain reaction (qPCR).

Section 5.3.1 Cytokine Release Syndrome Stopping Criteria

Footnote added under Table 6 Stopping Criteria for CRS-Adverse Events.

Note: in order to meet individual stopping criteria, the reported objective or subjective endpoints must be of different types during one 24 hour dosing period for any of the scenarios involving more than one endpoint.

Section 5.6.2 Study Medication Preparation, the following new bullets were added under bullet 2

- **Important Note:** When drawn into the syringe for administration to the patient it must be administered within 6 hours If needed an additional maximum of 30 minutes is allowed for tasks such as connection of line and filter, pump set up and priming and purging the lines. **However, every attempt should be made not to exceed a total time of 6 hours if possible.**
- **Important Note:** If the infusion period will exceed 6 hours, then the syringe and infusion materials (IV line, stopcock and PES filter) must be discarded and a new syringe of dose and infusion materials used. Preparation of syringes(s) must be recorded on the Test Article Administration Form.
- The dose will be drawn from a fresh bag of 0.1 mg/mL Otelixizumab solution.
- The pharmacist should allow sufficient time to prepare the final solution and must ensure that infusion components are changed at the appropriate times.
- The temperature must be controlled and should not exceed 25°C.
- The temperature will be recorded at the pharmacy (when the IV bag is ready to be transferred to the dosing unit) and at the dosing unit (upon receipt).

Section 5.6.3 Study Medication Administration, additional text added to first bullet

PREVIOUS TEXT

Withdraw the total required volume of Otelixizumab Solution for Infusion, 0.1 mg/mL or 0.9% Sodium Chloride for the placebo, using the syringe(s) that will be used for administration with the infusion pump.

REVISED TEXT

Withdraw the total required volume of Otelixizumab Solution for Infusion, 0.1 mg/mL or 0.9% Sodium Chloride for the placebo, using the syringe(s) that will be used for administration with the infusion pump **(see Section 5.6.2 regarding stability time and time allowed for preparation).**

Section 6.2.2 Dosing and Follow-up, row 16 amended to include EBV IgG and IgM sample at Day -1

PREVIOUS TEXT

EBV Serology - IgG and IgM [7]								X		X		X	X	X	X		X		X	

REVISED TEXT

EBV Serology - IgG and IgM [7]		**X**					X		X		X	X	X	X		X		X	

AMENDMENT 4

Where the Amendment Applies

All sites

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

To increase flexibility for patients, dosing on Day 4, 5 & 6 may be performed on an out-patient basis if the Investigator is satisfied with the clinical status of the patient. Clarification that the requirement to replace a withdrawn patient will be based on the reason for withdrawal and that patient assessments following withdrawal will include safety monitoring and may include pharmacodynamic measures if appropriate. Inclusion criteria # 3 was amended to remove the need for intensive insulin therapy and 3 insulin injections daily as this is considered unnecessary. Screen failure data are to be collected so that CONSORT publication requirements can be met. Clarified that i.v. infusion kits are supplied to sites due to the need for kits to be constructed of specific types of materials. Assessment of EBV reactivation will now be conducted at 6 weeks after the first active dose (reduced from 12 weeks) as this is considered a sufficient period for adequate monitoring. The blinding status was amended to clarify that only the patient is blinded to treatment and not site, CRO or sponsor staff. A requirement for pharmacy staff to document investigational product shipping conditions were within a 2-8°C range to ensure product quality was added. The use of an anti-emetic was added as a permitted concomitant medication to be used in the case of nausea and vomiting. A window of ± 1 day was added to the Day 14 and 21 visits and Week 4 telephone call to increase flexibility for both the site and patient. Section 6.2.2 was amended to include a telephone phone call at Week 4 to discuss with the patient AEs, hyperglycaemic and hypoglycaemic events and concomitant medications to check for CRS symptoms; and addition of assessments at Week 6 to facilitate the checking of EBV reactivation following the reduction of the monitoring period from 12 to 6 weeks after the last patient in a cohort receives active treatment. The endpoints were amended to reflect the changes to Week 4 and Week 6. Section 6.2.3 was amended to include ECG at 3 hours as a safety check prior to discharge and to clarify that assessments (ECGs and vital signs) may stop at 3 hours post dose if the patient is discharged, but may continue if the Investigator has any concerns about the clinical status of the patient. Clarification that it is not mandatory to measure fractionated bilirubin if total bilirubin is not above the normal range as this is considered unnecessary. Clarification that insulin is to be recorded for a week prior to outpatient visits and phone calls. Clarification that the grading of cytokine release syndrome adverse events in Section 7.1.5 is shown in Table 5 and subjective and objective endpoints related to stopping criteria are shown in Table 6. Clarification on CRO responsibilities included in several areas in Section 10.5 and Section 10.6. Appendix 5 amended to clarify that CRO/GSK will supply Ensure powder to ensure consistency across sites.

LIST OF SPECIFIC CHANGES

Section 2. OBJECTIVES AND ENDPOINTS, change of period of assessment times (only endpoints with changes are shown below)

PREVIOUS TEXT

Primary Endpoints (Safety)
• Incidence of adverse events (AEs) particularly those related to Cytokine release syndrome (CRS). • Epstein-Barr virus (EBV) reactivation over Months 1-24. • Changes in laboratory values, electrocardiograms (ECGs) and vital signs over Months 1- 24.
Secondary Endpoints (Efficacy)
• Change from baseline in mean daily insulin use over 7 consecutive days during the week preceding the visit over Day 14 and 21 and Months 1-24.
Exploratory Endpoints*
• Change from baseline in absolute lymphocyte counts and subsets (CD3+ CD4+, CD3+ CD8+, and CD19+ cells) and phenotype (eg effector, memory, regulatory T cells, eg CD45RA, CCR7+) over Months 1-24.
• Change from baseline in demethylated FoxP3 expression in whole blood over Months 1-24.
• Change from baseline in absolute numbers of HLA-A2-restricted CD8 T lymphocytes reactive to specific auto-antigens (by multimer) over Months 1-24.
• Change from baseline in frequency of cytokine producing cells following in vitro stimulation with auto-antigens (by ELISPOT) over Months 1-24.

• Change from baseline in auto-antibody titres (using a panel of common auto-antibodies associated with T1DM antigens and possibly other auto-antigens) and serum analytes (such as cytokines/ chemokines) over Months 1-24.
• Change from baseline in T cell clonal repertoire by TCR deep sequencing over Months 1-24.
• Change from baseline in serum by measuring relative levels of unmethylated *INS* DNA and/or other biomarkers for β-cell death in serum over Month 1-24.
• Change from baseline in relative levels of T lymphocyte suppression using micro suppression assay over Month 1- 24.

REVISED TEXT

Primary Endpoints (Safety)
• Incidence of adverse events (AEs) particularly those related to Cytokine release syndrome (CRS). • Epstein-Barr virus (EBV) reactivation over **Day 21** to Month 24. • Changes in laboratory values, electrocardiograms (ECGs) and vital signs over **Day 14** to Month 24.

Secondary Endpoints (Efficacy)
• Change from baseline in mean daily insulin use over 7 consecutive days during the week preceding **all visits and phone calls**.

Exploratory Endpoints*
• Change from baseline in absolute lymphocyte counts and subsets (CD3+ CD4+, CD3+ CD8+, and CD19+ cells) and phenotype (eg effector, memory, regulatory T cells, eg CD45RA, CCR7+) over **Week 6 to** Month 24.
• Change from baseline in demethylated FoxP3 expression in whole blood over **Week 6 to** Month 24.
• Change from baseline in absolute numbers of HLA-A2-restricted CD8 T lymphocytes reactive to specific auto-antigens (by multimer) over **Week 6** to Month 24.
• Change from baseline in frequency of cytokine producing cells following in vitro stimulation with auto-antigens (by ELISPOT) over **Week 6** to Month 24.
• Change from baseline in auto-antibody titres (using a panel of common auto-antibodies associated with T1DM antigens and possibly other auto-antigens) and serum analytes (such as cytokines/ chemokines) over **Week 6** to Month 24.
• Change from baseline in T cell clonal repertoire by TCR deep sequencing over **Week 6** to Month 24.
• Change from baseline in serum by measuring relative levels of unmethylated *INS* DNA and/or other biomarkers for β-cell death in serum over **Week 6** to Month 24.
• Change from baseline in relative levels of T lymphocyte suppression using micro suppression assay over **Week 6** to Month 24.

