INTEGRATED DATA ANALYSIS of studies for the therapy of type 1 diabetes with ex vivo expanded CD4+CD25+CD127- T regulatory cells (Tregs) and anti-CD20 monoclonal antibody (rituximab)

Maciej Zieliński PhD[1,2]*, Magdalena Żalińska MD[3]*, Dorota Iwaszkiewicz-Grześ PhD[1,2], Mateusz Gliwiński MSc[1,2], Matylda Hennig MD PhD[3], Anna Jaźwińska-Curyłło MD[4], Halla Kamińska MD PhD[5], Justyna Sakowska MSc[1,2], Anna Wołoszyn-Durkiewicz MD[3], Radosław Owczuk Professor[6], Wojciech Młynarski Professor[7], Przemysława Jarosz-Chobot Professor[5], Artur Bossowski Professor[8], Agnieszka Szadkowska Professor[9], Janusz Siebert Professor[10], Małgorzata Myśliwiec Professor[2,3], Natalia Marek-Trzonkowska Professor [2,10,11], Piotr Trzonkowski Professor [1,2]
* These authors contributed equally to this work

[1] Department of Medical Immunology, Medical University of Gdańsk, Debinki 7, 80-210 Poland
[2] Poltreg S.A., Wały Piastowskie 1 Street, 80-855 Gdańsk, Poland
[3] Department of Pediatric Diabetology and Endocrinology, Medical University of Gdańsk, Debinki 7, 80-210 Poland
[4] Regional Center of Blood Donation and Treatment, Hoene-Wrońskiego 4 80-210 Gdańsk, Poland
[5] Department of Children's Diabetology, Medical University of Silesia, Medykow 16, 40-752 Katowice, Poland
[6]Department of Anaesthesiology and Critical Care, Medical University of Gdańsk, Debinki 7, 80-210 Poland
[7]Department of Paediatrics, Oncology and Haematology, Medical University of Lodz, Sporna 36/50, 91-738 Lodz Poland
[8]Department of Peadiatrics, Endocrinology, Diabetology with Cardiology Division, Medical University of Bialystok, Jana Kilińskiego 1, 15-089 Białystok Poland
[9]Department of Pediatrics, Diabetology, Endocrinology and Nephrology, Medical University of Lodz, Sporna 36/50, 91-738 Lodz Poland
[10] Department of Family Medicine, Laboratory of Immunoregulation and Cellular Therapies, Medical University of Gdańsk, Debinki 2, 80-210 Poland
[11] International Centre for Cancer Vaccine Science, University of Gdańsk, Wita Stwosza 63, 80-308 Gdańsk, Poland

Corresponding author:
Piotr Trzonkowski, M.D., Ph.D., Medical University of Gdansk, Department of Medical Immunology, Debinki 7, 80-952 Gdansk, Poland
Tel.: 0048 58 3491590, 0048 58 3491593. Fax: 0048 58 3491591. E-mail: ptrzon@gumed.edu.pl
ORCID ID: 0000-0001-5287-5210

INTEGRATED DATA ANALYSIS – TregVAC2.0 and TN-05

TABLE OF CONTENTS

INTEGRATED DATA ANALYSIS – TregVAC2.0 and TN-05

1. Trial Registration

TregVac 1.0 study

Registration for the TregVac 1.0 study was retrospectively submitted to ISRCTN Registry (No. ISRCTN06128462) on 24 August 2013.[1] The first patient was recruited on 06 January 2011, and the first study intervention was on 09 March 2011.

TregVac 2.0 study

Registration for the TregVac 2.0 study was submitted to the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Poland on 30 September 2014 (EUDRA-CT 2014-004319-35) and retrospectively submitted to ISRCTN Registry (No. ISRCTN37116985) on 22 January 2021. The first patient was randomized on 19 May 2015, and the first study intervention was on 15 June 2015.

TN-05 study

Registration for TN05 study (P-IND 73,190) was submitted to ClinicalTrials.gov (No. NCT00279305) on 19 January 2006.[2] The first patient was randomized on 14 June 2006, and the first study intervention was on 15 June 2006.

2. Study Methods

Analyses in this IDA were performed on the clinical data captured from three different studies:

1) TregVac 2.0: Prospective randomized phase 1/2 clinical trial with EudraCT number 2014-004319-35, of the University Clinical Center in Gdańsk financed from STRATEGMED project by National Center for Research and Development performed in pediatric patients with type 1 diabetes (T1D). (EUDRA-CT No. 2014-004319-35) [TregVac 2.0] with the trial protocol (final version 09_2-14, dated 30.09.2014)
2) TN-05: Effects of rituximab on the progression of type 1 diabetes in new onset subjects (# P-IND 73,190) with the trial protocol (version August 30, 2009)
3) TregVac1.0: Cellular Therapy of Type 1 Diabetes with ex vivo expanded CD4+CD25+CD127- T regulatory cells

The analyses in the IDA are based mainly on the trial protocol of TregVac 2.0 combining the different time structures of the three trials and taking into account the ICH guideline E9.[3]

Inclusion criteria

TregVac 1.0

Tregs study arm

1. Male and female patients 5 to 18 years of age.

2. Ability to provide written informed consent by parents (and patients if above 16 years old).

3. Clinical history of autoimmune type 1 diabetes diagnosed within 2 months and the presence of at least one anti-islet autoantibody: anti-GAD, anti-IA2, -IAA, -ICA (high titer).

4. Fasting plasma C-peptide more than 0.4 ng/mL.

5. Involvement of the patients and parents in intensive diabetes management defined as self-monitoring of glucose values no less than three times / day and the administration of insulin injections each day or insulin pump therapy.

6. Patient and parents mentally stable and able to comply with the procedures of the study protocol.

7. Appropriate venous access for blood drawing.

Control group arm

1. Patients fulfilling the inclusion criteria from 1 to 6 *but*

2. EXCLUDED from blood drawing due to inappropriate venous access.

TregVac 2.0

1. 8 to 16 years of age.

2. Body mass index (BMI) in the range of the 25th-75th percentile (according to the OLAF project)[4].

3. Fasting plasma C-peptide more than 0.7 ng/mL and in stimulation test the increase ≥ 100%.

4. The presence of at least one anti-islet autoantibody (ICA, IAA, GAD): a high titer of IAA or GAD (≥ 4 times the norm) or a low titer (2-4 times the norm) of at least two of these antibodies.

5. Ability to provide written informed consent by parents (and patients if above 16 years old).

6. Involvement of the patients and parents in intensive diabetes management defined as self-monitoring of glucose values no less than three times / day and the administration of insulin.

7. Appropriate venous access for blood drawing.

TN-05

1. Between the ages of 8 and 45 years (note that in the present integrated analysis, only participants aged ≤18 years were included).

2. Within 3-months (100 days) of diagnosis of type 1 diabetes based on American Diabetes Association (ADA) criteria[5].

3. At least one diabetes–related autoantibody.

4. Stimulated C-peptide levels ≥ 0.2 pmol/mL measured during a MMTT conducted at least 21 days from diagnosis of diabetes and within one month (37 days) of randomization.

5. If participant is female with reproductive potential, she must be willing to avoid pregnancy and have a negative pregnancy test.

6. At least one month from last immunization received.

7. Must be willing to comply with intensive diabetes management.

8. Must weigh at least 25 kg at study entry.

Exclusion criteria

TregVac 1.0

1. No agreement for participation in the study and no inform consent signed.

2. Other than autoimmune type 1 diabetes.

3. Age below 5 and above 18 years at the time of recruitment.

4. Carriage of HLA-DQB1*0602 allele.

5. IgA deficiency or other genetic defect present.

6. Body mass index (BMI) outside the range of 25-75 percentiles for a particular age.

7. Presence or history of active infection including hepatitis B, hepatitis C, HIV, syphilis or tuberculosis (TB). Subjects with laboratory evidence of active infection are excluded even in the absence of clinical evidence of active infection.

8. Invasive aspergillus, histoplasmosis, or coccidioidomycosis infection within one year prior to study enrollment.

9. Any history of malignancy.

10. Baseline Hb below the lower limits of the reference range; lymphopenia (<l,000/µL), neutropenia (<l,500/µL), or thrombocytopenia (platelets <100,000/µL).

11. Known hypercoagulative state.

12. Medical treatment requiring chronic use of drugs other than insulin.

13. Treatment with any anti-diabetic medication other than insulin within 4 weeks of enrolment (special attention to exclude anti-CD3 treated patients).

14. Diabetic retinopathy.

15. Arterial hypertension.

16. Presence or history of macroalbuminuria (>300 mg/g creatinine).

17. For female subjects older than 15 years positive pregnancy test, unwillingness to use effective contraceptive measures for the duration of the study and 4 months after discontinuation, when appropriate. For male subjects: intent to procreate during the duration of the study or within 4 months after discontinuation or unwillingness to use effective measures of contraception when appropriate.

18. Excessive anxiety of the patient or parents related to the procedures.

19. Any medical condition that, in the opinion of the investigator, will interfere with safe participation in the trial.

20. For parents and pediatric patients older than 15 years: known active alcohol or substance abuse.

TregVac 2.0

1. No agreement for participation in the study and no inform consent signed.

2. Other than autoimmune type 1 diabetes.

3. Age below 8 and above 16 years.

4. IgA deficiency or other genetic defect present.

5. BMI < 25th or >75th percentile for a particular age.

6. Hypersensitivity to anti-CD20 antibody rituximab or other components of the preparation.

7. Presence or history of active infection, including hepatitis B, hepatitis C, HIV, tuberculosis (TB) or syphilis. Subjects with laboratory evidence of active infection were excluded even in the absence of clinical evidence of active infection.

8. Presence of active EBV virus infection (positive IgM).

9. Presence or history of active systemic fungal infection.

10. Any history of malignancy.

11. Anemia, lymphopenia, neutropenia, or thrombocytopenia below the lower limits of the reference range during the 6 weeks before study.

12. Known hypercoagulative state.

13. Medical treatment requiring chronic use of drugs other than insulin longer than 3 months.

14. Treatment with any anti-diabetic medication other than insulin within 4 weeks of enrolment.

15. Diabetic retinopathy.

16. Arterial hypertension.

17. Presence or history of macroalbuminuria.

18. For female subjects older than 15 years: a positive pregnancy test or an unwillingness to use effective contraceptive measures for the duration of the study and 4 months after discontinuation, when appropriate.

19. For male subjects: intent to procreate during the duration of the study or within 4 months after discontinuation when appropriate.

20. Excessive anxiety of the patient or parents related to the procedures.

21. Any medical condition that, in the opinion of the investigator, will interfere with safe participation in the trial.

22. For parents and pediatric patients older than 15 years: known active alcohol or substance abuse.

TN-05

1. Immunodeficient or clinically significant chronic lymphopenia.

2. Active infection or positive PPD test result.

3. Currently pregnant or lactating or anticipate getting pregnant.

4. Require chronic use of steroids.

5. Require use of other immunosuppressive agents.

6. Serologic evidence of current or past HIV, Hepatitis B, or Hepatitis C infection.

7. Any complicating medical issues that interfere with study conduct or cause increased risk to include pre-existing cardiac disease, COPD, neurological disease, or blood count abnormalities (such as lymphopenia, leukopenia, or thrombocytopenia).

8. History of malignancies.

9. Currently using non-insulin pharmaceuticals that affect glycemic control.

10. Currently participating in another type 1 diabetes treatment study.

Primary Endpoints

- C-peptide level (post mixed meal tolerance test (MMTT) stimulation) at 1 year [week 52] and 2 years [week 104] (TregVac 2.0 and TN-05) after first dose as clinical endpoint
- C-peptide level (fasting) at 1 year [week 52] (TregVac 1.0 and 2.0 and 2 years [week 104] (TregVac 2.0 only) after first dose as clinical endpoint
- Exogenous daily insulin dose per kg of body weight (DDI) at 1 year [week 52] (all 3 trials) and 2 years [week 104] (TregVac 2.0 and TN-05) after the first dose as clinical endpoint
- Number of treated patients in remission 1 [week 52] at 1 year [week 52] (all 3 trials) and 2 years [week 104] (TregVac 2.0 and TN-05) after first dose defined as the number of patients with exogenous daily insulin dose lower than 0.5U/kg/day and HbA1c lower than 6.5% as clinical endpoint
- Number of adverse events reported up to 1 year [week 52] (all 3 trials) and 2 years [week 104] (TregVac 2.0 and TN-05) after the first dose as safety endpoint

Secondary Endpoints

Safety: To assess hypersensitivity reactions and immunosuppressive side effects Tregs or Tregs in combination with anti-CD20 rituximab antibody

- Assessment of the occurrence and severity of side effects directly related to Tregs (hypersensitivity reactions, injection-site thromboembolic events) (Tregs administration only) and blood sampling (>2g/dL drop in hemoglobin levels) on the day of Tregs administration (days 0 and 90)
- Assessment of the occurrence and severity of effects directly related to rituximab administration (hypersensitivity reactions) (rituximab administration only) on days with rituximab administration (days 14, 22, 29, and 36)
- Assessment of the occurrence and severity of side effects associated with administration of Tregs or rituximab antibody, primarily immunosuppressive effects: occurrence of infections of any etiology and de novo tumors detected
- Any serious AE in two or more patients with confirmed association to the administration of therapy
- These four secondary safety endpoints will be documented as AEs of special importance (AESI) and related treatment-emergent AEs (TEAEs), where appropriate

Efficacy: To investigate further efficacy and side effect parameters for the investigational medicinal product (IMP) given

- C-peptide level (post mixed meal tolerance test [MMTT] stimulation and in glucagon test) – (weeks 12, 26, 52, 78, and104)
- Exogenous insulin dose per kg of body weight – (weeks 2, 3, 4, 5, 12, 14, 26, 39, 52, 65, 78, 92, and 104)
- The proportion of insulin-independent patients – (weeks 52 and 104)
- The proportion of patients with exogenous daily insulin dose per kg of body weight (DDI) ≤ 0.5UI/kg b.w. – (weeks 52 and 104)

- HbA1c level (%) – (weeks 2, 5, 12, 26, 39, 52, 65, 78, 92, and 104) as glycemic control (fasting average of 7 days)
- The amount and intensity of side effects of therapy – (weeks 52 and 104)

Study Treatment Allocation

Treatments

Patients with type 1 diabetes took part in a 24-month (104 weeks) study period in TregVac 2.0 and TN-05 and a 12-month study period in TregVac 1.0 with a 24-month follow up.

Patients aged 5-18 years from the three trials were assigned to four groups (safety set): Tregs group (N=25), rituximab (34), Tregs+rituximab (N=12), and control (N=44) **(Table S1a)**. Efficacy endpoints were evaluated in the intention-to-treat set (N=25, 33, 12, and 44, respectively). At baseline, the mean body mass index (BMI), DDI per kg b.w., and glucose were significantly different among the groups (p=0023, 0.028, and 0.004, respectively), and all were highest in the rituximab group. Patients in this group was slightly older (p=0.573), and this may explain the higher BMI, which may have affected both DDI and glucose. However, there was no significant difference in the primary endpoint assessments AUC of C peptide (MMTT; p=0.417), C-peptide (MMTT) concentration (p=0.967), C-peptide (fasting) concentration (p=0.756), and HbA1c (p=0.091) (**Table S1b**). The statistical analyses of both primary and secondary endpoints accounted for these intergroup baseline differences. The integrated data analysis investigated the following treatment groups:

Table S1a. Treatment Groups.

Treatment group	Treatment
Tregs+rituximab	(TregVac 2.0 only) (1) Tregs infusion at time "0" + 4 doses of rituximab (each one week apart starting at Day 0) and a (2) second infusion of Tregs at time 90 ± 30 days
Tregs	This group pooled from the TregVac 2.0 and 1.0 studies: In TregVac 2.0: (1) Tregs infusion at time "0" + 4 placebo doses of rituximab and (2) a second infusion of Tregs at time 90 ± 30 days (the total administered Tregs dose was up to $60x10^6$ per kg b.w) In TregVac 1.0, (1) Tregs infusion at time "0" with or without (2) a second infusion of Tregs after a 6- to 9-month interval (the total administered Tregs dose was $10x10^6$ per kg b.w. in a single infusion in 3 patients and $20x10^6$ of Tregs per kg b.w. in a single infusion followed by $30x10^6$ of Tregs per kg b.w. in a second infusion 25-45 weeks later in 6 patients)
Rituximab	In only TN-05 only, rituximab infusion from TN-05 in four doses of rituximab; infusion with 375 mg/m² (each one week apart starting Day 0) (infusion duration 3-8 h)
Control	No intervention (TregVac 2.0) or placebo treatment (TN-05 and TregVac 1.0) (pooled)

Abbreviations: Tregs=T regulatory cells, b.w.=body weight, h=hours

Statistical Analyses

Due to the exploratory nature of this integrated data analysis the statistical tests have not been specifically powered for the pairwise treatment comparisons between the different treatment groups. Nevertheless, the number of participants is expected to be adequate for this exploratory analysis. The alpha-level for multiplicity of tests was not controlled.