Section 3.1. Study Design Detail, paragraph 3 and 4

PREVIOUS TEXT

Patients will be dosed within approximately 28 days of diagnosis (not more than 32 days). Insulin usage will be documented for approximately 7 days prior to Day -1. There will be a 7 – 21 day period from screening to admission to the clinic on Day -2 for the first overnight stay of the in-patient period, this time period will ensure appropriate time to review laboratory results prior to randomisation. During the screening period total lymphocytes will be quantified on two occasions at least 3 days apart (one of the assessments may be performed on Day -1); lymphocytes must be confirmed as being within normal limits before administration of the first dose. All screening procedures are outlined in the Time and Events Table in Section 6.2.

On Day -1 safety assessments will be performed as outlined in the Time and Events Table in Section 6.2. If the investigator is satisfied that the patient still meets the entry criteria they will be randomized to treatment and the hyperglycemic clamp procedure performed. Dosing will start on Day 1 and patients will remain in the unit as an in-patient for 6 days for intravenous dosing of otelixizumab. If the investigator is satisfied with the clinical condition of the patient, they will be discharged on Day 6 after completion of dosing and all study procedures. If the investigator considers additional safety monitoring is necessary, the patient will be asked to stay in the unit after Day 6 until they are in a satisfactory condition to be discharged. CRS experienced from dosing to the resolution of symptoms and EBV clinical reactivation will be monitored in all the patients dosed and specific decision criteria will be used for dose escalation based on these assessments.

REVISED TEXT

Screening Period: Patients will be dosed within approximately 28 days of diagnosis (not more than 32 days). Insulin usage will be documented for approximately 7 days prior to Day -1. There will be a 7 – 21 day period from screening to admission to the clinic on Day -2 for the first overnight stay of the in-patient period, this time period will ensure appropriate time to review laboratory results prior to randomisation. During the screening period total lymphocytes will be quantified on two occasions at least 3 days apart (one of the assessments may be performed on Day -1); lymphocytes must be confirmed as being within normal limits before administration of the first dose. All screening procedures are outlined in the Time and Events Table in Section 6.2.

Pre-Treatment Period: On Day -1 safety assessments will be performed as outlined in the Time and Events Table in Section 6.2. If the investigator is satisfied that the patient still meets the entry criteria they will be randomized to treatment and the hyperglycemic clamp procedure performed.

Treatment Period: Dosing will start on Day 1 and patients will remain in the unit as an in-patient for **Days 1, 2 and 3** for intravenous dosing of **study treatment**.

Patients will be given the following flexible options for dosing on Days 4, 5 and 6:

- **Option 1: Receive study treatment on an out-patient basis on any of Days 4, 5 or 6, if the Investigator is satisfied with the clinical condition of the patient. For these patients, safety monitoring will continue up to a minimum of 3 hours post-dose.**

- **Option 2: Patients will remain in the unit if there are any concerns about their clinical status, or if the patient prefers to remain in the unit for logistical reasons. Patients will be fully discharged from the hospital unit on Day 6 after completion of dosing and all study procedures. If the Investigator considers additional safety monitoring is necessary, the patient will be asked to stay in the unit after Day 6 until they are in a satisfactory condition to be discharged.**

CRS experienced from dosing to the resolution of symptoms and EBV clinical reactivation will be monitored in all the patients dosed and specific decision criteria will be used for dose escalation based on these assessments.

Section 3.2 Figure 4 Study Visits Schematic, note added under figure

Note: Dosing on Days 4-6 inclusive may be performed on an out-patient basis, if judged acceptable on the basis of clinical condition of the patient by the Investigator.

Section 3.3.2 Dose Rationale, text added under Table 1

If there is any need to reduce the infusion rate or temporarily stop the infusion, the Investigator should first consult with the Medical Monitor who will consult with the Sponsor. However, the Investigator has the flexibility to reduce or temporarily stop the infusion immediately (with no prior consultation with the Medical Monitor), if there are any immediate safety/tolerability concerns. In this case the Investigator must inform the Medical Monitor as soon as possible after reducing or stopping the dosing.

Section 3.4 Risk Management, Table 2 Summary of Key Issues, their impact and Strategy to Mitigate Risk. Column 4 Strategy-Monitoring/Stopping Criteria related to Cytokine Release Syndrome, 2nd bullet point

PREVIOUS TEXT

- **Inpatient clinical observation;** Patients will be in-house for the entire duration of the infusion (six days) and will be discharged only after Investigator clinical approval. The facilities will be located within a hospital with provision for Intensive Care facilities and with immediate access to resuscitation and emergency care.

REVISED TEXT

- **Inpatient clinical observation; <u>at a minimum</u>** patients will be in-house for the **<u>first 3 days of the infusion period. Days 4, 5 & 6 may be on an out-patient basis with safety monitoring for at least 3 hours post dose</u>**. **<u>Patients</u>** will be discharged only after Investigator clinical approval. The facilities will be located within a hospital with provision for Intensive Care facilities and with immediate access to resuscitation and emergency care

Section 4.1 Number of Subjects, 2nd paragraph

PREVIOUS TEXT

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment at the discretion of the Sponsor in consultation with the investigator. Replacement subject numbers will be assigned to the additional subjects.

REVISED TEXT

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment at the discretion of the Sponsor in consultation with the Investigator.

<u>The decision whether to replace the patient will be based on the reason for premature discontinuation (see Section 4.5 for further information).</u>

Replacement subject numbers will be assigned to the additional subjects.

Section 4.2.1 Inclusion criteria #3

PREVIOUS TEXT

Currently requires insulin treatment for T1DM and has received intensive insulin therapy (at least three injections per day) for at least 7 days prior to screening.

REVISED TEXT

Currently requires insulin treatment for T1DM and has received ~~intensive~~ insulin therapy ~~(at least three injections per day)~~ for at least 7 days prior to screening.

Section 4.4 Screen and Baseline Failures

PREVIOUS TEXT

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to GSK.

REVISED TEXT

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure data to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including:

- **Demography,**
- **Reason for screen failure,**
- **Eligibility criteria,**
- **Serious adverse events.**

Section 4.5 Withdrawal Criteria and Procedures

PREVIOUS TEXT

A patient may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. Subjects who withdraw will be replaced to ensure that data on 40 subjects are obtained. Subjects that have received treatment and who withdraw should continue to undergo all safety assessments as per protocol if possible. The date of withdrawal must be recorded in the eCRF.

Refer to Section 5.3.1 for dose adjustment/stopping criteria.

Liver chemistry threshold stopping criteria have been designed to assure patient safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). See Section 5.3.4 for details.

REVISED TEXT

A patient may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. Subjects who withdraw **may** be replaced to ensure that data on 40 subjects are obtained.

The decision on whether to replace the patient will be based on the reason for premature discontinuation, as described in Table 3.

Table 3 Patient replacement

Patients **will be** replaced if:	• The reason for withdrawal was not treatment related (e.g. patient withdrew consent for personal reasons). • Adverse event judged unrelated to treatment.
Patients **will not be** replaced if:	• There is a lack of tolerability to treatment. • Individual or group stopping criteria are met. • Significant changes in any of the safety assessments (e.g. ECG, vital signs, laboratory tests, etc).

Decisions regarding patient replacement will be made in consultation with the Medical Monitor who will discuss with GSK.

Subjects that have received treatment and who withdraw should continue to undergo all safety assessments as per protocol including PK sampling, if possible**. However, efficacy (hyperglycaemic clamp and MMTT) pharmacodynamic (PD) assessments may not always be performed. The need to perform PD assessments will be agreed on a case-by-case basis. The date of withdrawal must be recorded in the eCRF. If the patient agrees they will follow the original scheduled visit plan after withdrawal.**

Refer to Section 5.3.1 for dose adjustment/stopping criteria.

Liver chemistry threshold stopping criteria have been designed to assure patient safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). See Section 5.3.4 for details.

Section 5.1 Investigational Product and Other Study Treatment, row 4 in table - Route/Administration/Duration:

PREVIOUS TEXT

Route/ Administration/ Duration:	Intravenous infusion via syringe pump; administration duration varies	Intravenous infusion via syringe pump; administration duration varies

REVISED TEXT

Route/ Administration/ Duration:	Intravenous infusion via syringe pump; **using only the infusion kits supplied by CRO/GSK**, administration duration varies	Intravenous infusion via syringe pump; **using only the infusion kits supplied by CRO/GSK**, administration duration varies

Section 5.2 Treatment Assignment

PREVIOUS TEXT

A description of each regimen is provided in Table 3

REVISED TEXT

A description of each regimen is provided in Table **4**

5.3 Patient Specific and Dose Escalation Stopping Criteria

PREVIOUS TEXT

Table 4 CRS AE Grading System

Table 5 Stopping Criteria for CRS-Adverse Events

Table 6 Parameters used to Assess EBV Reactivation

Table 7 Assessment of EBV Reactivation

REVISED TEXT

Table **5** CRS AE Grading System

Table **6** Stopping Criteria for CRS-Adverse Events

Table **7** Parameters used to Assess EBV Reactivation

Table **8** Assessment of EBV Reactivation

PREVIOUS TEXT

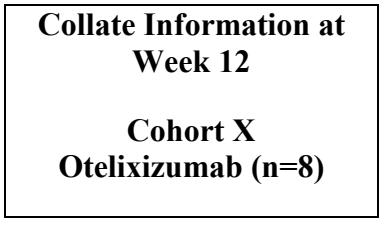
Table 7 shows the possible combinations of the three EBV parameters that will be used to assess whether the patient has clinical EBV reactivation for the purpose of the stopping criteria. The assessment will be conducted for each subject at approximately 12 weeks post dose.

REVISED TEXT

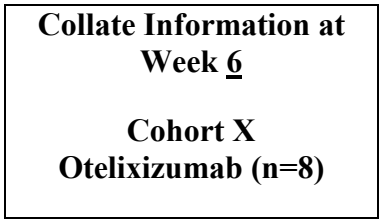
Table 8 shows the possible combinations of the three EBV parameters that will be used to assess whether the patient has clinical EBV reactivation for the purpose of the stopping criteria. The assessment will be conducted for each subject at approximately **6** weeks post **first active** dose.

Figure 5 Dose Escalation Schematic, top section of figure

PREVIOUS TEXT



REVISED TEXT



5.4 Blinding

PREVIOUS TEXT

This will be a single blind study. The patients will not be aware of the treatment they receive. In addition, some site staff will also be blinded, i.e. the study nurse or other member(s) of the clinical team who will administer the infusion and assess the patient for CRS and EBV symptoms and other AEs. The Diabetologist or Physician/Designee responsible for following up the management of the patient will also be blinded across the duration of the study. Unblinded personnel include the Pharmacist when preparing the dose for infusion; the Investigator to enable ongoing assessment and overview of patient safety; the Medical Monitor (CRO and GSK) and members of the GSK team who will review data at dose escalation meetings. See Table 8.

Table 8 Summary of blinding status of personnel

Role	Blinded
GSK & CRO Medical Monitor	N
Therapeutic Area Representative	N
Study Operations Scientist	N
GCSP Representative	N
Pharmacokineticist	N
Data Manager	N
Statistician	N
Programmer(s)	N
Investigator	N
Site Pharmacist	N
Diabetologist and or physician assessing the patients during follow-up	Y
All Other Clinical Site Staff (e.g. infusion administration, AE assessment)	Y
CRO study Manager	N
Site Monitors	Y
Pharmacy Monitors	N

REVISED TEXT

This will be a single blind study **where t**he patients will not be aware of the treatment they receive. **All staff including site personnel, CRO and sponsor team members will be unblinded. However, the randomisation code will be restricted to the pharmacist preparing the infusions** ~~In addition, some site staff will also be blinded, i.e. the study nurse or other member(s) of the clinical team who will administer the infusion and assess the patient for CRS and EBV symptoms and other AEs. The Diabetologist or Physician/Designee responsible for following up the management of the patient will also be blinded across the duration of the study. Unblinded personnel include the Pharmacist when preparing the dose for infusion; the Investigator to enable ongoing assessment and overview of patient safety; the Medical Monitor (CRO and GSK) and members of the GSK team who will review data at dose escalation meetings. See Table 8.~~

Table 8 Summary of blinding status of personnel

~~Role~~	~~Blinded~~
~~GSK & CRO Medical Monitor~~	~~N~~
~~Therapeutic Area Representative~~	~~N~~
~~Study Operations Scientist~~	~~N~~
~~GCSP Representative~~	~~N~~
~~Pharmacokineticist~~	~~N~~
~~Data Manager~~	~~N~~
~~Statistician~~	~~N~~
~~Programmer(s)~~	~~N~~
~~Investigator~~	~~N~~
~~Site Pharmacist~~	~~N~~
~~Diabetologist and or physician assessing the patients during follow up~~	~~Y~~
~~All Other Clinical Site Staff (e.g. infusion administration, AE assessment)~~	~~Y~~
~~CRO study Manager~~	~~N~~
~~Site Monitors~~	~~Y~~
~~Pharmacy Monitors~~	~~N~~

Section 5.6 Preparation/Handling/Storage/Accountability, 3rd paragraph, 3rd sentence

PREVIOUS TEXT

The responsible person(s) will document the amount of study medication received from GSK and destroyed at end of study and the amount administered to subjects.

REVISED TEXT

The responsible person(s) will document the amount of study medication received from GSK, **document that it was shipped at 2-8°C by checking the temperature monitor, document the amount** destroyed at end of study and the amount administered to subjects.

Section 5.6.3 Study Medication Administration, text added at end of section

If there is any need to reduce the infusion rate or temporarily stop the infusion, the Investigator should first consult with the Medical Monitor who will consult with the Sponsor. However, the Investigator has the flexibility to reduce or temporarily stop the infusion immediately (with no prior consultation with the Medical Monitor), if there are any immediate safety/tolerability concerns. In this case the Investigator must inform the Medical Monitor as soon as possible after reducing or stopping the dosing.

Section 5.10.1.2 Treatment, 1st paragraph

PREVIOUS TEXT

If cytokine release symptoms persist despite the prophylactic treatment, additional treatment may be given at the discretion of the investigator, including more potent analgesics (e.g., opioids, such as acetaminophen with codeine, and/or triptans, for headache.

REVISED TEXT

If cytokine release symptoms persist despite the prophylactic treatment, additional treatment may be given at the discretion of the investigator, including more potent analgesics (e.g., opioids, such as acetaminophen with codeine, and/or triptans, for headache**. An anti-emetic such as ondansetron may be given for nausea and/or vomiting).**

Section 6.1 Visit Windows, 1st and 2nd bullet points

PREVIOUS TEXT

- No windows are permitted up to and including the Day 21 visit
- Visits from Month 1 to Month 3 inclusive are permitted a ± 3 day window

REVISED TEXT

- **A ± 1 day window is permitted for the Day 14 and Day 21 visits and Week 4 telephone call**
- Visits from **Week 6** to Month 3 inclusive are permitted a ± 3 day window

Section 6.2.2 Dosing and Follow-up, assessment time changed from Month 1 to Week 4 and Week 6

PREVIOUS TEXT

			Day								Month								
	-2	-1	1	2	3	4	5	6	14	21	1	2	3	6	9	12	18	24	36, 48 & 60#

REVISED TEXT

			Day								Month								
	-2	-1	1	2	3	4	5	6	14	21	Week 4	Week 6	2	3	6	9	12	18	24	36, 48 & 60#

Section 6.2.2 Dosing and Follow-up, row 2 of table and footnote 2

PREVIOUS TEXT

In Patient		X	X	X	X	X	X	X											

2. Discharged on Day 6 if health considered satisfactory by the investigator.

REVISED TEXT

In Patient		X	X	X	X	X[2]	X[2]	X[2]											

2. Discharged on Day 6 if health considered satisfactory by the investigator. **Dosing Day 4-6 may be performed on out-patient basis (see Section 3.1)**

Following row added (6th row)

			Day								Month									
	-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**14**	**21**	**Week 4**	**Week 6**	**2**	**3**	**6**	**9**	**12**	**18**	**24**	**36, 48 & 60#**
Telephone call to collect AEs, hypoglycaemic and hyperglycaemic events and concomitant medication use											**X**									

Section 6.2.2 Dosing and Follow-up, row 19

PREVIOUS TEXT

Record insulin usage for 7 days before visit		X							X	X	X	X	X	X	X	X	X	X	X

REVISED TEXT

Record insulin usage for 7 days before visit / call		X							X	X	**X**	X	X	X	X	X	X	X	X	X