To perform comparisons of efficacy between treatment groups (Tregs+rituximab/Control, Tregs/Control, and Tregs/rituximab), analysis of covariance (ANCOVA) was performed on logarithmized values for the following parameters for baseline to the 24-month visit and for all visits: area under the curve (AUC) of C-peptide levels (MMTT, 0-240 min), AUC of C-peptide levels (glucagon test, 0 to 6 min), C-peptide concentration (glucagon test, 0 to 6 minutes), C-peptide levels (MMTT, 0-240 min), and C-peptide levels (fasting). These values were back-transformed to the normal scale to obtain geometric mean ratios and their 90% confidence limits. For DDI, an ANCOVA based on the original values was performed to obtain DDI differences and 90% CIs. The group comparison were performed as follows:

1. [Tregs+rituximab] /Control: 1-sided test for superiority, alpha level 5%
2. Tregs/Control: 1-sided test for superiority, alpha level 5%
3. [Rituximab] /Control: 1-sided test for superiority, alpha level 5%
4. Tregs/[Tregs+rituximab]: 1-sided test for non-inferiority, alpha level 5%, non-inferiority margin 20%, i.e., critical ratio level 0.8

5. Rituximab /[Tregs+rituximab]: 1-sided test for non-inferiority, alpha level 5%, non-inferiority margin 20%, i.e., critical ratio level 0.8
6. Tregs/rituximab: 1-sided test for non-inferiority, alpha level 5%, non-inferiority margin 20%, i.e., critical ratio level 0.8

Repeated Measures Analysis of Covariance (RMANCOVA) was performed for all follow-up visits (starting from month 3) to analyze comparisons of geometric mean ratios between treatment groups and their 90% confidence intervals by the following parameters: AUC of C-peptide (MMTT), AUC of C-peptide and C-peptide concentration (glucagon test, 0 to 6 min), C-peptide levels (MMTT, 0-240 min), C-peptide levels (fasting), HbA1c values, glucose levels, and DDI.

Survival analysis was performed for remission and time to first loss of insulin independence starting from month 3. Contingency tables resulting from exact permutation test analyses with p-values are also provided for these parameters. Safety parameters were analyzed using descriptive statistics. Quantitative data (e.g. hematology, blood chemistry, urinalysis, and vital signs) were described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum and presented by renal function group for the original data as well as for the difference to the respective baseline, if appropriate.

3. Results

Efficacy (Table S2)

C-peptide (MMTT)

At month 12 visit, all 3 treatments were statistically superior to the control at all 6 available timepoints (0-120 min) (**Table S3; Fig. S2**). Their effects subsequently decreased, with the Tregs+rituximab group remaining superior at the majority of timepoints at both months 18 and 24, the rituximab group at all and half of the timepoints at both months 18 and 24, respectively, and the Tregs group at a minority of timepoints at month 18 and none at month 24 (**Fig. S3**). Importantly, even though the rituximab group was superior to the control group at more timepoints that the Tregs group, the Tregs group was never non-inferior to either other treatment group at any timepoint. The rituximab group was inferior to the Tregs+rituximab group at multiple timepoints, including the final (120 min) timepoint in both months 18 and 24. Overall, these data provide further evidence that of the three treatments, the combination therapy provided the strongest and most enduring benefit to the patients.

Fasting C-peptide

All three treatment groups were generally superior to the control at months 12 (all 3 groups) and 24 (the Tregs+rituximab and rituximab groups), however none of the treatment groups was inferior to the other two treatment groups (**Table S6**). Additionally, between months 12 and 24, only the Tregs+rituximab group showed an increased ratio when compared to the control, while both Tregs and rituximab groups showed decreases (**Fig. S4**). These results also support the possible best long-term benefit of the combination therapy.

At month 12, all three treatment groups were superior to the control group, including Tregs+rituximab (GMR, 1.949; 90% CI, 1.316 to 2.888), Tregs (GMR, 2.131; 90% CI, 1.574 to 2.884), and rituximab (GMR, 1.919; 90% CI, 1.457 to 2.527). At month 24, only the Tregs+rituximab (GMR, 2.012; 90% CI, 1.150 to 3.522) and rituximab (GMR, 1.523; 90% CI, 1.008- to 2.301) groups were statistically superior to the control group. The non-inferiority comparisons at both months 12 and 24 reported CIs in 5/6 cases partially below the non-inferiority margin. Of note, the CI from the Tregs/rituximab comparison (GMR, 1.110; 90% CI, 0.803-1.535) was completely above the non-inferiority margin but only partially above unity,

indicating that the Tregs monotherapy was neither superior nor non-inferior to the rituximab monotherapy.

Geometric mean fasting C-peptide levels decreased throughout the study in all 4 study groups. While the control group consistently presented the lowest levels, the standard deviations of the 3 active treatment groups were broadly overlapped throughout the study; however, at month 24, the geometric mean for the Tregs+rituximab group (0.609 μg/L) appears to be approximately double the distance from the geometric mean of the control group (0.307 μg/L; difference, 0.302 μg/L) as the next closest group, the rituximab monotherapy (0.432 μg/L; difference: 0.125 μg/L) (**Fig. 1C**).

RMANCOVA of C peptide levels (fasting) at months 3, 6, 12, 18, and 24 showed that all 3 active treatment groups were superior to the control group at 4/5 of the visits (**Fig. 1C**). Only the 2 rituximab groups (the combination group and the monotherapy group) were superior to the control at the month 24 (GMR, 2.127; 90% CI, 1.270 to 3.560 and GMR, 1.574; 90% CI, 1.084 to 2.286). At month 24, compared with the control group, the Tregs+rituximab group had a much higher geometric ratio (GMR, 2.127; 90% CI, 1.270 to 3.560) than either Tregs group (GMR, 1.195; 90% CI, 0.754 to 1.895) or the rituximab group (GMR, 1.574; 90% CI, 1.084 to 2.286). Compared with the control group, all three treatments benefited patients (when compared to the control) during most of the study duration. The combination therapy provided a more substantial benefit than either monotherapy.

Daily insulin dose

Exogenous daily insulin dose per kg body weight indicates a beneficial effect from all three active treatments during the first 12 months, only the Tregs group was superior to the control group at month 24 (**Fig. S5**). Non-inferiority was not supported in any of the subsequent treatment group comparisons.

All three treatment groups were superior to the control group at month 12, only the Tregs treatment group remained superior to the control group at month 24 (treatment difference, -0.273; 90% CI, -0.525 to -0.021) (**Table S8**). Comparisons of differences in the means for all three treatment groups *versus* the control group showed that the active treatments were superior to the control group at multiple timepoints (the Tregs+rituximab group and Tregs group at 5/6 and the rituximab group at 3/6 timepoints) (**Fig. S6**). While no treatment group was found to be inferior

to any other treatment group, the results show that the most substantial difference was between the Tregs+rituximab group and the rituximab group. These results indicate that while all three treatments provided a benefit to patients, both the combination therapy and the monotherapy that included Tregs did so more consistently than was observed in the rituximab group.

HbA1c

The data show that the Tregs+rituximab group was by far the most consistent in maintaining HbA1c (%) at lower levels compared with other groups (**Table S10**). Geometric mean HbA1c (%) decreased during the 2-year duration of the studies in the combination therapy group (baseline, 6.411; month 24, 6.202; 3.3% decrease) and the Tregs group (baseline, 7.088; month 24, 6.500; 8.3% decrease) but increased in both the rituximab (7.077; 7.388; 4.4% increase) and control groups (7.264; 7.581; 4.4% increase) (**Fig. 2B**). Specifically, compared with the control group, the Tregs+rituximab group was always superior at all 6 visits, the Tregs group was superior at only the month 24 visit, and the rituximab monotherapy was superior at only the months 3 and 6 visits (**Fig. S7**). Compared with the combination therapy, the Tregs group and the rituximab group were *inferior* at month 9 (GMR, 1.136; 90% CI, 1.031 to 1.251) and month 24 (GMR, 1.163; 90% CI, 1.064 to 1.270), respectively (**Table S10**).

The two Tregs groups, especially the combination therapy group, provided a more substantial benefit to patients at month 24 with a clear separation of standard deviations between the two Tregs groups at the lower end of values and both the control group and rituximab group at the upper end of values (**Fig. S7**). Thus, the combination therapy provided a more substantial and consistent benefit to the patients throughout the study course.

Glucose

With regard for the maintenance of lower blood glucose levels, the Tregs group was superior to the control group (GMR, 0.600; 90% CI, 0.447 to 0.805) at month 6 and the rituximab group at month 6 (GMR, 0.677; 90% CI, 0.502 to 0.914), 12 (GMR, 0.859; 90% CI, 0.744 to 0.991), and 24 (GMR, 0.802; 90% CI, 0.669 to 0.961) (**Table S16; Fig. S8**). The rituximab group was also *inferior* to the control group at month 12 (GMR, 1.132; 90% CI, 1.002 to 1.279) and to the Tregs+rituximab group at month 24 (GMR, 1.264; 90% CI, 1.071 to 1.492). Overall, Tregs applied without or with rituximab were better at maintaining lower glucose levels than either the

control or the rituximab monotherapy with the lowest geometric mean glucose level at all timepoints.

Insulin independence

Comparisons of proportion of insulin-independent patients only detected statistically significant differences between the Tregs+rituximab group and the control group at both months 3 and 6 (p=0.05 and 0.01, respectively) and between the Tregs+rituximab group and the rituximab group at month 3 (p=0.05) (**Table S17; Fig. S9**).

Safety

Frequency of AEs by System Organ Class

Across all groups, of 837 total AEs reported in 91 patients (79.1% of all patients) (**Table S12**). The most frequently reported AEs were nausea and headache (35 events in 24 [20.9%] and 19 patients [16.5%], respectively), vomiting (32 events in 22 [19.1%] patients), pyrexia (26 events in 19 [16.5%] patients) and rash (24 events in 21 [18.3%] patients). Nausea was reported as 4 events in 3 (25.0%) patients in the combination therapy group, 27 events in 18 (53%) patients in the rituximab group, and 4 events in 3 (6.8%) patients in the control group. Of these, 4 events in 3 (25.0%) patients in the combination therapy group, and 21 events in 16 (47.1%) patients in rituximab group were assessed as related to study treatment (**Table S13**). Headache was reported as 3 events in 2 (16.7%) patients in the combination therapy group, 1 event in 1 (4.0%) patient in the Tregs monotherapy group, 11 events in 7 (21%) patients in the rituximab group, and 20 events in 9 (21%) patients in the control group. Of these, 3 events in 2 (16.7%) patients in the combination therapy group, 1 event in 1 (4.0%) patient in the Tregs monotherapy group, 6 events in 5 (14.7%) patients in the rituximab group, and 11 events in 5 (11.4%) patients in the control group were assessed as related to study treatment. Vomiting was reported as 3 events in 2 (17%) patients in the combination therapy group, 24 events in 16 (47%) patients in the rituximab group, and 5 events in 4 (9.1%) patients in the control group. Of these, 3 events in 2 (16.7%) patients in the combination therapy group, 16 events in 14 (41.2%) patients in the rituximab group, and 1 event in 1 (2.3%) patient in the control group were assessed as related to study treatment. Pyrexia was reported as 14 events in 12 (35.3%) patients in the rituximab group and 12 events in 7 (15.9%) patients in the control group. Of these, 10 events in 9 (26.5%) patients in the rituximab

group and 8 events in 5 (11.4%) patients in the control group were assessed as related to treatment. Rash was reported in 1 event in 1 (8.3%) patient in the combination therapy group, 18 events in 16 (47%) patients in the rituximab group, and 5 events in 4 (9.1%) patients in the control group. Of these, 1 event in 1 (8.3%) patient in the combination therapy group, 16 events in 14 (41.2%) patients in the rituximab group, and 3 events in 2 (4.5%) patients in the control group were assessed as related to study treatment.

Deaths, serious AEs and AEs leading to withdrawal of study treatment

No Deaths or AEs leading to withdrawal of a study treatment were reported in any of the patients. Serious AEs (**Table S14**) occurred in 9 (7.8%, 21 events) participants, including 6 (17.6%, 8 events) in the rituximab group and 3 (6.8%, 13 events) in the control group.

Adverse events of special importance (AESI)

Four groups of AESIs included AEs related with blood collection, administration of the Tregs, or Treg product contamination; AEs related with the immunosuppressive activity of Tregs; and AEs related with administration of the rituximab. For all included groups, specific AEs or broader types of AEs which should be considered as belonging to the groups were outlined in the IDAP and Section 6.3 of the TregVac 2.0 protocol. AESIs that occurred in the included groups are presented in **Table S15** and those that occurred in >5% of patients (≥6 patients) are briefly outlined below.

Identification of AESIs was done via manual review of the MedDRA-coded AE data by medical data managers. Note that there was some overlap among the groups in selected preferred terms (PTs). PTs are therefore shown in the table according to System Organ Class (SOC) rather than AESI group. No PTs were associated with Tregs product contamination. AESIs related with blood collection and administration of the Tregs included AEs typical of peripheral vascular puncture and blood transfusion preparation. The PTs selected for this group were pyrexia, chills, vessel puncture site hematoma, erythema, presyncope, syncope, hypersensitivity, and anaphylactic reaction. AESIs related with the immunosuppressive activity of Tregs included any AEs with PTs in the SOC Infections and infestations. AESIs related with the administration of rituximab also included all AEs with PTs in the SOC Infections and infestations in addition to the PTs nausea, vomiting, pyrexia, chills, asthenia, rhinorrhea, dyspnea, bronchospasm, infusion-

related reaction, rash, pruritis, urticaria, rash pruritis, diffuse alopecia, headache, somnolence, neutropenia, leukopenia, and thrombocytopenia.

The most common AESIs were nausea (p<0.001) and vomiting (p<0.001) in the SOC gastrointestinal disorders, pyrexia (p=0.001) in the SOC general disorders and administration site conditions, rash (p<0.001) in the SOC skin and subcutaneous tissue disorders, and headache (p=0.294) in the SOC nervous system disorders. Note that with the exception of headache, there was a significant difference in the incidence of these PTs among the groups, with all except headache occurring with the highest frequency in the rituximab monotherapy group. All events in these PTs with information for severity were considered mild.

Nausea occurred in 35 events in 24 (20.9%) patients, including 4 events (all related) in 3 (25.0%) patients in the Tregs+anti-CD20 antibody rituximab group, 27 events (21 related) in 18 (52.9%) patients in the anti-CD20 antibody rituximab group, and 4 events in 3 (6.8%) patients in the control group (p=0.768) (**Table S13**).

Vomiting occurred in 32 events in 22 (19.1%) patients, including 3 events (all related) in 2 (16.7%) patients in the Tregs+ anti-CD20 antibody rituximab group, 24 events in 16 (47.1%) patients in the anti-CD20 antibody rituximab group (15 of these events were assessed as related to treatment), and 5 events in 4 (9.1%) patients in the control group (p=0.682).

Pyrexia occurred in 26 events in 19 (16.5%) patients, including 14 events (10 related) in 12 patients (35.3%) in the anti-CD20 antibody rituximab group and 12 events (8 related) in 7 patients (15.9%) in the control group (p=0.724).

Rash occurred in 24 events in 21 (18.3%) of the patients, including 1 event (related) in 1 (8.3%) patient in the Tregs+anti-CD20 antibody rituximab group, 5 events in (3 related) 4 (9.1%) patients in the control group, and 18 events (15 related) in 16 (47.1%) patients in the anti-CD20 antibody rituximab group (p=0.682).

Headache occurred in 35 events in 19 patients (16.5%), including 3 events (all related) in 2 (16.7%) patients in the combination therapy group, 1 event (related) in 1 (4.0%) patient in the Tregs monotherapy group, 11 events (6 related) in 7 (20.6%) patients in the rituximab monotherapy group, and 20 events (11 related) in 9 (20.5%) patients in the control group.

All PTs in the SOC infections and infestations were considered AESIs. In this SOC, the most common were respiratory tract infection, viral infection, and upper respiratory tract infection. There was no significant difference across the groups in the incidence of these PTs.