6.2.3 Detail for Vitals, ECG and Pharmacokinetic and Pharmacodynamic Monitoring over the Infusion Period (Cohorts 1-4), Day 4, 5 and 6

PREVIOUS TEXT

Day	Cohort	Assessment	Pre Dose	0 H	30 M	1 H	2 H	3 H	4 H	5 H	6 H	7 H	8 H	9 H	10 H	11 H	12 H	13 H	14 H	15 H	16 H
4	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X	X	X			X				X				X
		ECG	X			X					X										
		PK/CD3 Saturation	X																		
5	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X	X	X			X				X				X
		ECG	X			X					X										
		PK/CD3 Saturation	X																		
6	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X	X												
		ECG	X			X					X										
		PK/CD3 Saturation	X			X															

1. Blood pressure to be taken in triplicate at Pre-dose
2. Vitals to be repeated at 30 min intervals should there be any safety concern

REVISED TEXT

Day	Cohort	Assessment	Pre Dose	0 H	30 M	1 H	2 H	3 H	4 H	5 H	6 H	7 H	8 H	9 H	10 H	11 H	12 H	13 H	14 H	15 H	16 H
4	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X[3]													
		ECG	X			X		**X[3]**													
		PK/CD3 Saturation	X																		
5	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X[3]													
		ECG	X			X		**X[3]**													
		PK/CD3 Saturation	X																		
6	C1-C4	Dosing																			
		Vitals[1,2]	X	X		X	X	X[3]													
		ECG	X			X		**X[3]**													
		PK/CD3 Saturation	X			X															

1. Blood pressure to be taken in triplicate at Pre-dose
2. Vitals to be repeated at 30 min intervals should there be any safety concern
3. **If patients are dosed on an out-patient basis on Day 4, 5 and 6, vital signs and ECGs will stop after the 3 hour post dose timepoint (if the Investigator is satisfied with the clinical status of the patient), if there are any concerns then vital signs and ECGs may be continued as judged necessary by the investigator until the investigator is satisfied**

6.4.4.2 Clinical Chemistry, footnote added

- **It is not mandatory to measure fractionated bilirubin if total bilirubin is not above the normal range.**

6.7.3. Daily Insulin Use, 1st sentence

PREVIOUS TEXT

Patients will be asked to record their daily insulin usage thoroughly and accurately for 7 consecutive days in a diary during the week before all outpatient visits, ie, at Baseline, Day 14 and 21, and Months 1, 2, 3, 6, 9, 12, 18, and 24, and before each telephone call in the long term follow-up period (Month 36, 48 and 60). Information on insulin usage will be transcribed from diaries into the eCRF.

REVISED TEXT

Patients will be asked to record their daily insulin usage thoroughly and accurately for 7 consecutive days in a diary during the week before all outpatient visits **or phone calls**, ie, at Baseline, Day 14 and 21, **Week 4 and 6** and Months ~~1~~, 2, 3, 6, 9, 12, 18, and 24, and before each telephone call in the long term follow-up period (Month 36, 48 and 60). Information on insulin usage will be transcribed from diaries into the eCRF.

Section 7.1.5 Cytokine Release Syndrome Adverse Events

PREVIOUS TEXT

CRS is a well-known consequence of anti-CD3 therapy when administered via intravenous injection or infusion and therefore any CRS AEs experienced during the dosing period will be assessed against the grading system shown in Table 4 and Table 5. This grading system has been developed using NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 (Table 5) by selecting AEs that are specifically thought to be associated with cytokine release syndrome.

REVISED TEXT

CRS is a well-known consequence of anti-CD3 therapy when administered via intravenous injection or infusion and therefore any CRS AEs experienced during the dosing period will be assessed against the grading system shown in Table **5.** ~~and Table 6~~. This grading system has been developed using NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 (Table 5) by selecting AEs that are specifically thought to be associated with cytokine release syndrome. **Pre-specified CRS individual patient and study dosing stopping criteria are shown in Table 6. The symptoms in Table 6 have been classified as objective and subjective endpoints as follows:**

- **Objective Endpoints: Fever, Diarrhoea, Vomiting, Hypotension**
- **Subjective Endpoints: Headache, Chills, Nausea, Arthralgia, Myalgia**

Section 9.3.1.2 Dose Escalation, 1st and 2nd bullet points

PREVIOUS TEXT

- Data will be reviewed after 10 patients have been dosed in cohort 1 (8 patients on otelixizumab 9 mg and 2 patients on placebo) and have completed approximately 12 weeks of the study and required data is available.
- If required, data reviews prior to 12 weeks may also be conducted to facilitate dose escalation to the next cohort.

REVISED TEXT

- Data will be reviewed after 10 patients have been dosed in cohort 1 (8 patients on otelixizumab 9 mg and 2 patients on placebo) and have completed approximately **6** weeks of the study **after the first active dose**, and required data is available.
- If required, data reviews prior to **6** weeks may also be conducted to facilitate dose escalation to the next cohort.

Section 10.5 and Section 10.6

CRO added as jointly responsible with Sponsor for activities

Appendix 5: Mixed Meal Tolerance Test (MMTT), 5th paragraph, 1st sentence

PREVIOUS TEXT

When both unstimulated and Mixed Meal stimulated C-peptide analysis should be done, each subject will consume a standardized amount of Ensure Powder (Abbott) drink.

REVISED TEXT

When both unstimulated and Mixed Meal stimulated C-peptide analysis should be done, each subject will consume a standardized amount of Ensure Powder (Abbott) drink **supplied by the CRO/GSK**.

Footnote added under table of Weight and volume

Please see the SPM for further details regarding volumes

AMENDMENT 3

Where the Amendment Applies

All sites

Summary of Amendment Changes with Rationale

The third medical monitor had changed, the contact details were therefore updated.

It was not clear that staggering the start of treatment by three days across each centre only applies to the first three patients in a cohort, as stated in the SPM.

The eligibility inclusion criterion number 4 was changed from positive for at least two autoantibodies associated with T1DM to positive for at least one autoantibody. The rationale for this change is that two positive antibodies are only relevant when excluding LADA (also referred to as latent autoimmune diabetes in adults), typically manifesting around the age of 40. However, in this study the target population is between 16-27 years old and is insulin dependent at the time of recruitment, thus the need to show two positive autoantibodies is not scientifically relevant and was included in error. This proposed modification of the eligibility criteria does not have any impact on the safety of the patients.

List of Specific Changes

Sponsor/medical monitor Information Page

Medical Monitor and Sponsor Contact Information (third row):

PREVIOUS TEXT

Third Medical Monitor (GSK)	PPD				Experimental Medicine Unit, Immuno-inflammation Therapy Unit GlaxoSmithKline Medicines Stevenage Hertfordshire SG1 2NY, UK

REVISED TEXT

Third Medical Monitor (GSK)	PPD				Experimental Medicine Unit, Immuno-inflammation Therapy Unit GlaxoSmithKline Medicines Stevenage Hertfordshire SG1 2NY, UK

Section 3.1. Study Design Detail, paragraph 5

PREVIOUS TEXT

Within each cohort administration of study treatment will be staggered by at least three days across each centre.

REVISED TEXT

Within each cohort administration of study treatment **for the first three patients** will be staggered by at least three days across each centre.

Section 4.2.1. Inclusion Criteria

PREVIOUS TEXT

4. Positive for at least two of the following autoantibodies associated with T1DM: antibody to glutamic acid decarboxylase (anti GAD), antibody to protein tyrosine phosphatase-like protein (anti IA 2), antibody to islet-cell antigen (ICA) or ZnT8 Autoantibody.

REVISED TEXT

4. Positive for at least ~~two of the following autoantibodies~~ **one** autoantibod**y** associated with T1DM: antibody to glutamic acid decarboxylase (anti GAD), antibody to protein tyrosine phosphatase-like protein (anti IA 2), antibody to islet-cell antigen (ICA) or ZnT8 Autoantibody.

AMENDMENT 2

Where the Amendment Applies

All sites

Summary of Amendment Changes with Rationale

Hyperglycaemic events included as a follow up endpoint and in the time and events table for consistency with the secondary efficacy endpoints for Month 1 – 24.

Information for the screening syphilis test was updated because the laboratory performing the test has changed in order to provide faster analysis, therefore the wording Immuno-Assay was removed as this is not the procedure followed by the site that will now perform the test.

The volume of dose preparation required to prime/purge the IV infusion line was increased from 6mLs to approximately 8mLs. The increase in overage is required for the effective and complete delivery of the planned dose to the patient, as during the first infusion the pump was not able to administer the last 1mL of the planned infusion.

The time period for collecting AE and SAE information was clarified by removing reference to collecting medical history.

List of Specific Changes

Section 2 OBJECTIVES AND ENDPOINTS: Follow up Endpoints (Data collected at Month 36, 48 & 60 if Available)

PREVIOUS TEXT

Follow up Objectives	**Follow up Endpoints (Data Collected at Month 36, 48 & 60 if Available)**
• To assess long term safety follow-up with otelixizumab treatment.	• Significant adverse events. • Severe (as per ADA classification, Appendix 7) hypoglycemic events which occurred between Months 24 up to 60. • Mean daily insulin use over 7 consecutive days preceding the call. • HbA1c results around time of the phone call.

REVISED TEXT

Follow up Objectives	**Follow up Endpoints (Data Collected at Month 36, 48 & 60 if Available)**
• To assess long term safety follow-up with otelixizumab treatment.	• Significant adverse events. • Severe (as per ADA classification, Appendix 7) hypoglycemic events which occurred between Months 24 up to 60. • **Severe hyperglycemic events which occurred between Months 24 up to 60.** • Mean daily insulin use over 7 consecutive days preceding the call. • HbA1c results around time of the phone call.

Section 4.2.2 Exclusion Criteria, bullet point number 20

PREVIOUS TEXT

20. A positive result on an Immuno-Assay test for syphilis; and, if result of Immuno-assay test is positive, then a confirmatory test will be performed.

REVISED TEXT

20. A positive result on ~~an Immuno-Assay~~ **a** test for syphilis; and if result of ~~Immuno-Assay~~ **the first** test is positive, then a confirmatory test **using another method** will be performed.

Section 5.6.2 Study Medication Preparation, 3rd bullet point

PREVIOUS TEXT

The required volume of Otelixizumab Solution for Infusion, 0.1 mg/mL (varies depending on target dose and includes an excess 6 mL volume to account for prime/ purge) must be withdrawn into an suitable size polypropylene syringe as close to the time of the start of the infusion as possible, to ensure product quality.

REVISED TEXT

The required volume of Otelixizumab Solution for Infusion, 0.1 mg/mL (varies depending on target dose) and includes an excess **of approximately 8 mL** volume to

account for prime/purge **(6 mLs – see Section 5.6.3) plus an additional 2 mLs (or more if required) as an overage volume required for the syringe pump to deliver the exact volume to the patient as specified in Table 9 column 7. The additional overage must not be administered to the patient. The required volume** must be withdrawn into a suitable size polypropylene syringe as close to the time of the start of the infusion as possible, to ensure product quality.

Section 5.6.2 Study Medication Preparation, Table 9 Study Medication Dose Preparation, table header, column 8

PREVIOUS TEXT

Total Vol. Filled into Syringe, Includes 6 mL Fill Overage (Vol. not Infused)

REVISED TEXT

Total Vol. Filled into Syringe, Includes **approximately 8 m**L Fill Overage (Vol. not Infused)

Section 5.6.2 Study Medication Preparation, Table 9 Study Medication Dose Preparation, change of total volume filled into syringe in column 8 and footnote added under table

PREVIOUS TEXT

Table 9 Study Medication Dose Preparation

Treat-ment Regimen (cohort)	Cumul-ative Dose (mg)	Dose per day (mg)	Day of Dosing	Period of Dosing (hours)	# of Syringes	Total Dosing Solution Volume to be Infused	Total Vol. Filled into Syringe, Includes 6 mL Fill Overage (Vol. not Infused)
A (1)	9	1.5	Day 1	9	2	15 mL (7.5 mL x 2 syringes)	13.5 mL x 2 syringes
			Day 2	6	1	15 mL	21 mL
			Day 3	3	1	15 mL	21 mL
			Day 4-6	1	1	15 mL	21 mL
B (2)	18	3	Day 1	12	2	30 mL (15 mL x 2 syringes)	21 mL x 2 syringes
			Day 2	6	1	30 mL	36 mL

Treat-ment Regimen (cohort)	Cumul-ative Dose (mg)	Dose per day (mg)	Day of Dosing	Period of Dosing (hours)	# of Syringes	Total Dosing Solution Volume to be Infused	Total Vol. Filled into Syringe, Includes 6 mL Fill Overage (Vol. not Infused)
			Day 3	3	1	30 mL	36 mL
			Day 4-6	1	1	30 mL	36 mL
C (3)	27	4.5	Day 1	12	2	45 mL (22.5 mL x 2 syringes)	28.5 mL x 2 syringes
			Day 2	6	1	45 mL	51 mL
			Day 3	3	1	45 mL	51 mL
			Day 4-6	1	1	45 mL	51 mL
D (4)	36	6	Day 1	12	2	60 mL (30 mL x 2 syringes)	36 mL x 2 syringes
			Day 2	6	2	60 mL (30 mL x 2 syringes)	36 mL x 2 syringes
			Day 3	3	2	60 mL (30 mL x 2 syringes)	36 mL x 2 syringes
			Day 4-6	1	2	60 mL (30 mL x 2 syringes)	36 mL x 2 syringes
P	0	0	0.9% w/v sodium chloride administered by intravenous infusion in the same manner as the active by study personnel following specified regimens				

REVISED TEXT

Table 9 Study Medication Dose Preparation

Treat-ment Regimen (cohort)	Cumul-ative Dose (mg)	Dose per day (mg)	Day of Dosing	Period of Dosing (hours)	# of Syringes	Total Dosing Solution Volume to be Infused	Total Vol. Filled into Syringe, Includes Approximately *8 mL Fill Overage (Vol. not Infused)
A (1)	9	1.5	Day 1	9	2	15 mL (7.5 mL x 2 syringes)	***15.5** mL x 2 syringes
			Day 2	6	1	15 mL	***23** mL
			Day 3	3	1	15 mL	***23** mL
			Day 4-6	1	1	15 mL	***23** mL
B (2)	18	3	Day 1	12	2	30 mL (15 mL x 2 syringes)	***23** mL x 2 syringes
			Day 2	6	1	30 mL	***38 m**L
			Day 3	3	1	30 mL	***38 m**L
			Day 4-6	1	1	30 mL	***38 m**L
C (3)	27	4.5	Day 1	12	2	45 mL (22.5 mL x 2 syringes)	***30.5** mL x 2 syringes
			Day 2	6	1	45 mL	***53** mL
			Day 3	3	1	45 mL	***53** mL
			Day 4-6	1	1	45 mL	***53** mL
D (4)	36	6	Day 1	12	2	60 mL (30 mL x 2 syringes)	***38 m**L x 2 syringes
			Day 2	6	2	60 mL (30 mL x 2 syringes)	***38 m**L x 2 syringes
			Day 3	3	2	60 mL (30 mL x 2 syringes)	***38 m**L x 2 syringes
			Day 4-6	1	2	60 mL (30 mL x 2 syringes)	***38 m**L x 2 syringes
P	0	0	0.9% w/v sodium chloride administered by intravenous infusion in the same manner as the active by study personnel following specified regimens				

***Overage volume may be adjusted to ensure optimal efficiency of syringe pump to deliver the exact dosing volume to be infused. Note the overage volume must NOT be delivered to the patient but remain in the syringe and discarded**.

Section 5.6.3 Study Medication Administration, 3rd bullet point

PREVIOUS TEXT

The prime volume of the intravenous line and filter must not exceed a total of 3 mL. The 6 mL excess solution in the syringe(s) must be primed/purged (3 mL to waste, about 3 mL fills the IV line); target a priming/purging rate of 1 mL/min or lower. Purging 3 ml to waste is required to account for protein loss due to binding and to ensure that the full dose is administered.