Respiratory tract infection occurred in 12 events in 12 patients, including 4 patients (16.0%) in the Tregs group, 4 patients (9.1%) in the control group, and 3 patients (25.0%) in the Tregs+anti-CD20 antibody rituximab group (1 related event in each of these 3 groups) (p=0.131); viral infection occurred in 12 events in 11 patients (9.6%), including 6 events in 6 patients (17.6%) in the rituximab group and 6 events in 5 patients (11.4%) in the control group (p=0.086); and upper respiratory tract infection occurred in 15 events in 10 patients, including 3 patients (1 related event) in the anti-CD20 antibody rituximab group (8.8%), 1 patient (related event) in the Tregs+ anti-CD20 antibody rituximab group (8.3), and 6 patients (3 related events) in the control group (13.6%) (p=0.295). Infection occurred in 9 events in 9 patients (7.8%), including 1 each in the Tregs+anti-CD20 antibody rituximab group (8.3%), the Tregs group (4.0%), and the control group (9.1%) as well as 4 patients in the anti-CD20 antibody rituximab group (17.6%) (p=0.076); and nasopharyngitis occurred in 14 events in 8 patients (7.0%), including 6 events in 4 patients (11.8%) in the rituximab group and 8 events in 4 patients (9.1%) in the control group (p=0.235). All other PTs in this SOC occurred in fewer than 6 total patients.

Other PTs considered AESIs that occurred in at least 5% of the study population (N=6) included rhinorrhoea (SOC respiratory, thoracic and mediastinal disorders) in 8 (7.0%) patients (3 in the anti-CD20 antibody rituximab group [6.8%] and 5 in the control group [14.7%]) (p=0.118); pruritus in 9 (7.8%) patients (all 9 in the anti-CD20 antibody rituximab group [26.5%]) (p<0.001); and neutropenia in 7 (6.1%) patients, including 2 (16.7%) in the Tregs+anti-CD20 antibody rituximab group, 1 (2.3%) in the control group, and 4 (11.8%) in the anti-CD20 antibody rituximab group (p=0.74). All three of these PTs had the highest frequency in the rituximab monotherapy group. All other AESIs were reported as isolated incidents (fewer than 5% of the study population).

AESIs of moderate severity were rare (5 events in 4 [3.5%] patients) and are described as follows (note that severity was not available for patients in the TN-05 or TregVac 1 study):

- One patient (TregVac 2-TV01) in the Tregs group had vessel puncture site haematoma (SOC general disorders and administration site conditions) of moderate severity that developed as a result of blood donation and was considered related to study intervention. This patient had no other AEs.
- Patient TregVac 2-TV14 in the Treg+ anti-CD20 antibody rituximab group had influenza and upper respiratory tract infection, both of moderate severity, 10 days after the 1st dose of

Tregs. These were assessed as related to treatment. The same patient also experienced fatigue on the 1st day of rituximab administration. This AE (not and AESI) was mild and considered related to treatment (most likely due to premedication with clemastine).

- Patient TregVac 2-TV16 in the Tregs group had Mumps onset within 3 months of the first dose of Tregs. This AESI (SOC infections and infestations) was moderate in severity, was assessed as related to treatment, and led to the end of diabetes remission. The same patient also had keratitis bacterial (SOC infections and infestations) 15 months after the start of treatment. This AESI was mild in severity and considered unrelated to treatment.
- Patient TregVac 2-TV20 in the Tregs group had Herpes zoster (SOC infections and infestations) 18 months after the start of treatment. This AESI was moderate in severity and was assessed as related to treatment.

Clinical laboratory evaluation

Normal ranges were not provided in the data obtained for TN-05, and abnormal clinical laboratory values therefore could not be identified in the rituximab group. Hence, this analysis was not performed in this integrated analysis.

Autoantibodies

Descriptive statistics for autoantibodies in the safety set are shown in **Table S18** and **Fig. S10**.

4. Tables

Table S1b. Baseline Demographic and Clinical Characteristics of Patients (Intention-to-Treat Population).*

Characteristic	Tregs (N=25)	Rituximab (N=33)	Tregs+ rituximab (N=12)	Control (N=44)‡	P value
Male sex – no. (%)	13 (52.0)	22 (66.7)	5 (41.7%)	23 (52.3)	0.411
Age – yr	12.7±2.1	13.5±2.6	12.9±1.2	12.8±2.5	0.573
Body mass index – kg/m^2	18.6±2.8	21.3±3.9	18.1±1.8	19.5±4.0	0.023
Ethnicity – no. (%)					0.156
Hispanic or Latino	0	1 (3.0)	0	3 (6.8)	
Not Hispanic or Latino	0	32 (97.0)	0	20 (45.5)	
Missing	25 (100.0)	0	12 (100.0)	21 (47.7)	
Months since diagnosis	4.2±3.8	NA**	6.0±4.2	3.5±2.8	
Insulin (DDI per kg of body weight)	0.3±0.3	0.4±0.2	0.2±0.2	0.3±0.3	0.028
C-peptide					
Fasting C-peptide (μg/L)	1.1±0.5	1.2±0.7	1.1±0.3	1.1±0.5	0.756
Stimulated C-peptide AUC_{240} (h*μg/L)	10.3±2.4	9.3±4.5	11.0±3.7	9.1±3.3	0.417
Glycated hemoglobin (%)	7.4±2.7	7.2±1.1	6.5±1.2	8.1±2.5	0.091
Glucose (mg/dL)	201.6±137.1	111.2±33.5	108.4±11.2	169.0±127.1	0.004
Autoantibodies					
Glutamic acid decarboxylase – (IU/mL)	642.4±849.9	0.2±0.3	381.4±594.3	441.6±724.1	
Insulin autoantibody – (IU/mL)	7.7±8.1	0.6±1.0	5.3±5.5	2.7±4.1	
Islet cell antibody – (titer)	80.8±145.0	86.5±108.0	125.0±185.0	70.6±94.3	

Abbreviations: Treg, regulatory T cells; no., number included in the analysis; yr, years; DDI, daily dose of insulin; AUC, area under the curve. Baseline was defined as the last value of assessment prior to first drug administration. P-values are based on one-way ANOVA F-statistics for continuous and Kruskal-Wallis statistics for multilevel categorical data.

* Plus-minus values are means ± SD.

** The specific duration since diagnosis was not available for patients in the TN-05 study; however, an inclusion criterion of that study was initial diagnosis within 3 months (100 days).

Table S2. Key Efficacy Outcomes (Intention-to-Treat Population).

Outcome	Tregs (N=25)	Rituximab (N=33)	Tregs+rituximab (N=12)
AUC of C-peptide (MMTT) *versus* control			
Month 12 – geometric mean treatment ratio (90% CI)*	**1.5 (1.0-2.3)**	**1.6 (1.2-2.2)**	**1.8 (1.2-2.7)**
Effect size - mean (*d*)***	2.2 (0.5)	1.7 (0.4)	4.5 (0.9)
Month 24 – geometric mean treatment ratio (90% CI)*	1.8 (1.0-3.3)	1.5 (1.0-2.2)	**1.9 (1.1-3.3)**
Effect size - mean (*d*)**	1.1 (0.3)	1.1 (0.3)	3.5 (0.8)
Fasting C-peptide *versus* control			
Month 12 – treatment ratio (90% CI)*	**2.1 (1.6-2.9)**	**1.9 (1.5-2.5)**	**1.9 (1.3-2.9)**
Effect size - mean (*d*)**	0.4 (0.9)	0.5 (0.8)	0.4 (0.9)
Month 24 – treatment ratio (90% CI)*	1.2 (0.6-2.0)	**1.5 (1.0-2.3)**	**2.0 (1.2-3.5)**
Effect size - mean (*d*)**	−0.1 (−0.3)	0.2 (0.3)	0.3 (0.5)
Insulin (DD per kg b.w.) *versus* control			
Month 12 – treatment difference (90% CI)*	**-0.2 (-0.3 − -0.1)**	**−0.1 (−0.2-−0.03)**	**−0.3 (−0.4-−0.1)**
Effect size - mean (*d*)**	−0.3 (−0.8)	−0.1 (−0.3)	−0.4 (−1.1)
Month 24 – treatment ratio (90% CI)*	−0.2 (−0.5-0)	−0.03 (−0.2-0.2)	−0.2 (−0.4-0.1)
Effect size - mean (*d*)**	−0.3 (−0.8)	−0.05 (−0.1)	−0.3 (−0.8)
Remission *versus* control			
Month 12 - (%) (P value)	20.0 (0.7)	28.1 (0.4)	54.5 (0.1)
Month 24 - (%) (P value)	27.3 (0.2)	3.6 (0.7)	33.3 (0.1)

Abbreviations: Treg, regulatory T cells; CI, confidence interval; DDI, daily dose of insulin; b.w., body weight; AUC, area under the curve. Baseline was defined as the last value of assessment prior to first drug administration.

* ANCOVA of DDI per kg b.w. was performed using the DDI per kg b.w. at baseline as a continuous covariate and age group (> or ≤ 12 years), sex, and treatment as fixed categorical effects.

** Cohen's *d* was calculated for pairwise comparisons of treatment groups as [mean (groups 1) – mean (group 2)] / standard deviation (both groups pooled). Descriptors of magnitude were according to Cohen (1988): small = 0.2, medium = 0.5, large = 0.8.

Table S3. Area Under the Curve (AUC) of C-Peptide (MMTT, 0-240 min, 12- and 24-m Visit) – Comparison of Treatment Groups (ITT Set).

		Geometric mean		Treatment	
Visit	**Comparison**	**Test**	**Ref.**	**ratio**	**90% CI***
Month 12	Tregs+rituximab vs Control	6.916	3.808	1.816	1.207-2.733*
	Tregs vs Control	5.838	3.808	1.533	1.020-2.303*
	Rituximab vs Control	6.153	3.808	1.616	1.201-2.174*
	Tregs vs Tregs+rituximab	5.838	6.916	0.844	0.515-1.383
	Rituximab vs Tregs+rituximab	6.153	6.916	0.890	0.586-1.350
	Tregs vs Rituximab	5.838	6.153	0.949	0.628-1.433
Month 24	Tregs+rituximab vs Control	4.392	2.298	1.912	1.112-3.287*
	Tregs vs Control	4.136	2.298	1.800	0.991-3.270
	Rituximab vs Control	3.346	2.298	1.456	0.976-2.172
	Tregs vs Tregs+rituximab	4.136	4.392	0.942	0.465-1.907
	Rituximab vs Tregs+rituximab	3.346	4.392	0.762	0.439-1.323
	Tregs vs Rituximab	4.136	3.346	1.236	0.679-2.250

Abbreviations: Tregs: T regulatory cells, min: minutes, m: month; MMTT: mixed meal tolerance test, ITT: intention-to-treat, Ref.: reference, CI: confidence interval; * indicates a significant difference (these values also shown boxed)
Results of analysis of covariance (ANCOVA) of logarithmized AUC of C-peptide levels (MMTT, 0-240 min) at 24m, using the logarithmized AUC of C-peptide levels (MMTT, 0-240 min) at baseline (Day 0) as continuous covariate and age group (either ≤12 years or >12 years), gender and treatment as fixed categorical effects.
Residual were not normally distributed.

Table S4. Area Under the Curve (AUC) of C-Peptide (MMTT, 0-240 min, 12- and 24-m Visit) – Description of Treatment Group Differences (ITT Set).

Visit	Group Differences	N	Mean	Effect Size: Cohen's d
Month 12	Tregs+rituximab vs Control	44	4.513	0.882
	Tregs vs Control	45	2.227	0.525
	Rituximab vs Control	63	1.743	0.392
	Tregs vs Tregs+rituximab	23	-2.286	-0.483
	Rituximab vs Tregs+rituximab	41	-2.771	-0.568
	Tregs vs Rituximab	42	0.485	0.119
Month 24	Tregs+rituximab vs Control	45	3.508	0.786
	Tregs vs Control	43	1.062	0.281
	Rituximab vs Control	64	1.059	0.257
	Tregs vs Tregs+rituximab	22	-2.446	-0.610
	Rituximab vs Tregs+rituximab	43	-2.449	-0.556
	Tregs vs Rituximab	41	0.003	0.001

Abbreviations: Tregs: T regulatory cells, min: minutes, m: month; MMTT: mixed meal tolerance test, ITT: intention-to-treat.

Note(s): N: number of observations used in the analysis. Values indicating a large effect size are shown boxed.

Cohen's d was calculated for pairwise comparisons of treatment groups as [mean(group 1)- mean(group 2)] / standard deviation(both groups pooled). Descriptors of magnitude defined by Cohen (1988): small=0.2, medium=0.5, large=0.8.

Table S5. C-Peptide (MMTT, 0-240min, 12m and 24m Visit) – Comparison of Treatment Groups (ITT Set).

				Geometric Mean			
Visit	**Timepoint**	**Comparison**	**N**	**Test**	**Reference**	**Treatment Ratio**	**90% Confidence Interval***
Month 12	0 Minutes	Tregs+rituximab vs Control	87	0.664	0.397	1.670	1.090 - 2.560
		Tregs vs Control	87	0.614	0.397	1.546	1.025 - 2.332
		Rituximab vs Control	87	0.697	0.397	1.754	1.291 - 2.382
		Tregs vs Tregs+rituximab	87	0.614	0.664	0.926	0.555 - 1.542
		Rituximab vs Tregs+rituximab	87	0.697	0.664	1.050	0.681 - 1.620
		Tregs vs Rituximab	87	0.614	0.697	0.882	0.582 - 1.335
	15 Minutes	Tregs+rituximab vs Control	87	1.205	0.582	2.070	1.310 - 3.270
		Tregs vs Control	87	1.040	0.582	1.787	1.150 - 2.776
		Rituximab vs Control	87	0.973	0.582	1.672	1.204 - 2.321
		Tregs vs Tregs+rituximab	87	1.040	1.205	0.863	0.499 - 1.493
		Rituximab vs Tregs+rituximab	87	0.973	1.205	0.808	0.508 - 1.286
		Tregs vs Rituximab	87	1.040	0.973	1.069	0.685 - 1.668
	30 Minutes	Tregs+rituximab vs Control	86	1.675	0.779	2.151	1.316 - 3.518
		Tregs vs Control	86	1.444	0.779	1.855	1.156 - 2.976
		Rituximab vs Control	86	1.293	0.779	1.660	1.166 - 2.362
		Tregs vs Tregs+rituximab	86	1.444	1.675	0.862	0.480 - 1.548
		Rituximab vs Tregs+rituximab	86	1.293	1.675	0.772	0.469 - 1.268
		Tregs vs Rituximab	86	1.444	1.293	1.117	0.694 - 1.798
	60 Minutes	Tregs+rituximab vs Control	86	2.067	0.950	2.175	1.315 - 3.596
		Tregs vs Control	86	1.765	0.950	1.857	1.163 - 2.966
		Rituximab vs Control	86	1.507	0.950	1.586	1.119 - 2.248
		Tregs vs Tregs+rituximab	86	1.765	2.067	0.854	0.471 - 1.549
		Rituximab vs Tregs+rituximab	86	1.507	2.067	0.729	0.438 - 1.214
		Tregs vs Rituximab	86	1.765	1.507	1.171	0.730 - 1.879
	90 Minutes	Tregs+rituximab vs Control	87	2.473	1.050	2.355	1.470 - 3.773
		Tregs vs Control	87	1.990	1.050	1.896	1.204 - 2.983
		Rituximab vs Control	87	1.625	1.050	1.547	1.104 - 2.169
		Tregs vs Tregs+rituximab	87	1.990	2.473	0.805	0.458 - 1.414
		Rituximab vs Tregs+rituximab	87	1.625	2.473	0.657	0.407 - 1.060
		Tregs vs Rituximab	87	1.990	1.625	1.225	0.775 - 1.937
	120 Minutes	Tregs+rituximab vs Control	87	2.323	1.042	2.228	1.371 - 3.621
		Tregs vs Control	87	1.963	1.042	1.884	1.180 - 3.006
		Rituximab vs Control	87	1.642	1.042	1.575	1.112 - 2.231
		Tregs vs Tregs+rituximab	87	1.963	2.323	0.845	0.473 - 1.511
		Rituximab vs Tregs+rituximab	87	1.642	2.323	0.707	0.432 - 1.157
		Tregs vs Rituximab	87	1.963	1.642	1.196	0.746 - 1.917
	150 Minutes	Tregs+rituximab vs Control	87	2.056	0.983	2.091	1.313 - 3.331
		Tregs vs Control	87	1.716	0.983	1.745	1.115 - 2.732
		Rituximab vs Control	87	1.585	0.983	1.613	1.155 - 2.252
		Tregs vs Tregs+rituximab	87	1.716	2.056	0.835	0.478 - 1.457
		Rituximab vs Tregs+rituximab	87	1.585	2.056	0.771	0.481 - 1.238
		Tregs vs Rituximab	87	1.716	1.585	1.082	0.688 - 1.702
	180 Minutes	Tregs+rituximab vs Control	87	1.837	0.939	1.957	1.247 - 3.073
		Tregs vs Control	87	1.616	0.939	1.722	1.116 - 2.658
		Rituximab vs Control	87	1.480	0.939	1.577	1.141 - 2.179