REVISED TEXT

The prime volume of the intravenous line and filter must not exceed a total of 3 mL. The **approximate 8 m**L excess solution in the syringe(s) must be primed/purged (3 mL to waste, about 3 mL fills the IV line); target a priming/purging rate of 1 mL/min or lower. Purging 3 ml to waste is required to account for protein loss due to binding and to ensure that the full dose is administered. **The additional 2 mLs (or more if required) should remain as overage in the syringe and must not be administered to the patient.**

Table 6.2.2 Dosing and Follow-Up, 22nd row, addition of hyperglycaemic events

PREVIOUS TEXT

Hypoglycemic Events			<----------

REVISED TEXT

Hypoglycaemic / **Hyperglycaemic** Events			<----------

Table 6.2.2 Dosing and Follow-Up, main footnote under table

PREVIOUS TEXT

#Patients will record insulin usage for 7 days prior to out-patient visits (up to Month 24) and before phone calls in Month 36, 48 and 60. Significant AEs including hypoglycaemic events will be recorded in a diary whenever they occur, to include start and stop dates.

REVISED TEXT

#Patients will record insulin usage for 7 days prior to out-patient visits (up to Month 24) and before phone calls in Month 36, 48 and 60. Significant AEs including hypoglycaemic **(≤3.9 mmol/L; ≤70 mg dL) and hyperglycaemic (>13.9 mmol/L; >250 mg/dL)** events will be recorded in a diary whenever they occur, to include start and stop dates.

Section 7.1.1 Time Period for Collecting AE and SAE Information, 1st paragraph, 2nd sentence removed

PREVIOUS TEXT

AEs will be collected from signing the Informed Consent Form until the follow-up contact, approximately 5 years post last dose. Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions eCRF**.**

REVISED TEXT

AEs will be collected from signing the Informed Consent Form until the follow-up contact, approximately 5 years post last dose. ~~Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions eCRF~~.

Appendix 7 – Alert value for hyperglycaemia added as footnote under ADA classification table

REVISED TEXT

Alert Value for Hyperglycemia: >13.9 mmol/L; >250 mg/dL

AMENDMENT 1

Where the Amendment Applies

All sites

Summary of Amendment Changes with Rationale

An unblinded pharmacy monitor will check study drug records and this was clarified in Table 8. Reference to TCR complexes removed and CD3 requirements clarified throughout the protocol because terminology used was inaccurate; only CD3 saturation will be determined and not TCR. The time period for collecting information for the screening to start of dosing period was revised to improve logistics. The volume of dose preparation required to prime/purge the IV infusion line was changed from 5 mLs to 6 mLs (3 mL to waste, about 3 mL fills the IV line - increased from 2 mLs) and the total volume filled into syringes was amended to reflect the change in prime/purge volume; and the word “micropore” was removed from the description of the IV line. The reason for these changes is because a different type of infusion line was sourced with a slightly longer line to fill. Insulin will be recorded for 7 days before each outpatient visit, this was not clear in the original protocol Objectives and Endpoints table, Time and Events Table (Section 6.2.2) or Section 6.7.3 Daily Insulin Use. Footnote 13 of the Time and Events Table (Section 6.2.2) was amended to clarify that glucose will be measured in addition to C-peptide during the hyperglycaemic clamp procedure because this is required to gain a full understanding. Secondary endpoints were updated in Section 2 to clarify that glucose will be measured along with C-peptide during the MMTT and clamp procedures. A typo was corrected on footnote 18 of the Time and Events Table (Section 6.2.2) as Day 6 was added. In Section 6.2.3 (details for vitals, ECG, PK and PD Monitoring over the infusion period (cohorts 1-4)) it was clarified that ECG will be measured 6 hours after the start of infusion to be consistent with footnote 4 of Section 6.2.2. Section 6.4.3 was updated to clarify when triplicate and single ECGs will be collected as this was not clear in the original protocol. In Section 6.4.4 Exploratory Biomarkers, it was clarified that TCR deep sequencing will also be performed at Month 24, this was missed in error from the table listing biomarker analyses in the original protocol. Section 6.7.1 was amended to clarify that MMTT will be at least 7 days before the first dose of study medication for consistency with the table in Section 6.2.1. Appendix 5 was updated as it was subsequently decided when discussing logistics that c-peptide and glucose samples will be shipped frozen within 3 weeks of collection, and not 2 weeks. Appendix 6 was updated to clarify that the hyperglycaemic range of 180-240mg/dL is during 140 minutes (not 180 minutes) for consistency with blood sampling time points.

List of Specific Changes

Section 2 OBJECTIVES AND ENDPOINTS, 1st, 2nd and 3rd row under Secondary Objectives and Endpoints (Efficacy)

PREVIOUS TEXT

Secondary Objectives (Efficacy)	**Secondary Endpoints (Efficacy)**
• To assess the effect of a single course of otelixizumab treatment on the rate of decline of pancreatic β-cell function over 24 months in NOT1DM patients.	• Change from baseline in C-peptide AUC (0-120) after a Mixed Meal Tolerance Test at Month 3, 6, 12, 18 and 24.
• To assess the effect of a single course of otelixizumab treatment on the rate of decline of C-peptide response and insulin sensitivity of β-cell function determined after a hyperglycemic clamp over 24 months in NOT1DM patients.	• Change from baseline in C-Peptide AUC hyperglycemic phase [H60 to H140 minutes] and insulin sensitivity (IS) index after a hyperglycemic clamp at Months 6 and 24.
• To assess the effect of a single course of otelixizumab treatment on exogenous insulin use for otelixizumab over 24 months in NOT1DM patients.	• Change from baseline in mean daily insulin use over 7 consecutive days during the week preceding the visit over Months 1-24.

REVISED TEXT

Secondary Objectives (Efficacy)	**Secondary Endpoints (Efficacy)**
• To assess the effect of a single course of otelixizumab treatment on the rate of decline of pancreatic β-cell function over 24 months in NOT1DM patients.	• Change from baseline in C-peptide **and glucose** AUC (0-120) after a Mixed Meal Tolerance Test at Month 3, 6, 12, 18 and 24.
• To assess the effect of a single course of otelixizumab treatment on the rate of decline of C-peptide response and insulin sensitivity of β-cell function determined after a hyperglycemic clamp over 24 months in NOT1DM patients.	• Change from baseline in C-Peptide **and glucose** AUC hyperglycemic phase [H60 to H140 minutes] and insulin sensitivity (IS) index after a hyperglycemic clamp at Months 6 and 24.
• To assess the effect of a single course of otelixizumab treatment on exogenous insulin use for otelixizumab over 24 months in NOT1DM patients.	• Change from baseline in mean daily insulin use over 7 consecutive days during the week preceding the visit over **Day 14 and 21 and** Months 1-24.

Section 2 OBJECTIVES AND ENDPOINTS, 1st row under Secondary Objectives and Endpoints (Pharmacodynamics)

PREVIOUS TEXT

Secondary Objectives (Pharmacodynamics)	Secondary Endpoints (Pharmacodynamics)
• To assess the effect of a single course of otelixizumab treatment on the time course and magnitude of CD4 + and CD8+ cells and TCR/CD3 complex internalization and CD3 binding and saturation on all these cells during repeat dose administration of otelixizumab over 14 days in NOT1DM patients.	• Relative change from baseline (%) in CD4+ and CD8+ cells, CD3/TCR complexes, free CD3, bound otelixizumab and CD4+ and CD8+ cells on Days 1 through 14.

REVISED TEXT

Secondary Objectives (Pharmacodynamics)	Secondary Endpoints (Pharmacodynamics)
• To assess the effect of a single course of otelixizumab treatment on the time course and magnitude of CD4 + and CD8+ cells and ~~TCR/CD3 complex internalization and~~ CD3 binding and saturation on all these cells during repeat dose administration of otelixizumab over 14 days in NOT1DM patients.	• Relative change from baseline (%) in CD4+ and CD8+ cells, ~~CD3/TCR complexes~~, free CD3 **and** bound otelixizumab **on** ~~and~~ CD4+ and CD8+ cells on Days 1 through 14.

Section 3.1. Study Design Detail, 3rd Paragraph, 2nd and 3rd sentences

PREVIOUS TEXT

Patients will be dosed within approximately 28 days of diagnosis (not more than 32 days). Insulin usage will be documented for approximately 7 days prior to screening procedures. There will be an approximately 7 day period from screening to admission to the clinic on Day -2 for the first overnight stay of the in-patient period, this time period will ensure appropriate time to review laboratory results prior to randomisation

REVISED TEXT

Patients will be dosed within approximately 28 days of diagnosis (not more than 32 days). Insulin usage will be documented for approximately 7 days prior to ~~screening procedures~~ **Day -1**. There will be ~~an approximately a~~ 7**-21** day period from screening to admission to the clinic on Day -2 for the first overnight stay of the in-patient period, this time period will ensure appropriate time to review laboratory results prior to randomisation

Section 5.4 Blinding, addition of unblinded Pharmacy Monitors to Table 8

PREVIOUS TEXT (only last row of Table 8 shown)

Site Monitors	Y

REVISED TEXT

Site Monitors	Y
Pharmacy Monitors	**N**

Section 5.6.2 Study Medication Preparation, 3rd bullet point

PREVIOUS TEXT

The required volume of Otelixizumab Solution for Infusion, 0.1 mg/mL (varies depending on target dose and includes an excess 5 mL volume to account for prime/ purge) must be withdrawn into an suitable size polypropylene syringe as close to the time of the start of the infusion as possible, to ensure product quality.