Visit	Timepoint	Comparison	N	Geometric Mean		Treatment Ratio	90% Confidence Interval*
				Test	Reference		
		Tregs vs Tregs+rituximab	87	1.616	1.837	0.880	0.513 - 1.509
		Rituximab vs Tregs+rituximab	87	1.480	1.837	0.806	0.510 - 1.274
		Tregs vs Rituximab	87	1.616	1.480	1.092	0.704 - 1.693
	210 Minutes	Tregs+rituximab vs Control	86	1.532	0.808	1.896	1.227 - 2.928
		Tregs vs Control	86	1.334	0.808	1.651	1.086 - 2.509
		Rituximab vs Control	86	1.263	0.808	1.562	1.141 - 2.138
		Tregs vs Tregs+rituximab	86	1.334	1.532	0.871	0.518 - 1.465
		Rituximab vs Tregs+rituximab	86	1.263	1.532	0.824	0.529 - 1.284
		Tregs vs Rituximab	86	1.334	1.263	1.057	0.691 - 1.616
	240 Minutes	Tregs+rituximab vs Control	86	1.366	0.699	1.954	1.261 - 3.027
		Tregs vs Control	86	1.044	0.699	1.493	0.980 - 2.275
		Rituximab vs Control	86	1.072	0.699	1.534	1.118 - 2.104
		Tregs vs Tregs+rituximab	86	1.044	1.366	0.764	0.453 - 1.290
		Rituximab vs Tregs+rituximab	86	1.072	1.366	0.785	0.502 - 1.226
		Tregs vs Rituximab	86	1.044	1.072	0.973	0.635 - 1.492
Month 24	0 Minutes	Tregs+rituximab vs Control	85	0.363	0.266	1.365	0.790 - 2.358
		Tregs vs Control	85	0.322	0.266	1.212	0.678 - 2.164
		Rituximab vs Control	85	0.400	0.266	1.506	1.006 - 2.255
		Tregs vs Tregs+rituximab	85	0.322	0.363	0.887	0.442 - 1.782
		Rituximab vs Tregs+rituximab	85	0.400	0.363	1.103	0.634 - 1.918
		Tregs vs Rituximab	85	0.322	0.400	0.805	0.450 - 1.438
	15 Minutes	Tregs+rituximab vs Control	86	0.596	0.339	1.757	1.009 - 3.057
		Tregs vs Control	86	0.452	0.339	1.331	0.739 - 2.399
		Rituximab vs Control	86	0.521	0.339	1.536	1.022 - 2.309
		Tregs vs Tregs+rituximab	86	0.452	0.596	0.758	0.372 - 1.542
		Rituximab vs Tregs+rituximab	86	0.521	0.596	0.874	0.498 - 1.537
		Tregs vs Rituximab	86	0.452	0.521	0.867	0.480 - 1.566
	30 Minutes	Tregs+rituximab vs Control	86	0.894	0.417	2.144	1.165 - 3.944
		Tregs vs Control	86	0.643	0.417	1.542	0.806 - 2.948
		Rituximab vs Control	86	0.663	0.417	1.589	1.015 - 2.489
		Tregs vs Tregs+rituximab	86	0.643	0.894	0.719	0.329 - 1.572
		Rituximab vs Tregs+rituximab	86	0.663	0.894	0.741	0.399 - 1.379
		Tregs vs Rituximab	86	0.643	0.663	0.970	0.506 - 1.860
	60 Minutes	Tregs+rituximab vs Control	86	1.267	0.529	2.395	1.309 - 4.381
		Tregs vs Control	86	1.064	0.529	2.012	1.058 - 3.823
		Rituximab vs Control	86	0.826	0.529	1.562	1.001 - 2.436
		Tregs vs Tregs+rituximab	86	1.064	1.267	0.840	0.387 - 1.822
		Rituximab vs Tregs+rituximab	86	0.826	1.267	0.652	0.353 - 1.206
		Tregs vs Rituximab	86	1.064	0.826	1.288	0.676 - 2.455
	90 Minutes	Tregs+rituximab vs Control	86	1.438	0.611	2.352	1.275 - 4.338
		Tregs vs Control	86	1.297	0.611	2.121	1.106 - 4.067
		Rituximab vs Control	86	0.848	0.611	1.386	0.884 - 2.176
		Tregs vs Tregs+rituximab	86	1.297	1.438	0.902	0.411 - 1.978
		Rituximab vs Tregs+rituximab	86	0.848	1.438	0.590	0.316 - 1.100
		Tregs vs Rituximab	86	1.297	0.848	1.530	0.796 - 2.941
	120 Minutes	Tregs+rituximab vs Control	85	1.610	0.622	2.589	1.394 - 4.807
		Tregs vs Control	85	1.291	0.622	2.076	1.075 - 4.006
		Rituximab vs Control	85	0.860	0.622	1.383	0.875 - 2.184

Visit	Timepoint	Comparison	N	Geometric Mean		Treatment Ratio	90% Confidence Interval*
				Test	Reference		
		Tregs vs Tregs+rituximab	85	1.291	1.610	0.802	0.364 - 1.767
		Rituximab vs Tregs+rituximab	85	0.860	1.610	0.534	0.285 - 1.000
		Tregs vs Rituximab	85	1.291	0.860	1.501	0.778 - 2.898
	150 Minutes	Tregs+rituximab vs Control	86	1.449	0.551	2.631	1.443 - 4.797
		Tregs vs Control	86	1.456	0.551	2.645	1.397 - 5.007
		Rituximab vs Control	86	0.840	0.551	1.525	0.980 - 2.372
		Tregs vs Tregs+rituximab	86	1.456	1.449	1.005	0.465 - 2.170
		Rituximab vs Tregs+rituximab	86	0.840	1.449	0.579	0.315 - 1.068
		Tregs vs Rituximab	86	1.456	0.840	1.734	0.914 - 3.293
	180 Minutes	Tregs+rituximab vs Control	86	1.338	0.534	2.507	1.381 - 4.552
		Tregs vs Control	86	1.198	0.534	2.245	1.191 - 4.232
		Rituximab vs Control	86	0.784	0.534	1.469	0.947 - 2.278
		Tregs vs Tregs+rituximab	86	1.198	1.338	0.895	0.417 - 1.924
		Rituximab vs Tregs+rituximab	86	0.784	1.338	0.586	0.319 - 1.075
		Tregs vs Rituximab	86	1.198	0.784	1.529	0.809 - 2.890
	210 Minutes	Tregs+rituximab vs Control	86	1.154	0.496	2.326	1.305 - 4.145
		Tregs vs Control	86	1.076	0.496	2.169	1.174 - 4.009
		Rituximab vs Control	86	0.714	0.496	1.439	0.941 - 2.201
		Tregs vs Tregs+rituximab	86	1.076	1.154	0.933	0.445 - 1.956
		Rituximab vs Tregs+rituximab	86	0.714	1.154	0.619	0.344 - 1.114
		Tregs vs Rituximab	86	1.076	0.714	1.507	0.814 - 2.793
	240 Minutes	Tregs+rituximab vs Control	86	1.086	0.469	2.316	1.302 - 4.120
		Tregs vs Control	86	0.887	0.469	1.891	1.026 - 3.489
		Rituximab vs Control	86	0.662	0.469	1.412	0.924 - 2.157
		Tregs vs Tregs+rituximab	86	0.887	1.086	0.817	0.390 - 1.708
		Rituximab vs Tregs+rituximab	86	0.662	1.086	0.609	0.339 - 1.095
		Tregs vs Rituximab	86	0.887	0.662	1.340	0.725 - 2.477

Note(s): N: number of observations used in the analysis. * a box indicates a significant result.
Results of analysis of covariance (ANCOVA) of logarithmized C-peptide levels (MMTT Test) by time point, using the logarithmized C-peptide levels (MMTT, 0-240min) at baseline (day 0, 0 min) as continuous covariate and age group (either 12 years or >12 years), gender and treatment as fixed categorical effects.

Table S6. C-Peptide (Fasted, 12m and 24m Visit) – Comparison of Treatment Groups (ITT Set).

Visit	Comparison	N	Geometric Mean		Treatment Ratio	90% Confidence Interval*
			Test	Reference		
Month 12	Tregs+rituximab vs Control	106	0.680	0.349	1.949	1.316 - 2.888
	Tregs vs Control	106	0.743	0.349	2.131	1.574 - 2.884
	Rituximab vs Control	106	0.669	0.349	1.919	1.457 - 2.527
	Tregs vs Tregs+rituximab	106	0.743	0.680	1.093	0.712 - 1.677
	Rituximab vs Tregs+rituximab	106	0.669	0.680	0.984	0.655 - 1.480
	Tregs vs Rituximab	106	0.743	0.669	1.110	0.803 - 1.535
Month 24	Tregs+rituximab vs Control	87	0.568	0.283	2.012	1.150 - 3.522
	Tregs vs Control	87	0.326	0.283	1.153	0.649 - 2.047
	Rituximab vs Control	87	0.430	0.283	1.523	1.008 - 2.301
	Tregs vs Tregs+rituximab	87	0.326	0.568	0.573	0.285 - 1.150
	Rituximab vs Tregs+rituximab	87	0.430	0.568	0.757	0.428 - 1.339
	Tregs vs Rituximab	87	0.326	0.430	0.757	0.425 - 1.350

Note(s): N: number of observations used in the analysis. * indicates a significant difference (these values are boxed).
Results of analysis of covariance (ANCOVA) of logarithmized fasted C-peptide levels, using the logarithmized fasted C-peptide levels at baseline as continuous covariate
and age group (either <=12years or >12 years), gender and treatment as fixed categorical effects.

Table S7. C-Peptide (Fasted, 12m and 24m Visit) – Description of Treatment Group Differences (ITT Set).

Visit	Group Differences	N	Mean	Effect Size: Cohen's d
Month 12	Tregs+rituximab vs Control	54	0.433	0.92
	Tregs vs Control	65	0.381	0.858
	Rituximab vs Control	74	0.506	0.817
	Tregs vs Tregs+anti-CD20 rituximab	33	-0.052	-0.118
	Rituximab vs Tregs+rituximab	42	0.073	0.107
	Tregs vs Rituximab	53	-0.125	-0.203
Month 24	Tregs+rituximab vs Control	45	0.266	0.486
	Tregs vs Control	44	-0.13	-0.268
	Rituximab vs Control	64	0.203	0.318
	Tregs vs Tregs+rituximab	23	-0.396	-0.889
	Rituximab vs Tregs+rituximab	43	-0.063	-0.096
	Tregs vs Rituximab	42	-0.333	-0.522

Note(s): N: number of observations used in the analysis.
Cohen's d was calculated for pairwise comparisons of treatment groups as [mean(group 1)- mean(group 2)] / standard deviation(both groups pooled).
Descriptors of magnitude defined by Cohen (1988): small=0.2, medium=0.5, large=0.8.

Table S8. Daily Insulin Dose per kg Body Weight (12m and 24m Visit) – Comparison of Treatment Groups (ITT Set).

			Means			
Visit	**Comparison**	**N**	**Test**	**Reference**	**Treatment Difference**	**90% Confidence Interval***
Month 12	Tregs+rituximab vs Control	108	0.399	0.686	-0.287	-0.451 - -0.122
	Tregs vs Control	108	0.460	0.686	-0.226	-0.352 - -0.100
	Rituximab vs Control	108	0.548	0.686	-0.138	-0.249 - -0.026
	Tregs vs Tregs+rituximab	108	0.460	0.399	0.061	-0.116 - 0.237
	Rituximab vs Tregs+rituximab	108	0.548	0.399	0.149	-0.023 - 0.320
	Tregs vs Rituximab	108	0.460	0.548	-0.088	-0.223 - 0.047
Month 24	Tregs+rituximab vs Control	84	0.757	0.964	-0.207	-0.455 - 0.041
	Tregs vs Control	84	0.691	0.964	-0.273	-0.525 - -0.021
	Rituximab vs Control	84	0.878	0.964	-0.086	-0.270 - 0.098
	Tregs vs Tregs+rituximab	84	0.691	0.757	-0.066	-0.365 - 0.233
	Rituximab vs Tregs+rituximab	84	0.878	0.757	0.121	-0.141 - 0.382
	Tregs vs Rituximab	84	0.691	0.878	-0.187	-0.447 - 0.074

Note(s): N: number of observations used in the analysis. * a box indicates a significant result.
Results of analysis of covariance (ANCOVA) of daily dose of insulin by body weight, using the daily dose of insulin by body weight at baseline as continuous covariate and
age group (either <=12years or >12 years), gender and treatment as fixed categorical effects.

Table S9.

Daily Insulin Dose per kg Body Weight (12m and 24m Visit) – Description of Treatment Group Differences (ITT Set).

Visit	Group Differences	N	Mean	Effect Size: Cohen's d
Month 12	Tregs+rituximab vs Control	54	-0.376	-1.068
	Tregs vs Control	65	-0.281	-0.819
	Rituximab vs Control	75	-0.116	-0.349
	Tregs vs Tregs+rituximab	33	0.095	0.397
	Rituximab vs Tregs+rituximab	43	0.259	0.853
	Tregs vs Rituximab	54	-0.165	-0.55
Month 24	Tregs+rituximab vs Control	44	-0.295	-0.752
	Tregs vs Control	43	-0.288	-0.75
	Rituximab vs Control	61	-0.045	-0.094
	Tregs vs Tregs+rituximab	23	0.006	0.025
	Rituximab vs Tregs+rituximab	41	0.249	0.489
	Tregs vs Rituximab	40	-0.243	-0.48

Note(s): N: number of observations used in the analysis.
Cohen's d was calculated for pairwise comparisons of treatment groups as [mean(group 1)- mean(group 2)] / standard deviation(both groups pooled).
Descriptors of magnitude defined by Cohen (1988): small=0.2, medium=0.5, large=0.8.

Table S10. HbA1c (All Visits) – RMANCOVA (ITT Set).

Visit	Comparison	Geometric Means		Treatment Ratio	90% Confidence Interval*
		Test	Reference		
Month 3	Tregs+rituximab vs Control	6.180	6.678	0.925	0.866 - 0.989
	Tregs vs Control	6.380	6.678	0.955	0.899 - 1.015
	Rituximab vs Control	6.073	6.678	0.909	0.867 - 0.954
	Tregs vs Tregs+rituximab	6.380	6.180	1.032	0.958 - 1.113
	Rituximab vs Tregs+rituximab	6.073	6.180	0.983	0.919 - 1.050
	Tregs vs Rituximab	6.380	6.073	1.050	0.988 - 1.116
Month 6	Tregs+rituximab vs Control	6.215	6.944	0.895	0.824 - 0.972
	Tregs vs Control	6.632	6.944	0.955	0.895 - 1.019
	Rituximab vs Control	6.388	6.944	0.920	0.867 - 0.976
	Tregs vs Tregs+rituximab	6.632	6.215	1.067	0.978 - 1.164
	Rituximab vs Tregs+rituximab	6.388	6.215	1.028	0.946 - 1.117
	Tregs vs Rituximab	6.632	6.388	1.038	0.971 - 1.110
Month 9	Tregs+rituximab vs Control	6.077	7.045	0.862	0.787 - 0.945
	Tregs vs Control	6.901	7.045	0.980	0.912 - 1.052
	Rituximab vs Control	6.650	7.045	0.944	0.884 - 1.007
	Tregs vs Tregs+rituximab	6.901	6.077	1.136	1.031 - 1.251
	Rituximab vs Tregs+rituximab	6.650	6.077	1.094	0.998 - 1.200
	Tregs vs Rituximab	6.901	6.650	1.038	0.964 - 1.117
Month 12	Tregs+rituximab vs Control	6.397	7.149	0.895	0.815 - 0.982
	Tregs vs Control	6.930	7.149	0.969	0.902 - 1.042
	Rituximab vs Control	6.762	7.149	0.946	0.886 - 1.010
	Tregs vs Tregs+rituximab	6.930	6.397	1.083	0.980 - 1.197
	Rituximab vs Tregs+rituximab	6.762	6.397	1.057	0.961 - 1.163
	Tregs vs Rituximab	6.930	6.762	1.025	0.950 - 1.106
Month 18	Tregs+rituximab vs Control	6.574	7.301	0.900	0.827 - 0.980
	Tregs vs Control	6.816	7.301	0.934	0.868 - 1.004
	Rituximab vs Control	7.064	7.301	0.968	0.911 - 1.028
	Tregs vs Tregs+rituximab	6.816	6.574	1.037	0.944 - 1.139
	Rituximab vs Tregs+rituximab	7.064	6.574	1.075	0.986 - 1.171
	Tregs vs Rituximab	6.816	7.064	0.965	0.896 - 1.039
Month 24	Tregs+rituximab vs Control	6.404	7.504	0.853	0.782 - 0.931
	Tregs vs Control	6.908	7.504	0.921	0.849 - 0.998
	Rituximab vs Control	7.446	7.504	0.992	0.931 - 1.057
	Tregs vs Tregs+rituximab	6.908	6.404	1.079	0.975 - 1.193
	Rituximab vs Tregs+rituximab	7.446	6.404	1.163	1.064 - 1.270
	Tregs vs Rituximab	6.908	7.446	0.928	0.855 - 1.007

Note(s): * a box indicates a significant result. Results for a repeated measurement mixed model RMANCOVA for logarithmized HBA1C values, with log baseline value (last value prior to first treatment, Day 0) as continuous covariate, gender, age group (either <=12 years or > 12 years), treatment, visit and treatment*visit interaction as fixed categorical effects for the within subject repeated measurements during follow up visits will be performed, i.e. visits 3m, 6m, 9m, 12m, 18m and 24m will be inclu ded in this analysis.

Table S11. Remission (Months 12 and 24 Visits) - Contingency Table (ITT Set).

	Proportion of patients in remission		
Comparison	**Test [%]**	**Reference [%]**	**P value***
Month 12			
Tregs+rituximab vs Control	54.5	19.0	0.0570
Tregs vs Control	20.0	19.0	0.6539
Rituximab vs Control	28.1	19.0	0.3544
Tregs vs Tregs+rituximab	20.0	54.5	0.0964
Rituximab vs Tregs+rituximab	28.1	54.5	0.4649
Tregs vs Rituximab	20.0	28.1	0.6320
Month 24			
Tregs+rituximab vs Control	33.3	9.4	0.1027
Tregs vs Control	27.3	9.4	0.2327
Rituximab vs Control	3.6	9.4	0.7073
Tregs vs Tregs+rituximab	27.3	33.3	0.7584
Rituximab vs Tregs+rituximab	3.6	33.3	0.0159
Tregs vs Rituximab	27.3	3.6	0.0478

Abbreviations: Tregs: T regulatory cells, m: month, ITT: intention-to-treat

Note(s): p-value is calculated in a permutation exact test with significance level alpha 0.05. * indicates a significant difference (these values also boxed).

Table S12. Adverse Events – Frequency Table by Treatment Group (Safety Set).

System Organ Class Preferred Term	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+rituximab (N=12) n (%) E	Control (N=44) n (%) E	P value*
Any AE	**12 (48) 31**	**34 (100) 410**	**12 (100) 76**	**33 (75) 320**	**<0.001**
Infections and infestations	9 (36) 12	20 (59) 54	7 (58) 11	21 (48) 60	0.333
Respiratory tract infection	4 (16) 4	1 (2.9) 1	3 (25) 3	4 (9.1) 4	0.131
Viral infection	0	6 (17.6) 6	0	5 (11.4) 6	0.086
Upper respiratory tract infection	0	3 (8.8) 6	1 (8.3) 1	6 (13.6) 8	0.295
Infection	1 (4.0) 1	6 (17.6) 6	1 (8.3) 1	1 (2.3) 1	0.076
Nasopharyngitis	0	4 (11.8) 6	0	4 (9.1) 8	0.235
Gastrointestinal disorders	1 (4.0) 5	24 (70.6) 74	4 (33.3) 14	8 (18.2) 29	<0.001
Nausea	0	18 (52.9) 27	3 (25.0) 4	3 (6.8) 4	<0.001
Vomiting	0	16 (47.1) 24	2 (16.7) 3	4 (9.1) 5	<0.001
Abdominal pain	1 (4.0) 2	3 (8.8) 3	4 (33.3) 6	2 (4.5) 3	0.013
Diarrhoea	1 (4.0) 1	6 (17.6) 8	1 (8.3) 1	2 (4.5) 4	0.169
Abdominal pain upper	0	4 (11.8) 5	0	4 (9.1) 6	0.235
General disorders and administration site conditions	2 (8.0) 2	20 (58.8) 31	4 (33.3) 5	10 (22.7) 19	<0.001
Pyrexia	0	12 (35.3) 14	0	7 (15.9) 12	0.001
Chills	0	2 (5.9) 2	1 (8.3) 1	2 (4.5) 2	0.620
Fatigue	0	3 (8.8) 3	1 (8.3) 1	1 (2.3) 3	0.301
Malaise	0	3 (8.8) 4	0	1 (2.3) 1	0.223
Asthenia	1 (4.0) 1	0	2 (16.7) 2	0	0.009
Vessel puncture site haematoma	1 (4.0) 1	0	1 (8.3) 1	0	0.162
Respiratory, thoracic and mediastinal disorders	0	19 (55.9) 48	3 (25.0) 5	8 (18.2) 22	<0.001
Oropharyngeal pain	0	8 (23.5) 11	2 (16.7) 2	4 (9.1) 7	0.044
Cough	0	7 (20.6) 12	0	2 (4.5) 3	0.010
Rhinorrhoea	0	5 (14.7) 6	0	3 (6.8) 3	0.118
Nasal congestion	0	4 (11.8) 4	0	2 (4.5) 2	0.173
Investigations	1 (4.0) 1	12 (35.3) 40	2 (16.7) 2	14 (31.8) 52	0.027
Neutrophil count abnormal	0	5 (14.7) 7	0	5 (11.4) 9	0.144
Lymphocyte count decreased	0	4 (11.8) 4	0	2 (4.5) 2	0.173
Neutrophil count decreased	0	4 (11.8) 7	0	2 (4.5) 2	0.173
White blood count abnormal	0	4 (11.8) 8	0	2 (4.5) 2	0.173
Skin and subcutaneous tissue disorders	0	20 (58.8) 38	2 (16.7) 5	6 (13.6) 10	<0.001
Rash	0	16 (47.1) 18	1 (8.3) 1	4 (9.1) 5	<0.001
Pruritis	0	9 (26.5) 11	0	0	<0.001
Nervous system disorders	1 (4.0) 1	11 (32.4) 21	2 (16.7) 5	13 (29.5) 32	0.048
Headache	1 (4.0) 1	7 (20.6) 11	2 (16.7) 3	9 (20.5) 20	0.294
Metabolism and nutrition disorders	2 (8.0) 3	1 (2.9) 1	3 (25.0) 8	14 (31.8) 25	0.004
Hypoglycaemia	1 (4.0) 1	0	1 (8.3) 2	7 (15.9) 7	0.062
Vascular disorders	0	13 (38.2) 20	1 (8.3) 1	4 (9.1) 8	<0.001
Hypotension	0	10 (29.4) 13	0	4 (9.1) 8	0.002
Blood and lymphatic system disorders	0	7 (20.6) 13	4 (33.3) 4	6 (13.6) 7	0.037
Neutropenia	0	4 (11.8) 5	2 (16.7) 2	1 (2.3) 1	0.074
Cardiac disorders	0	10 (29.4) 14	2 (16.7) 3	1 (2.3) 2	<0.001
Tachycardia	0	9 (26.5) 10	2 (16.7) 3	0	<0.001

Abbreviation(s): Tregs: T regulatory cells, n: number of patients having an adverse event, N: number of patients at risk, E: number of events, AE: Adverse event

Note(s): Only % - (n/N)*100, where N is the number of patients in each group. * a box indicates a significant result. Note that only entries with n≥6 (5%) in the Total column are included in this table. In summarizing n(%), if a patient has multiple AEs for the same System Organ Class (SOC) or Preferred Term (PT), the patient is counted only once for the given SOC and PT, regardless of the actual number of occurred adverse events. All Events (E) are included in the Event totals. P-values are based on non-parametric Kruskal-Wallis test statistics per SOC and per PT. SOC and PT according to MedDRA dictionary Version 23.0.

Table S13. Adverse Events – Frequency Table by Treatment Group and Relationship to Study Drug (Safety Set).

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
Any AE	Related	8 (32.0) 10	32 (94.1) 227	12 (100) 57	20 (45.5) 135
	Not Related	5 (20.0) 18	30 (88.2) 173	8 (66.7) 19	32 (72.7) 180
	Unknown	3 (12.0) 3	4 (11.8) 10	0	2 (4.5) 5
Infections and infestations	Related	4 (16.0) 5	9 (26.5) 17	6 (50.0) 8	9 (20.5) 29
	Not Related	3 (12.0) 4	17 (50.0) 36	3 (25.0) 3	18 (40.9) 30
	Unknown	3 (12.0) 3	1 (2.9) 1	0	1 (2.3) 1
Respiratory tract infection	Related	1 (4.0) 1	1 (2.9) 1	1 (8.3) 1	0
	Not Related	3 (12.0) 3	0	2 (16.7) 2	4 (9.1) 4
	Unknown	0	0	0	0
Upper respiratory tract infection	Related	0	1 (2.9) 1	1 (8.3) 1	1 (2.3) 3
	Not Related	0	3 (8.8) 5	0	5 (11.4) 5
	Unknown	0	0	0	0
Viral infection	Related	0	2 (5.9) 2	0	3 (6.8) 4
	Not Related	0	4 (11.8) 4	0	2 (4.5) 2
	Unknown	0	0	0	0
Infection	Related	1 (4.0) 1	2 (5.9) 2	1 (8.3) 1	0
	Not Related	0	3 (8.8) 3	0	1 (2.3) 1
	Unknown	0	1 (2.9) 1	0	0
Nasopharyngitis	Related	0	3 (8.8) 3	0	3 (6.8) 7
	Not Related	0	2 (5.9) 3	0	1 (2.3) 1
	Unknown	0	0	0	0
Sinusitis	Related	0	1 (2.9) 1	0	2 (4.5) 4
	Not Related	0	2 (5.9) 2	0	0
	Unknown	1 (4.0) 1	0	0	0
Influenza	Related	0	0	1 (8.3) 1	0
	Not Related	0	2 (5.9) 2	0	1 (2.3) 1
	Unknown	1 (4.0) 1	0	0	0
Pharyngitis streptococcal	Related	0	1 (2.9) 1	0	0
	Not Related	0	3 (8.8) 4	0	1 (2.3) 1
	Unknown	0	0	0	0
Pneumonia	Related	0	1 (2.9) 1	0	1 (2.3) 1
	Not Related	0	0	0	2 (4.5) 2
	Unknown	0	0	0	0
Bacterial infection	Related	0	0	0	1 (2.3) 1
	Not Related	0	2 (5.9) 2	0	0
	Unknown	0	0	0	0
Urinary tract infection	Related	0	0	0	0
	Not Related	0	0	0	2 (4.5) 3
	Unknown	0	0	0	1 (2.3) 1
Gastroenteritis viral	Related	0	0	0	1 (2.3) 1
	Not Related	0	1 (2.9) 1	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Unknown	0	0	0	0
Respiratory tract infection bacterial	Related	1 (4.0) 1	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Rhinitis	Related	0	2 (5.9) 2	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Viral upper respiratory tract infection	Related	0	0	0	1 (2.3) 1
	Not Related	0	1 (2.9) 2	0	0
	Unknown	0	0	0	0
Acarodermatitis	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Appendicitis	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Atypical pneumonia	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Bronchitis	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Ear infection	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Ear infection bacterial	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Folliculitis	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Gastroenteritis	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Gastrointestinal infection	Related	0	0	0	0
	Not Related	0	0	0	0
	Unknown	1 (4.0) 1	0	0	0
H1N1 influenza	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Herpes zoster	Related	1 (4.0) 1	0	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Infectious mononucleosis	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Unknown	0	0	0	0
Keratitis bacterial	Related	0	0	0	0
	Not Related	1 (4.0) 1	0	0	0
	Unknown	0	0	0	0
Localised infection	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Lower respiratory tract infection	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Lyme disease	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Medical device site abscess	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Moraxella infection	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Mumps	Related	1 (4.0) 1	0	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Otitis media	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Pelvic inflammatory disease	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 2
	Unknown	0	0	0	0
Penile infection	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Pharyngitis	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Pharyngitis bacterial	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Respiratory tract infection viral	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Salmonellosis	Related	0	0	0	0
	Not Related	0	0	1 (8.3) 1	0
	Unknown	0	0	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
Sinusitis bacterial	Related	0	0	0	1 (2.3) 3
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Staphylococcal abscess	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Streptococcal infection	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Upper respiratory tract infection bacterial	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Varicella	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Viral pharyngitis	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Viral rash	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Gastrointestinal disorders	Related	0	20 (58.8) 45	4 (33.3) 12	3 (6.8) 7
	Not Related	1 (4.0) 5	15 (44.1) 28	1 (8.3) 2	6 (13.6) 21
	Unknown	0	1 (2.9) 1	0	1 (2.3) 1
Nausea	Related	0	16 (47.1) 21	3 (25.0) 4	0
	Not Related	0	6 (17.6) 6	0	3 (6.8) 4
	Unknown	0	0	0	0
Vomiting	Related	0	14 (41.2) 16	2 (16.7) 3	1 (2.3) 1
	Not Related	0	8 (23.5) 8	0	3 (6.8) 4
	Unknown	0	0	0	0
Abdominal pain	Related	0	2 (5.9) 2	4 (33.3) 5	0
	Not Related	1 (4.0) 2	1 (2.9) 1	1 (8.3) 1	2 (4.5) 3
	Unknown	0	0	0	0
Abdominal pain upper	Related	0	1 (2.9) 2	0	2 (4.5) 2
	Not Related	0	3 (8.8) 3	0	3 (6.8) 3
	Unknown	0	0	0	1 (2.3) 1
Diarrhoea	Related	0	2 (5.9) 3	0	1 (2.3) 2
	Not Related	1 (4.0) 1	4 (11.8) 5	1 (8.3) 1	1 (2.3) 2
	Unknown	0	0	0	0
Abdominal discomfort	Related	0	1 (2.9) 1	0	1 (2.3) 1
	Not Related	0	2 (5.9) 2	0	2 (4.5) 2
	Unknown	0	0	0	0
Coeliac disease	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
Constipation	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 2
	Unknown	0	0	0	0
Dyspepsia	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Food poisoning	Related	0	0	0	0
	Not Related	0	0	0	0
	Unknown	0	1 (2.9) 1	0	0
Gastrointestinal disorder	Related	0	0	0	0
	Not Related	1 (4.0) 1	0	0	0
	Unknown	0	0	0	0
Haematochezia	Related	0	0	0	0
	Not Related	1 (4.0) 1	0	0	0
	Unknown	0	0	0	0
Lip swelling	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Retching	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Tooth impacted	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
General disorders and administration site conditions	Related	2 (8.0) 2	16 (47.1) 21	4 (33.3) 5	7 (15.9) 12
	Not Related	0	7 (20.6) 9	0	7 (15.9) 7
	Unknown	0	1 (2.9) 1	0	0
Pyrexia	Related	0	9 (26.5) 10	0	5 (11.4) 8
	Not Related	0	3 (8.8) 3	0	4 (9.1) 4
	Unknown	0	1 (2.9) 1	0	0
Fatigue	Related	0	0	1 (8.3) 1	1 (2.3) 2
	Not Related	0	3 (8.8) 3	0	1 (2.3) 1
	Unknown	0	0	0	0
Chills	Related	0	2 (5.9) 2	1 (8.3) 1	1 (2.3) 1
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Malaise	Related	0	2 (5.9) 3	0	1 (2.3) 1
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Asthenia	Related	1 (4.0) 1	0	2 (16.7) 2	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Vessel puncture site haematoma	Related	1 (4.0) 1	0	1 (8.3) 1	0
	Not Related	0	0	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Unknown	0	0	0	0
Crying	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Impaired healing	Related	0	1 (2.9) 2	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Influenza like illness	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Infusion site extravasation	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Pain	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Peripheral swelling	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Suprapubic pain	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Thirst	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Related	0	12 (35.3) 26	2 (16.7) 4	4 (9.1) 12
	Not Related	0	11 (32.4) 20	1 (8.3) 1	5 (11.4) 9
	Unknown	0	1 (2.9) 2	0	1 (2.3) 1
Oropharyngeal pain	Related	0	3 (8.8) 5	2 (16.7) 2	3 (6.8) 5
	Not Related	0	6 (17.6) 6	0	2 (4.5) 2
	Unknown	0	0	0	0
Cough	Related	0	3 (8.8) 4	0	2 (4.5) 2
	Not Related	0	6 (17.6) 7	0	1 (2.3) 1
	Unknown	0	1 (2.9) 1	0	0
Rhinorrhoea	Related	0	1 (2.9) 1	0	1 (2.3) 1
	Not Related	0	3 (8.8) 4	0	2 (4.5) 2
	Unknown	0	1 (2.9) 1	0	0
Nasal congestion	Related	0	2 (5.9) 2	0	1 (2.3) 1
	Not Related	0	2 (5.9) 2	0	1 (2.3) 1
	Unknown	0	0	0	0
Laryngeal oedema	Related	0	4 (11.8) 5	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Dyspnoea	Related	0	2 (5.9) 2	1 (8.3) 1	1 (2.3) 1
	Not Related	0	0	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Unknown	0	0	0	0
Productive cough	Related	0	0	0	1 (2.3) 1
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Rhinitis allergic	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	1 (8.3) 1	0
	Unknown	0	0	0	0
Asthma	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Bronchospasm	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Dry throat	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Epistaxis	Related	0	0	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	1 (2.3) 1
Paranasal sinus discomfort	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Respiratory disorder	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Sinus congestion	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Sneezing	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Throat irritation	Related	0	1 (2.9) 3	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Nervous system disorders	Related	1 (4.0) 1	8 (23.5) 13	2 (16.7) 5	7 (15.9) 16
	Not Related	0	8 (23.5) 8	0	10 (22.7) 16
	Unknown	0	0	0	0
Headache	Related	1 (4.0) 1	5 (14.7) 6	2 (16.7) 3	5 (11.4) 11
	Not Related	0	5 (14.7) 5	0	6 (13.6) 9
	Unknown	0	0	0	0
Dizziness	Related	0	2 (5.9) 2	1 (8.3) 1	0
	Not Related	0	1 (2.9) 1	0	1 (2.3) 1
	Unknown	0	0	0	0
Hypoglycaemic seizure	Related	0	0	0	1 (2.3) 2
	Not Related	0	0	0	2 (4.5) 2
	Unknown	0	0	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
Migraine	Related	0	0	0	0
	Not Related	0	2 (5.9) 2	0	1 (2.3) 1
	Unknown	0	0	0	0
Lethargy	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Presyncope	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Hypoaesthesia	Related	0	1 (2.9) 2	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Hypoglycaemic unconsciousness	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Migraine with aura	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Paraesthesia	Related	0	1 (2.9) 2	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Somnolence	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Syncope	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Investigations	Related	0	9 (26.5) 23	1 (8.3) 1	8 (18.2) 27
	Not Related	1 (4.0) 1	5 (14.7) 14	1 (8.3) 1	7 (15.9) 25
	Unknown	0	2 (5.9) 3	0	0
Neutrophil count abnormal	Related	0	4 (11.8) 4	0	4 (9.1) 8
	Not Related	0	2 (5.9) 2	0	1 (2.3) 1
	Unknown	0	1 (2.9) 1	0	0
White blood cell count abnormal	Related	0	4 (11.8) 6	0	2 (4.5) 2
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	1 (2.9) 1	0	0
Lymphocyte count decreased	Related	0	3 (8.8) 3	0	2 (4.5) 2
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Neutrophil count decreased	Related	0	3 (8.8) 6	0	2 (4.5) 2
	Not Related	0	0	0	0
	Unknown	0	1 (2.9) 1	0	0
Protein urine present	Related	0	0	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Not Related	0	0	0	4 (9.1) 5
	Unknown	0	0	0	0
Blood glucose increased	Related	0	1 (2.9) 1	0	0
	Not Related	0	1 (2.9) 1	0	1 (2.3) 1
	Unknown	0	0	0	0
Blood urine present	Related	0	0	0	0
	Not Related	0	0	0	3 (6.8) 3
	Unknown	0	0	0	0
White blood cells urine positive	Related	0	0	0	0
	Not Related	0	0	0	3 (6.8) 4
	Unknown	0	0	0	0
Eosinophil count increased	Related	0	0	0	2 (4.5) 3
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Lymphocyte count abnormal	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Mean cell volume decreased	Related	0	0	0	1 (2.3) 2
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Monocyte count increased	Related	0	0	0	2 (4.5) 4
	Not Related	0	0	0	0
	Unknown	0	0	0	0
White blood cell count decreased	Related	0	2 (5.9) 2	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Alanine aminotransferase increased	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Anti-thyroid antibody positive	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Aspartate aminotransferase increased	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Blood creatinine abnormal	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 2
	Unknown	0	0	0	0
Blood glucose decreased	Related	0	0	0	1 (2.3) 2
	Not Related	0	0	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Unknown	0	0	0	0
Blood glucose fluctuation	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Blood immunoglobulin A increased	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Blood pressure increased	Related	0	0	0	0
	Not Related	0	0	1 (8.3) 1	0
	Unknown	0	0	0	0
Blood sodium decreased	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Haematocrit abnormal	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Haematocrit decreased	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Haemoglobin abnormal	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Haemoglobin decreased	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Inflammatory marker increased	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Monocyte count abnormal	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Neutrophil count increased	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Platelet count increased	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Red blood cell count abnormal	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Red blood cell count increased	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
Red cell distribution width decreased	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Urine ketone body present	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Weight decreased	Related	0	0	0	0
	Not Related	1 (4.0) 1	0	0	0
	Unknown	0	0	0	0
White blood cell count increased	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Injury, poisoning and procedural complications	Related	0	1 (2.9) 1	1 (8.3) 1	2 (4.5) 2
	Not Related	0	15 (44.1) 27	0	11 (25.0) 16
	Unknown	0	1 (2.9) 1	0	0
Hand fracture	Related	0	0	0	0
	Not Related	0	4 (11.8) 4	0	1 (2.3) 1
	Unknown	0	0	0	0
Limb injury	Related	0	0	0	0
	Not Related	0	2 (5.9) 2	0	2 (4.5) 2
	Unknown	0	0	0	0
Arthropod bite	Related	0	1 (2.9) 1	0	0
	Not Related	0	1 (2.9) 1	0	1 (2.3) 1
	Unknown	0	0	0	0
Skin abrasion	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	2 (4.5) 2
	Unknown	0	0	0	0
Skin laceration	Related	0	0	0	0
	Not Related	0	2 (5.9) 2	0	1 (2.3) 1
	Unknown	0	0	0	0
Clavicle fracture	Related	0	0	0	0
	Not Related	0	2 (5.9) 4	0	0
	Unknown	0	0	0	0
Concussion	Related	0	0	0	0
	Not Related	0	2 (5.9) 2	0	0
	Unknown	0	0	0	0
Fall	Related	0	0	0	0
	Not Related	0	2 (5.9) 2	0	0
	Unknown	0	0	0	0
Joint injury	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Upper limb fracture	Related	0	0	0	0
	Not Related	0	1 (2.9) 2	0	1 (2.3) 1