REVISED TEXT

The required volume of Otelixizumab Solution for Infusion, 0.1 mg/mL (varies depending on target dose and includes an excess **6 m**L volume to account for prime/ purge) must be withdrawn into an suitable size polypropylene syringe as close to the time of the start of the infusion as possible, to ensure product quality.

Section 5.6.2 Study Medication Preparation, Table 9 Study Medication Dose Preparation, table header, column 8

PREVIOUS TEXT

Total Vol. Filled into Syringe, Includes 5 mL Fill Overage (Vol. not Infused)

REVISED TEXT

Total Vol. Filled into Syringe, Includes **6 m**L Fill Overage (Vol. not Infused)

Section 5.6.2 Study Medication Preparation, Table 9 Study Medication Dose Preparation, change of total volume filled into syringe in column 8

PREVIOUS TEXT

Table 12 Study Medication Dose Preparation

Treat-ment Regimen (cohort)	Cumul-ative Dose (mg)	Dose per day (mg)	Day of Dosing	Period of Dosing (hours)	# of Syringes	Total Dosing Solution Volume to be Infused	Total Vol. Filled into Syringe, Includes 5 mL Fill Overage (Vol. not Infused)
A (1)	9	1.5	Day 1	9	2	15 mL (7.5 mL x 2 syringes)	12.5 mL x 2 syringes
			Day 2	6	1	15 mL	20 mL
			Day 3	3	1	15 mL	20 mL
			Day 4-6	1	1	15 mL	20 mL
B (2)	18	3	Day 1	12	2	30 mL (15 mL x 2 syringes)	20 mL x 2 syringes
			Day 2	6	1	30 mL	35 mL
			Day 3	3	1	30 mL	35 mL
			Day 4-6	1	1	30 mL	35 mL
C (3)	27	4.5	Day 1	12	2	45 mL (22.5 mL x 2 syringes)	27.5 mL x 2 syringes
			Day 2	6	1	45 mL	50 mL
			Day 3	3	1	45 mL	50 mL
			Day 4-6	1	1	45 mL	50 mL
D (4)	36	6	Day 1	12	2	60 mL (30 mL x 2 syringes)	35 mL x 2 syringes
			Day 2	6	2	60 mL (30 mL x 2 syringes)	35 mL x 2 syringes
			Day 3	3	2	60 mL (30 mL x 2 syringes)	35 mL x 2 syringes
			Day 4-6	1	2	60 mL (30 mL x 2 syringes)	35 mL x 2 syringes
P	0	0	0.9% w/v sodium chloride administered by intravenous infusion in the same manner as the active by study personnel following specified regimens				

REVISED TEXT

Treat-ment Regimen (cohort)	Cumul-ative Dose (mg)	Dose per day (mg)	Day of Dosing	Period of Dosing (hours)	# of Syringes	Total Dosing Solution Volume to be Infused	Total Vol. Filled into Syringe, Includes 6 mL Fill Overage (Vol. not Infused)
A (1)	9	1.5	Day 1	9	2	15 mL (7.5 mL x 2 syringes)	13.5 mL x 2 syringes
			Day 2	6	1	15 mL	21 mL
			Day 3	3	1	15 mL	21 mL
			Day 4-6	1	1	15 mL	21 mL
B (2)	18	3	Day 1	12	2	30 mL (15 mL x 2 syringes)	21 mL x 2 syringes
			Day 2	6	1	30 mL	36 mL
			Day 3	3	1	30 mL	36 mL
			Day 4-6	1	1	30 mL	36 mL
C (3)	27	4.5	Day 1	12	2	45 mL (22.5 mL x 2 syringes)	28.5 mL x 2 syringes
			Day 2	6	1	45 mL	51 mL
			Day 3	3	1	45 mL	51 mL
			Day 4-6	1	1	45 mL	51 mL
D (4)	36	6	Day 1	12	2	60 mL (30 mL x 2 syringes)	36 mL x 2 syringes
			Day 2	6	2	60 mL (30 mL x 2 syringes)	36 mL x 2 syringes
			Day 3	3	2	60 mL (30 mL x 2 syringes)	36 mL x 2 syringes
			Day 4-6	1	2	60 mL (30 mL x 2 syringes)	36 mL x 2 syringes
P	0	0	0.9% w/v sodium chloride administered by intravenous infusion in the same manner as the active by study personnel following specified regimens				

Section 5.6.3 Study Medication Administration, 2nd bullet point

PREVIOUS TEXT

Connect a micropore polyethylene intravenous line with an in-line 0.2 μm polyethersulfone (PES) filter to the syringe. If a second syringe is needed to provide the dose, a separate infusion line with 0.2 μm PES filter is required.

REVISED TEXT

Connect a ~~micropore~~ polyethylene intravenous line with an in-line 0.2 μm polyethersulfone (PES) filter to the syringe. If a second syringe is needed to provide the dose, a separate infusion line with 0.2 μm PES filter is required.

Section 5.6.3 Study Medication Administration, 3rd bullet point

PREVIOUS TEXT

The prime volume of the intravenous line and filter must not exceed a total of 2 mL. The 5 mL excess solution in the syringe(s) must be primed/purged (3 mL to waste, about 2 mL fills the IV line); target a priming/purging rate of 1 mL/min or lower. Purging 3 ml to waste is required to account for protein loss due to binding and to ensure that the full dose is administered.

REVISED TEXT

The prime volume of the intravenous line and filter must not exceed a total of **3** mL. The **6 m**L excess solution in the syringe(s) must be primed/purged (3 mL to waste, about **3** mL fills the IV line); target a priming/purging rate of 1 mL/min or lower. Purging 3 ml to waste is required to account for protein loss due to binding and to ensure that the full dose is administered.

Section 6.2.2 Dosing and Follow-Up, 18th row, removal of TCR complexes, addition of "Saturation" after CD3

PREVIOUS TEXT

CD3/TCR complexes, free CD3 bound otelixizumab /CD4+/CD8+ Blood Sample[6]			X	X	X	X	X	X	X[11]										

REVISED TEXT

CD3 Saturation~~/TCR complexes~~, free CD3 bound otelixizumab /CD4+/CD8+ Blood Sample[6]			X	X	X	X	X	X	X[11]										

Section 6.2.2 Dosing and Follow-Up, 19th row, addition of Day 14 and 21, and Month 1, 9, 36, 48 and 60 for collection of 7 days of insulin usage prior to the visit

PREVIOUS TEXT

			Day								Month								
	-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**14**	**21**	**1**	**2**	**3**	**6**	**9**	**12**	**18**	**24**	**36, 48 & 60**
Record insulin usage for 7 days before visit		X										X	X	X		X	X	X	

REVISED TEXT

			Day								Month								
	-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**14**	**21**	**1**	**2**	**3**	**6**	**9**	**12**	**18**	**24**	**36, 48 & 60**
Record insulin usage for 7 days before visit		X							**X**	**X**	**X**	X	X	X	**X**	X	X	X	**X**

Section 6.2.2 Dosing and Follow-Up, footnote 13, addition of glucose

PREVIOUS TEXT

13. Plasma C-peptide levels will be measured during the hyperglycaemic clamp procedure at the following time points: L150, L165 and L180 minutes [during the euglycaemic (L)ow phase], H0, H60, H90, H120 and H140 minutes [during the hyperglycaemic (H)igh phase]

REVISED TEXT

13. Plasma C-peptide **and glucose** levels will be measured during the hyperglycaemic clamp procedure at the following time points: L150, L165 and L180 minutes [during the euglycaemic (L)ow phase], H0, H60, H90, H120 and H140 minutes [during the hyperglycaemic (H)igh phase]

Section 6.2.2 Dosing and Follow-Up, footnote 18, addition of Day 6

PREVIOUS TEXT

18. One PGx (DNA) saliva sample taken between Day 1 and

REVISED TEXT

18. One PGx (DNA) saliva sample taken between Day 1 and **6**

Section 6.2.3 Details for Vitals, ECG and Pharmacokinetic and Pharmacodynamic Monitoring over the Infusion Period (Cohorts 1 – 4).