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Unknown	0	0	0	0
Wound	Related	0	0	0	0
	Not Related	0	0	0	2 (4.5) 2
	Unknown	0	0	0	0
Alcohol poisoning	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Animal bite	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Back injury	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Fibula fracture	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Frostbite	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Incorrect dose administered	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Infusion related reaction	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Jaw fracture	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Joint dislocation	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Ligament injury	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Ligament sprain	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Muscle injury	Related	0	0	0	0
	Not Related	0	0	0	0
	Unknown	0	1 (2.9) 1	0	0
Muscle strain	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Road traffic accident	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Unknown	0	0	0	0
Wrist fracture	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Skin and subcutaneous tissue disorders	Related	0	17 (50.0) 31	2 (16.7) 5	2 (4.5) 3
	Not Related	0	6 (17.6) 7	0	4 (9.1) 7
	Unknown	0	0	0	0
Rash	Related	0	14 (41.2) 16	1 (8.3) 1	2 (4.5) 3
	Not Related	0	2 (5.9) 2	0	2 (4.5) 2
	Unknown	0	0	0	0
Pruritus	Related	0	9 (26.5) 11	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Urticaria	Related	0	2 (5.9) 2	0	0
	Not Related	0	1 (2.9) 1	0	1 (2.3) 2
	Unknown	0	0	0	0
Rash pruritic	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Acne	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Blood blister	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Diffuse alopecia	Related	0	0	1 (8.3) 2	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Erythema	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Hyperhidrosis	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Mechanical urticaria	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 2
	Unknown	0	0	0	0
Skin discolouration	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Skin hyperpigmentation	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Skin lesion	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Unknown	0	0	0	0
Metabolism and nutrition disorders	Related	1 (4.0) 1	1 (2.9) 1	3 (25.0) 5	3 (6.8) 5
	Not Related	1 (4.0) 2	0	3 (25.0) 3	13 (29.5) 20
	Unknown	0	0	0	0
Hypoglycaemia	Related	1 (4.0) 1	0	1 (8.3) 2	2 (4.5) 2
	Not Related	0	0	0	5 (11.4) 5
	Unknown	0	0	0	0
Iron deficiency	Related	0	0	0	0
	Not Related	0	0	1 (8.3) 1	4 (9.1) 6
	Unknown	0	0	0	0
Diabetes mellitus inadequate control	Related	0	0	0	0
	Not Related	1 (4.0) 1	0	1 (8.3) 1	2 (4.5) 2
	Unknown	0	0	0	0
Hyperglycaemia	Related	0	0	2 (16.7) 2	0
	Not Related	0	0	0	2 (4.5) 2
	Unknown	0	0	0	0
Decreased appetite	Related	0	1 (2.9) 1	0	1 (2.3) 1
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Diabetic ketoacidosis	Related	0	0	0	1 (2.3) 2
	Not Related	0	0	0	2 (4.5) 4
	Unknown	0	0	0	0
Hyperinsulinism	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Ketoacidosis	Related	0	0	0	0
	Not Related	1 (4.0) 1	0	0	0
	Unknown	0	0	0	0
Vitamin D deficiency	Related	0	0	0	0
	Not Related	0	0	1 (8.3) 1	0
	Unknown	0	0	0	0
Blood and lymphatic system disorders	Related	0	6 (17.6) 11	3 (25.0) 3	2 (4.5) 3
	Not Related	0	2 (5.9) 2	1 (8.3) 1	4 (9.1) 4
	Unknown	0	0	0	0
Neutropenia	Related	0	4 (11.8) 5	2 (16.7) 2	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Eosinophilia	Related	0	0	0	0
	Not Related	0	0	1 (8.3) 1	2 (4.5) 2
	Unknown	0	0	0	0
Leukopenia	Related	0	2 (5.9) 2	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Blood disorder	Related	0	1 (2.9) 1	0	1 (2.3) 1

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Lymphadenopathy	Related	0	0	0	0
	Not Related	0	2 (5.9) 2	0	0
	Unknown	0	0	0	0
White blood cell disorder	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Iron deficiency anaemia	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Lymphopenia	Related	0	1 (2.9) 2	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Thrombocytopenia	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Vascular disorders	Related	0	13 (38.2) 20	1 (8.3) 1	4 (9.1) 8
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Hypotension	Related	0	10 (29.4) 13	0	4 (9.1) 8
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Hypertension	Related	0	4 (11.8) 4	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Diastolic hypotension	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Flushing	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Pallor	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Venous thrombosis limb	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Surgical and medical procedures	Related	1 (4.0) 1	1 (2.9) 1	1 (8.3) 1	1 (2.3) 1
	Not Related	1 (4.0) 1	6 (17.6) 6	0	5 (11.4) 6
	Unknown	0	0	0	0
Wisdom teeth removal	Related	0	0	0	0
	Not Related	0	4 (11.8) 4	0	0
	Unknown	0	0	0	0
Antibiotic therapy	Related	0	0	1 (8.3) 1	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Not Related	1 (4.0) 1	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Central venous catheterisation	Related	0	1 (2.9) 1	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Symptomatic treatment	Related	0	0	0	0
	Not Related	0	0	0	2 (4.5) 2
	Unknown	0	0	0	0
Adenotonsillectomy	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Appendicectomy	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Drug therapy	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Labial frenectomy	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Therapy cessation	Related	1 (4.0) 1	0	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Tonsillectomy	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Cardiac disorders	Related	0	10 (29.4) 14	2 (16.7) 3	1 (2.3) 2
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Tachycardia	Related	0	9 (26.5) 10	2 (16.7) 3	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Bradycardia	Related	0	1 (2.9) 3	0	1 (2.3) 2
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Arrhythmia	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Musculoskeletal and connective tissue disorders	Related	0	0	1 (8.3) 1	2 (4.5) 3
	Not Related	0	3 (8.8) 3	0	3 (6.8) 3
	Unknown	0	1 (2.9) 1	0	0
Myalgia	Related	0	0	0	1 (2.3) 1
	Not Related	0	1 (2.9) 1	0	1 (2.3) 1
	Unknown	0	1 (2.9) 1	0	0
Arthralgia	Related	0	0	0	1 (2.3) 1

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Pain in extremity	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	1 (2.3) 1
	Unknown	0	0	0	0
Muscle spasms	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Muscle twitching	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Musculoskeletal pain	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Psychiatric disorders	Related	0	1 (2.9) 1	0	1 (2.3) 1
	Not Related	1 (4.0) 4	1 (2.9) 1	2 (16.7) 7	3 (6.8) 7
	Unknown	0	0	0	0
Adjustment disorder	Related	0	0	0	0
	Not Related	1 (4.0) 2	0	2 (16.7) 2	1 (2.3) 1
	Unknown	0	0	0	0
Emotional disorder	Related	0	0	0	0
	Not Related	1 (4.0) 1	0	1 (8.3) 1	2 (4.5) 3
	Unknown	0	0	0	0
Depression	Related	0	0	0	0
	Not Related	1 (4.0) 1	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Behaviour disorder	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 2
	Unknown	0	0	0	0
Confusional state	Related	0	0	0	1 (2.3) 1
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Eating disorder	Related	0	0	0	0
	Not Related	0	0	1 (8.3) 1	0
	Unknown	0	0	0	0
Enuresis	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Intentional self-injury	Related	0	0	0	0
	Not Related	0	0	1 (8.3) 2	0
	Unknown	0	0	0	0
Mental disorder	Related	0	0	0	0
	Not Related	0	0	1 (8.3) 1	0
	Unknown	0	0	0	0
Restlessness	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Unknown	0	0	0	0
Eye disorders	Related	0	0	0	0
	Not Related	1 (4.0) 1	2 (5.9) 6	0	2 (4.5) 2
	Unknown	0	0	0	1 (2.3) 2
Ocular hyperaemia	Related	0	0	0	0
	Not Related	0	2 (5.9) 2	0	2 (4.5) 2
	Unknown	0	0	0	0
Conjunctivitis allergic	Related	0	0	0	0
	Not Related	1 (4.0) 1	0	0	0
	Unknown	0	0	0	0
Corneal oedema	Related	0	0	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	1 (2.3) 1
Dry eye	Related	0	0	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	1 (2.3) 1
Erythema of eyelid	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Eye discharge	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Eye pruritus	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Eye swelling	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Immune system disorders	Related	0	1 (2.9) 1	0	1 (2.3) 4
	Not Related	0	1 (2.9) 1	0	2 (4.5) 2
	Unknown	0	0	0	0
Hypersensitivity	Related	0	0	0	1 (2.3) 1
	Not Related	0	1 (2.9) 1	0	1 (2.3) 1
	Unknown	0	0	0	0
Anaphylactic reaction	Related	0	1 (2.9) 1	0	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Milk allergy	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Seasonal allergy	Related	0	0	0	1 (2.3) 3
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Related	0	1 (2.9) 1	0	0
	Not Related	0	2 (5.9) 2	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Unknown	0	0	0	0
Skin papilloma	Related	0	1 (2.9) 1	0	0
	Not Related	0	2 (5.9) 2	0	0
	Unknown	0	0	0	0
Endocrine disorders	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	1 (2.3) 1
	Unknown	0	0	0	0
Endocrine disorder	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	1 (2.3) 1
	Unknown	0	0	0	0
Product issues	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Device breakage	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Device malfunction	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Renal and urinary disorders	Related	0	0	0	0
	Not Related	0	0	0	2 (4.5) 2
	Unknown	0	0	0	0
Albuminuria	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Ketonuria	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Social circumstances	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	1 (8.3) 1	0
	Unknown	0	0	0	0
Death of relative	Related	0	0	1 (8.3) 1	0
	Not Related	0	0	0	0
	Unknown	0	0	0	0
Patient uncooperative	Related	0	0	0	0
	Not Related	0	0	1 (8.3) 1	0
	Unknown	0	0	0	0
Ear and labyrinth disorders	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Ear disorder	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Pregnancy, puerperium and perinatal conditions	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0

System Organ Class Preferred Term	Relationship	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E
	Unknown	0	0	0	0
Pregnancy	Related	0	0	0	0
	Not Related	0	1 (2.9) 1	0	0
	Unknown	0	0	0	0
Reproductive system and breast disorders	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0
Ovarian cyst	Related	0	0	0	0
	Not Related	0	0	0	1 (2.3) 1
	Unknown	0	0	0	0

Abbreviation(s): n – Number of patients having an adverse event, N – Number of patients at risk, E – Number of events, AE – Adverse event.
Note(s): % - (n/N)*100, where N is the number of patients in each group.
Related AE: possibly related or probably related or definitely related or related AE; Not Related AE: impossible or definitely unrelated or unlikely or unrelated AE.; Unknown AE: missing or unknown.
System Organ Class and Preferred Term according to MedDRA dictionary Version 23.0.

Table S14. Serious Adverse Events - Frequency Table by Treatment Group (Safety Set).

System Organ Class Preferred Term	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+rituximab (N=12) n (%) E	Control (N=44) n (%) E
Any SAE	0	6 (17.6) 8	0	3 (6.8) 13
Blood and lymphatic system disorders	0	2 (5.9) 2	0	0
Neutropenia	0	2 (5.9) 2	0	0
Infections and infestations	0	1 (2.9) 1	0	1 (2.3) 3
Infection	0	1 (2.9) 1	0	0
Pneumonia	0	0	0	1 (2.3) 2
Sinusitis	0	1 (2.9) 1	0	0
Upper respiratory tract infection	0	0	0	1 (2.3) 1
Investigations	0	1 (2.9) 1	0	1 (2.3) 2
Neutrophil count decreased	0	1 (2.9) 1	0	1 (2.3) 1
Neutrophil count abnormal	0	0	0	1 (2.3) 1
Metabolism and nutrition disorders	0	0	0	2 (4.5) 5
Diabetic ketoacidosis	0	0	0	2 (4.5) 5
Immune system disorders	0	1 (2.9) 1	0	0
Anaphylactic reaction	0	1 (2.9) 1	0	0
Injury, poisoning and procedural complications	0	1 (2.9) 1	0	0
Hand fracture	0	1 (2.9) 1	0	0
Nervous system disorders	0	1 (2.9) 1	0	0
Headache	0	1 (2.9) 1	0	0
Product issues	0	0	0	1 (2.3) 1
Device malfunction	0	0	0	1 (2.3) 1
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (2.3) 1
Oropharyngeal pain	0	0	0	1 (2.3) 1
Surgical and medical procedures	0	0	0	1 (2.3) 1
Tonsillectomy	0	0	0	1 (2.3) 1

Abbreviation(s): n – Number of patients having an adverse event, N – Number of patients at risk, E – Number of events, SAE - Serious Adverse Event. Note(s): % - (n/N)*100, where N is the number of patients in each group. In summarizing n(%), if a patient has multiple AEs for the same SOC or PT, the patient is counted only once for the given System Organ Class and Preferred Term, regardless of the actual number of occurred adverse events. All Events (E) are included in the Event totals. System Organ Class and Preferred Term according to MedDRA dictionary Version 23.0.

Table S15. Adverse Events of Special Importance - Frequency Table by Treatment Group (Safety Set).

Preferred Term	Tregs (N=25) n (%) E	Rituximab (N=34) n (%) E	Tregs+ rituximab (N=12) n (%) E	Control (N=44) n (%) E	P value*
All AESIs	11 (44) 15	33 (97.1) 185	9 (75.0) 33	26 (56.8) 122	<0.001
Infections and infestations	9 (36) 12	20 (58.8) 54	7 (58.3) 11	21 (48) 60	0.333
Respiratory tract infection	4 (16) 4	1 (2.9) 1	3 (25) 3	4 (9.1) 4	0.131
Viral infection	0	6 (18) 6	0	5 (11) 6	0.086
Upper respiratory tract infection	0	3 (8.8) 6	1 (8.3) 1	6 (14) 8	0.295
Infection	1 (4.0) 1	6 (18) 6	1 (8.3) 1	1 (2.3) 1	0.076
Nasopharyngitis	0	4 (12) 6	0	4 (9.1) 8	0.235
Influenza	1 (4.0) 1	2 (5.9) 2	1 (8.3) 1	1 (2.3) 1	0.776
Sinusitis	1 (4.0) 1	2 (5.9) 3	0	2 (4.5) 4	0.863
Pharyngitis streptococcal	0	3 (8.8) 5	0	1 (2.3) 1	0.223
Bacterial infection	0	2 (5.9) 2	0	1 (2.3) 1	0.489
Pneumonia	0	1 (2.9) 1	0	2 (4.5) 3	0.650
Gastroenteritis viral	0	1 (2.9) 1	0	1 (2.3) 1	0.800
Respiratory tract infection bacterial	1 (4.0) 1	0	0	1 (2.3) 1	0.655
Rhinitis	0	2 (5.9) 2	0	0	0.186
Urinary tract infection	0	0	0	2 (4.5) 4	0.354
Viral upper respiratory tract infection	0	1 (2.9) 2	0	1 (2.3) 1	0.800
Acarodermatitis	0	1 (2.9) 1	0	0	0.497
Appendicitis	0	0	0	1 (2.3) 1	0.656
Atypical pneumonia	0	0	0	1 (2.3) 1	0.656
Bronchitis	0	0	0	1 (2.3) 1	0.656
Ear infection	0	0	0	1 (2.3) 1	0.656
Ear infection bacterial	0	1 (2.9) 1	0	0	0.497
Folliculitis	0	1 (2.9) 1	0	0	0.497
Gastroenteritis	0	0	0	1 (2.3) 1	0.656
Gastrointestinal infection	1 (4.0) 1	0	0	0	0.308
H1N1 influenza	0	1 (2.9) 1	0	0	0.497
Herpes zoster	1 (4.0) 1	0	0	0	0.308
Infectious mononucleosis	0	0	0	1 (2.3) 1	0.656
Keratitis bacterial	1 (4.0) 1	0	0	0	0.308
Localised infection	0	1 (2.9) 1	0	0	0.497
Lower respiratory tract infection	0	1 (2.9) 1	0	0	0.497
Lyme disease	0	0	0	1 (2.3) 1	0.656
Medical device site abscess	0	1 (2.9) 1	0	0	0.497

Moraxella infection	0	0	1 (8.3) 1	0	0.035
Mumps	1 (4.0) 1	0	0	0	0.308
Otitis media	0	1 (2.9) 1	0	0	0.497
Pelvic inflammatory disease	0	0	0	1 (2.3) 2	0.656
Penile infection	0	1 (2.9) 1	0	0	0.497
Pharyngitis	0	0	1 (8.3) 1	0	0.035
Pharyngitis bacterial	0	0	0	1 (2.3) 1	0.656
Respiratory tract infection viral	0	0	1 (8.3) 1	0	0.035
Salmonellosis	0	0	1 (8.3) 1	0	0.035
Sinusitis bacterial	0	0	0	1 (2.3) 3	0.656
Staphylococcal abscess	0	0	0	1 (2.3) 1	0.656
Streptococcal infection	0	0	0	1 (2.3) 1	0.656
Upper respiratory tract infection bacterial	0	1 (2.9) 1	0	0	0.497
Varicella	0	1 (2.9) 1	0	0	0.497
Viral pharyngitis	0	0	0	1 (2.3) 1	0.656
Viral rash	0	0	1 (8.3) 1	0	0.035
Gastrointestinal disorders	0	22 (64.7) 51	3 (25.0) 7	5 (11.4) 9	<0.001
Nausea	0	18 (53) 27	3 (25.0) 4	3 (6.8) 4	<0.001
Vomiting	0	16 (47.1) 24	2 (16.7) 3	4 (9.1) 5	<0.001
General disorders and administration site conditions	2 (8.0) 2	14 (41.2) 16	3 (25.0) 4	8 (18.2) 14	0.020
Pyrexia	0	12 (35.3) 14	0	7 (15.9) 12	0.001
Chills	0	2 (5.9) 2	1 (8.3) 1	2 (4.5) 2	0.620
Asthenia	1 (4.0) 1	0	2 (16.7) 2	0	0.009
Vessel puncture site haematoma	1 (4.0) 1	0	1 (8.3) 1	0	0.162
Skin and subcutaneous tissue disorders	0	19 (55.9) 34	2 (16.7) 3	6 (13.6) 8	<0.001
Rash	0	16 (47.1) 18	1 (8.3) 1	4 (9.1) 5	<0.001
Pruritus	0	9 (26.5) 11	0	0	<0.001
Urticaria	0	3 (8.8) 3	0	1 (2.3) 2	0.223
Rash pruritic	0	1 (2.9) 1	0	1 (2.3) 1	0.800
Diffuse alopecia	0	0	1 (8.3) 2	0	0.035
Erythema	0	1 (2.9) 1	0	0	0.497
Nervous system disorders	1 (4.0) 1	8 (23.5) 12	2 (16.7) 4	11 (25.0) 22	0.164
Headache	1 (4.0) 1	7 (20.6) 11	2 (16.7) 3	9 (20.5) 20	0.294
Presyncope	0	0	0	2 (4.5) 2	0.354
Somnolence	0	0	1 (8.3) 1	0	0.035
Syncope	0	1 (2.9) 1	0	0	0.497

Respiratory, thoracic and mediastinal disorders	0	7 (20.6) 9	1 (8.3) 1	4 (9.1) 4	0.080
Rhinorrhoea	0	5 (14.7) 6	0	3 (6.8) 3	0.118
Dyspnoea	0	2 (5.9) 2	1 (8.3) 1	1 (2.3) 1	0.476
Bronchospasm	0	1 (2.9) 1	0	0	0.497
Blood and lymphatic system disorders	0	5 (14.7) 7	2 (16.7) 2	2 (4.5) 3	0.100
Neutropenia	0	4 (11.8) 5	2 (16.7) 2	1 (2.3) 1	0.074
Leukopenia	0	2 (5.9) 2	0	1 (2.3) 1	0.489
Thrombocytopenia	0	0	0	1 (2.3) 1	0.656
Immune system disorders	0	2 (5.9) 2	0	2 (4.5) 2	0.562
Hypersensitivity	0	1 (2.9) 1	0	2 (4.5) 2	0.650
Anaphylactic reaction	0	1 (2.9) 1	0	0	0.497
Injury, poisoning and procedural complications	0	0	1 (8.3) 1	0	0.035
Infusion related reaction	0	0	1 (8.3) 1	0	0.035

Abbreviation(s): n: number of patients having an adverse event, N – Number of patients at risk, E – Number of events, AESI – Adverse event of special importance.

Note(s): * a box indicates a significant result. % - (n/N)*100, where N is the number of patients in each group. In summarizing n(%), if a patient has multiple AEs for the same SOC or PT, the patient is counted only once for the given System Organ Class and Preferred Term, regardless of the actual number of occurred adverse events. All Events (E) are included in the Event totals. P-values are based on non-parametric Kruskal-Wallis test statistics per System Organ Class and per Preferred Term. Total group was not included in statistical testing. System Organ Class and Preferred Term according to MedDRA dictionary Version 23.0.

Table S16. Glucose (All Visits) – RMANCOVA (ITT Set).

		Geometric Means			
Visit	**Comparison**	**Test**	**Reference**	**Treatment Ratio**	**90% Confidence Interval***
Month 3	Tregs+rituximab vs Control	109.601	121.644	0.901	0.774 - 1.049
	Tregs vs Control	106.843	121.644	0.878	0.765 - 1.009
	Rituximab vs Control	122.585	121.644	1.008	0.902 - 1.126
	Tregs vs Tregs+rituximab	106.843	109.601	0.975	0.819 - 1.161
	Rituximab vs Tregs+rituximab	122.585	109.601	1.118	0.960 - 1.303
	Tregs vs Rituximab	106.843	122.585	0.872	0.757 - 1.003
Month 6	Tregs+rituximab vs Control	108.948	141.201	0.772	0.542 - 1.099
	Tregs vs Control	84.717	141.201	0.600	0.447 - 0.805
	Rituximab vs Control	125.092	141.201	0.886	0.682 - 1.151
	Tregs vs Tregs+rituximab	84.717	108.948	0.778	0.530 - 1.140
	Rituximab vs Tregs+rituximab	125.092	108.948	1.148	0.802 - 1.643
	Tregs vs Rituximab	84.717	125.092	0.677	0.502 - 0.914
Month 9	Tregs+rituximab vs Control	110.865	123.159	0.900	0.747 - 1.085
	Tregs vs Control	122.200	123.159	0.992	0.846 - 1.163
	Tregs vs Tregs+rituximab	122.200	110.865	1.102	0.923 - 1.317
Month 12	Tregs+rituximab vs Control	111.435	121.809	0.915	0.771 - 1.085
	Tregs vs Control	118.397	121.809	0.972	0.852 - 1.108
	Rituximab vs Control	137.895	121.809	1.132	1.002 - 1.279
	Tregs vs Tregs+rituximab	118.397	111.435	1.062	0.882 - 1.280
	Rituximab vs Tregs+rituximab	137.895	111.435	1.237	1.040 - 1.473
	Tregs vs Rituximab	118.397	137.895	0.859	0.744 - 0.991
Month 18	Tregs+rituximab vs Control	117.469	120.674	0.973	0.839 - 1.130
	Tregs vs Control	124.078	120.674	1.028	0.884 - 1.196
	Tregs vs Tregs+rituximab	124.078	117.469	1.056	0.919 - 1.213
Month 24	Tregs+rituximab vs Control	119.504	139.997	0.854	0.724 - 1.007
	Tregs vs Control	121.145	139.997	0.865	0.722 - 1.037
	Rituximab vs Control	151.083	139.997	1.079	0.954 - 1.221
	Tregs vs Tregs+rituximab	121.145	119.504	1.014	0.820 - 1.253
	Rituximab vs Tregs+rituximab	151.083	119.504	1.264	1.071 - 1.492
	Tregs vs Rituximab	121.145	151.083	0.802	0.669 - 0.961

Note(s): * a box indicates a significant result. Results for a repeated measurement mixed model RMANCOVA for logarithmized glucose values, with log baseline value (last value prior to first treatment, Day 0) as continuous covariate, gender, age group (either <=12 years or > 12 years), treatment, visit and treatment*visit interaction as fixed categorical effects for the within subject repeated measurements during follow up visits will be performed, , i.e. visits 3m, 6m, 9m, 12m, 18m and 24m will be incl uded in this analysis.

Table S17. Insulin Independent Patients (DDI = 0 U/kg/day) – Contingency Table (ITT Set).