Removal of TCR complexes, CD3/CD4/CD8 and addition of "Saturation" after CD3 on each day in the table, only column 3 of table shown below

PREVIOUS TEXT

Assessment
Dosing
VItals[1,2]
ECG
PK/CD3/TCR complexes free CD3 /CD4/CD8

REVISED TEXT

Assessment
Dosing
VItals[1,2]
ECG
PK/CD3 **Saturation**~~/TCR complexes free CD3 /CD4/CD8~~

Update to Footnote 1

PREVIOUS TEXT

1. Blood pressure to be taken in triplicate

REVISED TEXT

1. Blood pressure to be taken in triplicate at pre-dose

Section 6.2.3 Details for Vitals, ECG and Pharmacokinetic and Pharmacodynamic Monitoring over the Infusion Period (Cohorts 1 – 4), clarification that ECG will be measured 6 hours post start of infusion. Table shows ECG only on dosing Day 3-6

PREVIOUS TEXT

Day	Cohort	Assessment	Pre Dose	0 H	30 M	1 H	2 H	3 H	4 H	5 H	6 H	7 H	8 H	9 H	10 H	11 H	12 H	13 H	14 H	15 H	16 H
3	C1-C4	ECG	X					X													
4	C1-C4	ECG	X			X															
5	C1-C4	ECG	X			X															
6	C1-C4	ECG	X			X															

REVISED TEXT

Day	Cohort	Assessment	Pre Dose	0 H	30 M	1 H	2 H	3 H	4 H	5 H	6 H	7 H	8 H	9 H	10 H	11 H	12 H	13 H	14 H	15 H	16 H
3	C1-C4	ECG	X					X			**X**										
4	C1-C4	ECG	X			X					**X**										
5	C1-C4	ECG	X			X					**X**										
6	C1-C4	ECG	X			X					**X**										

Section 6.4.3 Electrocardiograms (ECG), second paragraph, clarification of triple or single recordings

PREVIOUS TEXT

At baseline (Day -1) ECG assessments will be performed in triplicate (5 minutes apart) to obtain an average, single ECGs will be performed at other timepoints. Refer to Section 5.3.5 for QTc withdrawal criteria, which requires triplicate ECGs to assess QTc.

REVISED TEXT

At **screening,** baseline (Day -1) **and predose on dosing days** ECG assessments will be performed in triplicate (5 minutes apart) to obtain an average, single ECGs will be performed at other timepoints. Refer to Section 5.3.5 for QTc withdrawal criteria, which requires triplicate ECGs to assess QTc.

Section 6.6.3. CD4+, CD8+ Levels and CD3/TCR Complexes. Free CD3 and bound otelixizumab on CD4 and CD8+ Cells

PREVIOUS TEXT

Whole blood samples will be drawn, as detailed on the Time and Events Table, for determining CD4+ and CD8+ levels, together with CD3/TCR complexes, free CD3 and bound otelixizumab on CD4 and CD8+ cells, respectively. The samples will be analysed by flow cytometry.

REVISED TEXT

Section 6.6.3. CD4+, CD8+ Levels and CD3~~/TCR Complexes~~. Free CD3 and bound otelixizumab on CD4 and CD8+ Cells

Whole blood samples will be drawn, as detailed on the Time and Events Table, for determining CD4+ and CD8+ levels, together with CD3~~/TCR complexes~~, free CD3 and bound otelixizumab on CD4 and CD8+ cells, respectively. The samples will be analysed by flow cytometry.

Section 6.6.4. Exploratory Biomarkers, Table showing Biomarker assay, 7th row, addition of TCR deep sequencing to Month 24

PREVIOUS TEXT

TCR deep sequencing	PAXgene Blood RNA Tube	X	X[1]	X	X	X	X	

REVISED TEXT

TCR deep sequencing	PAXgene Blood RNA Tube	X	X[1]	X	X	X	X	**X**

Section 6.7.1. Mixed Meal Tolerance Test, (C-Peptide Unstimulated, Serum Stimulated C-Peptide Peak Levels and C-Peptide AUC), 2nd papagraph

PREVIOUS TEXT

An MMTT test will be performed in the screening period, at least 5 days before the first dose of study medication is given.

REVISED TEXT

An MMTT test will be performed in the screening period, at least **7** days before the first dose of study medication is given.

Section 6.7.2. Hyperglycaemic Clamp Serum Stimulated C-Peptide Levels and C-Peptide AUC, 1st paragraph, addition of glucose

PREVIOUS TEXT

Plasma C-peptide levels will be measured during the hyperglycaemic clamp procedure at the following time points: L150, L165 and L180 minutes [during the euglycaemic (L)ow phase], H0, H60, H90, H120 and H140 minutes [during the hyperglycaemic (H)igh phase].

REVISED TEXT

Plasma C-peptide **and glucose** levels will be measured during the hyperglycaemic clamp procedure at the following time points: L150, L165 and L180 minutes [during the euglycaemic (L)ow phase], H0, H60, H90, H120 and H140 minutes [during the hyperglycaemic (H)igh phase].

Section 6.7.3 Daily Insulin Use, 1st Paragraph

PREVIOUS TEXT

Patients will be asked to record their daily insulin usage thoroughly and accurately for 7 consecutive days in a diary during the week before the visits at Baseline and Months 1, 2, 3, 6, 12, 18, and 24, and before each telephone call in the long term follow-up period (Month 36, 48 and 60). Information on insulin usage will be transcribed from diaries into concomitant medication pages of the eCRF.

REVISED TEXT

Patients will be asked to record their daily insulin usage thoroughly and accurately for 7 consecutive days in a diary during the week before **all outpatient** visits, **ie**, at Baseline, **Day 14 and 21** and Months 1, 2, 3, 6, **9**, 12, 18, and 24, and before each telephone call in the long term follow-up period (Month 36, 48 and 60). Information on insulin usage will be transcribed from diaries into ~~concomitant medication pages of~~ the eCRF.

Section 9.3.7 Pharacokinetic/Pharmacodynamic Analyses

PREVIOUS TEXT

The relationship between dose, free serum otelixizumab concentration and pharmacodynamic endpoints including CD3/TCR complex, free CD3, CD4+ and CD8+ cells may be investigated first by exploratory graphical analysis and then by non-linear mixed effects modelling. Further details of model terms and possible covariates will be included in the RAP.

REVISED TEXT

The relationship between dose, free serum otelixizumab concentration and pharmacodynamic endpoints including ~~CD3/TCR complex,~~ free CD3 **or bound otelixizumab on** CD4+ and CD8+ cells may be investigated first by exploratory graphical analysis and then by non-linear mixed effects modelling. Further details of model terms and possible covariates will be included in the RAP.

Appendix 5: Mixed Meal Tolerance Test, last paragraph

PREVIOUS TEXT

The tubes with the blood samples will be kept on ice during collection, until centrifuged for 15 min at 1530 x g and 4°C. The plasma will be harvested into 2 green cap transfer vials 2.0 mL and stored at <-15°C until shipment (max 2 weeks). The tubes will be sent at the end of each cohort for analysis. The tubes must be shipped on dry ice and remained frozen until analysis. Further details will be provided in the SPM.

REVISED TEXT

The tubes with the blood samples will be kept on ice during collection, until centrifuged for 15 min at 1530 x g and 4°C. The plasma will be harvested into 2 green cap transfer vials 2.0 mL and stored at <-15°C until shipment (~~max 2 weeks~~ **within 3 weeks of collection**). ~~The tubes will be sent at the end of each cohort for analysis~~. The tubes must be shipped on dry ice and remain~~ed~~ frozen until analysis. Further details will be provided in the SPM.

Appendix 6: Hyperglycaemic Clamp Procedure, C. Hyperglycemic Phase Start BG 180-240mg/dL, first sentence

PREVIOUS TEXT

AIM: Keep blood glucose between 180-240mg/dL during 180 minutes.

REVISED TEXT

AIM: Keep blood glucose between 180-240mg/dL during 1**4**0 minutes.