Visit	Comparison	Proportion of insulin independent patients Test [%]	Proportion of insulin independent patients Reference [%]	P-value*
Month 3	Tregs+rituximab vs Control	25.0	3.0	0.0538
	Tregs vs Control	8.3	3.0	0.5300
	Rituximab vs Control	3.0	3.0	1.0000
	Tregs vs Tregs+rituximab	8.3	25.0	0.2083
	Rituximab vs Tregs+rituximab	3.0	25.0	0.0538
	Tregs vs Rituximab	8.3	3.0	0.5300
Month 6	Tregs+rituximab vs Control	25.0	0.0	0.0113
	Tregs vs Control	12.5	0.0	0.0701
	Rituximab vs Control	3.2	0.0	0.6351
	Tregs vs Tregs+rituximab	12.5	25.0	0.7392
	Rituximab vs Tregs+rituximab	3.2	25.0	0.0589
	Tregs vs Rituximab	12.5	3.2	0.2921
Month 9	Tregs+rituximab vs Control	16.7	3.2	0.1914
	Tregs vs Control	8.7	3.2	0.5760
	Rituximab vs Control	3.2	3.2	1.0000
	Tregs vs Tregs+rituximab	8.7	16.7	0.7259
	Rituximab vs Tregs+rituximab	3.2	16.7	0.1914
	Tregs vs Rituximab	8.7	3.2	0.5760
Month 12	Tregs+rituximab vs Control	9.1	2.3	0.3284
	Tregs vs Control	9.1	2.3	0.2718
	Rituximab vs Control	6.3	2.3	0.4609
	Tregs vs Tregs+rituximab	9.1	9.1	1.0000
	Rituximab vs Tregs+rituximab	6.3	9.1	1.0000
	Tregs vs Rituximab	9.1	6.3	0.7733
Month 18	Tregs+rituximab vs Control	8.3	3.2	0.6719
	Tregs vs Control	0.0	3.2	1.0000
	Rituximab vs Control	3.2	3.2	1.0000
	Tregs vs Tregs+rituximab	0.0	8.3	0.5432
	Rituximab vs Tregs+rituximab	3.2	8.3	0.6719
	Tregs vs Rituximab	0.0	3.2	1.0000
Month 24	Tregs+rituximab vs Control	0.0	3.1	0.5238
	Tregs vs Control	0.0	3.1	0.5119
	Rituximab vs Control	0.0	3.1	0.7262
	Tregs vs Tregs+rituximab	0.0	0.0	1.0000
	Rituximab vs Tregs+rituximab	0.0	0.0	1.0000
	Tregs vs Rituximab	0.0	0.0	1.0000

Note(s): P-value is calculated in a permutation exact test with significance level alpha 0.05. * a box indicates a significant result. Visits 3m, 6m, 9m, 12m, 18m and 24m are included in the analysis.
Each time point was assessed independently. Hence patients can be observed as insulin independent at a later timepoint even whe n they had a loss of insulin independence
in the Kaplan Meier analysis before due to the fact that their glucose levels had been regulated in between.

Table S18. Autoantibodies – Descriptive Statistics (Safety Set).

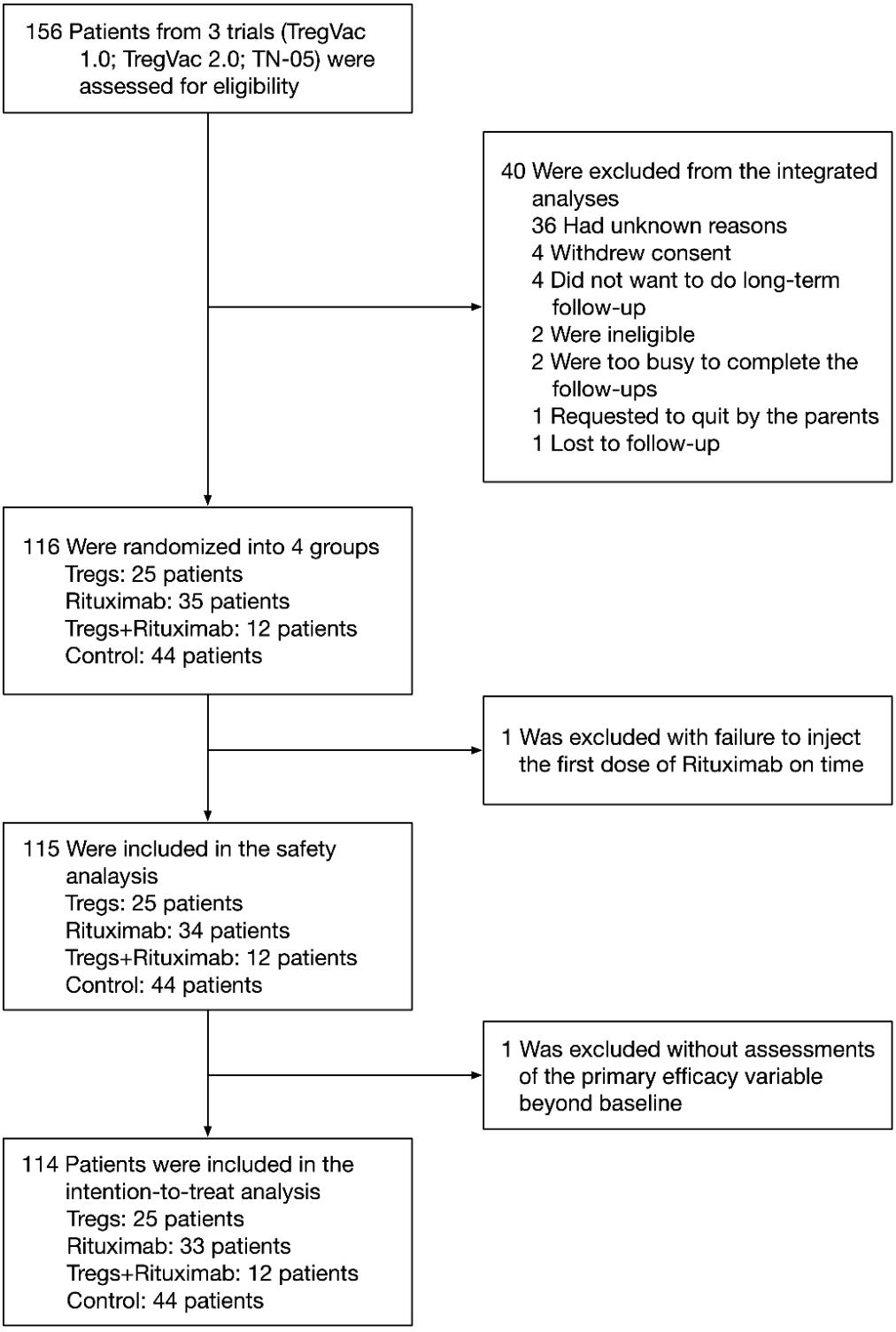
Study Day	Tregs (N=25)	Rituximab (N=34)	Tregs+ rituximab (N=12)	Control (N=44)
Glutamic Acid Decarboxylase Antibody (IU/mL)				
Baseline	(24) 642±850	(26) 0.182±0.28	(12) 381±594	(38) 442±724
Day 14	(13) 804±938	0	(11) 407±641	(9) 900±893
Month 3	(12) 725±944	(27) 0.104±0.153	(11) 215±268	(29) 293±643
Month 6	(13) 676±922	(29) 0.110±0.149	(12) 325±563	(33) 230±581
Month 12	(12) 649±880	(28) 0.078±0.121	(11) 340±590	(33) 232±594
Month 18	(12) 677±927	(31) 0.079±0.149	(12) 179±370	(30) 162±507
Month 24	(10) 629±947	(30) 0.062±0.122	(12) 255±563	(33) 201±559
Islet Cell Antibody (titer)				
Baseline	(25) 80.80±145	(23) 86.5±108	(12) 125±185	(34) 70.6±94.32
Day 14	(13) 66.90±95.86	0	(11) 70.0±97.47	(9) 182±264
Month 3	(12) 45.00±61.57	(31) 51.0±74.63	(11) 56.4±92.44	(32) 114±238
Month 6	(13) 44.60±58.97	(30) 59.0±134	(12) 71.7±120	(34) 73.5±129
Month 12	(12) 100±193	(30) 48.3±77.29	(11) 35.5±51.65	(33) 132±238
Month 18	(12) 20.00±26.97	(30) 37.3±56.50	(12) 45.0±59.16	(31) 98.7±142
Month 24	(10) 38.40±57.42	(31) 42.6±75.67	(12) 70.0±99.64	(33) 69.1±87.76
Insulin Autoantibody (IU/mL)				
Baseline	(24) 7.67±8.10	(26) 0.61±1.03	(12) 5.32±5.52	(35) 2.67±4.12
Day 14	(13) 5.03±6.01	0	(11) 3.81±4.53	(9) 4.30±4.96
Month 3	(12) 5.47±11.70	(27) 0.22±0.34	(11) 1.40±1.82	(29) 1.38±2.08
Month 6	(13) 1.96±2.03	(29) 0.12±0.31	(12) 2.40±3.28	(33) 1.06±1.28
Month 12	(11) 1.63±2.85	(28) 0.36±0.63	(11) 1.01±0.86	(33) 0.69±0.52
Month 18	(12) 1.43±1.744	(31) 0.50±0.55	(12) 3.70±6.78	(30) 0.84±0.68
Month 24	(10) 2.16±4.86	(30) 0.66±0.70	(12) 1.08±1.57	(33) 0.76±0.64

Abbreviation(s): Tregs: T regulatory cells, n: number of patients included in the analysis, N: number of treated patients.

Note(s): Data were reported as mean±standard deviation (SD). Baseline is defined as last value of assessment prior to first drug administration.

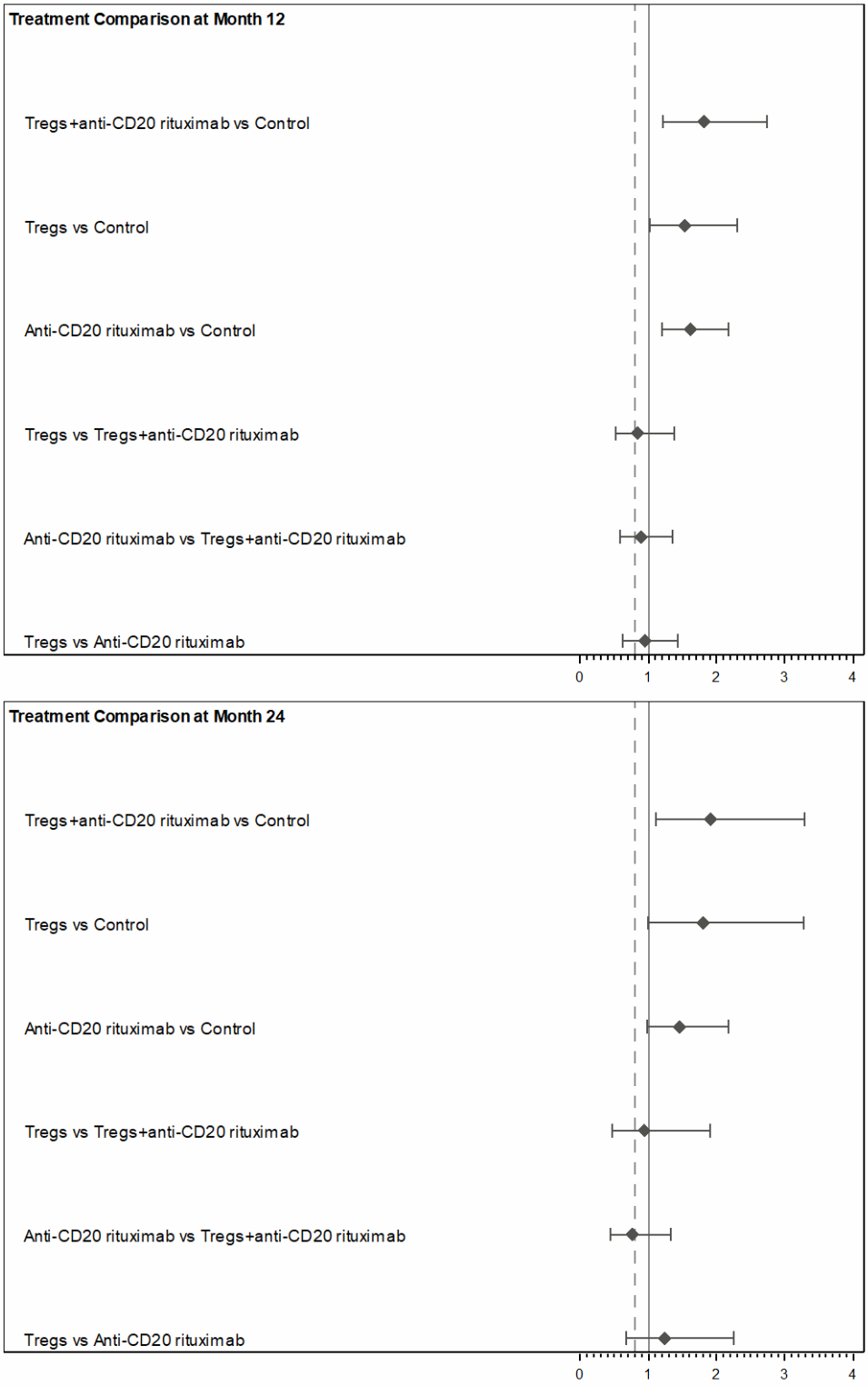
5. Figures

Figure S1. Study Enrolment, Treatment Assignments, and Analysis Populations.



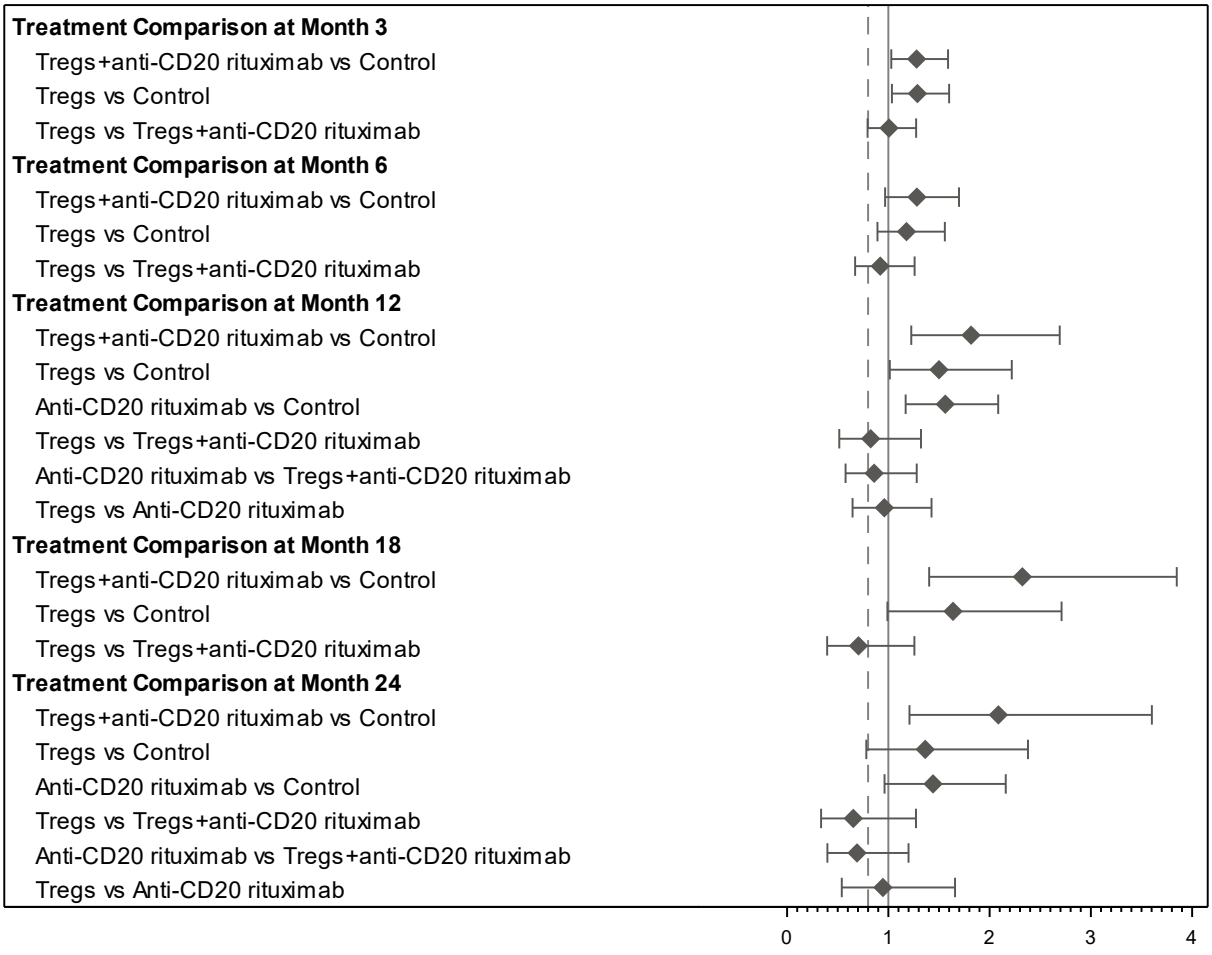
Note(s): Of 156 patients assessed for eligibility, 116 were enrolled. Of these, 115 were considered treated and included in the Safety population, 114 received at least one dose of trial medication and had at least one assessment of the primary efficacy variables beyond baseline and were included in the intention-to-treat (ITT) population.

Figure S2. Forest Plot (ANCOVA) of Geometric Mean Ratios of C-peptide AUC (MMTT, 0-240 min) at Months 12 and 24 (ITT Set).



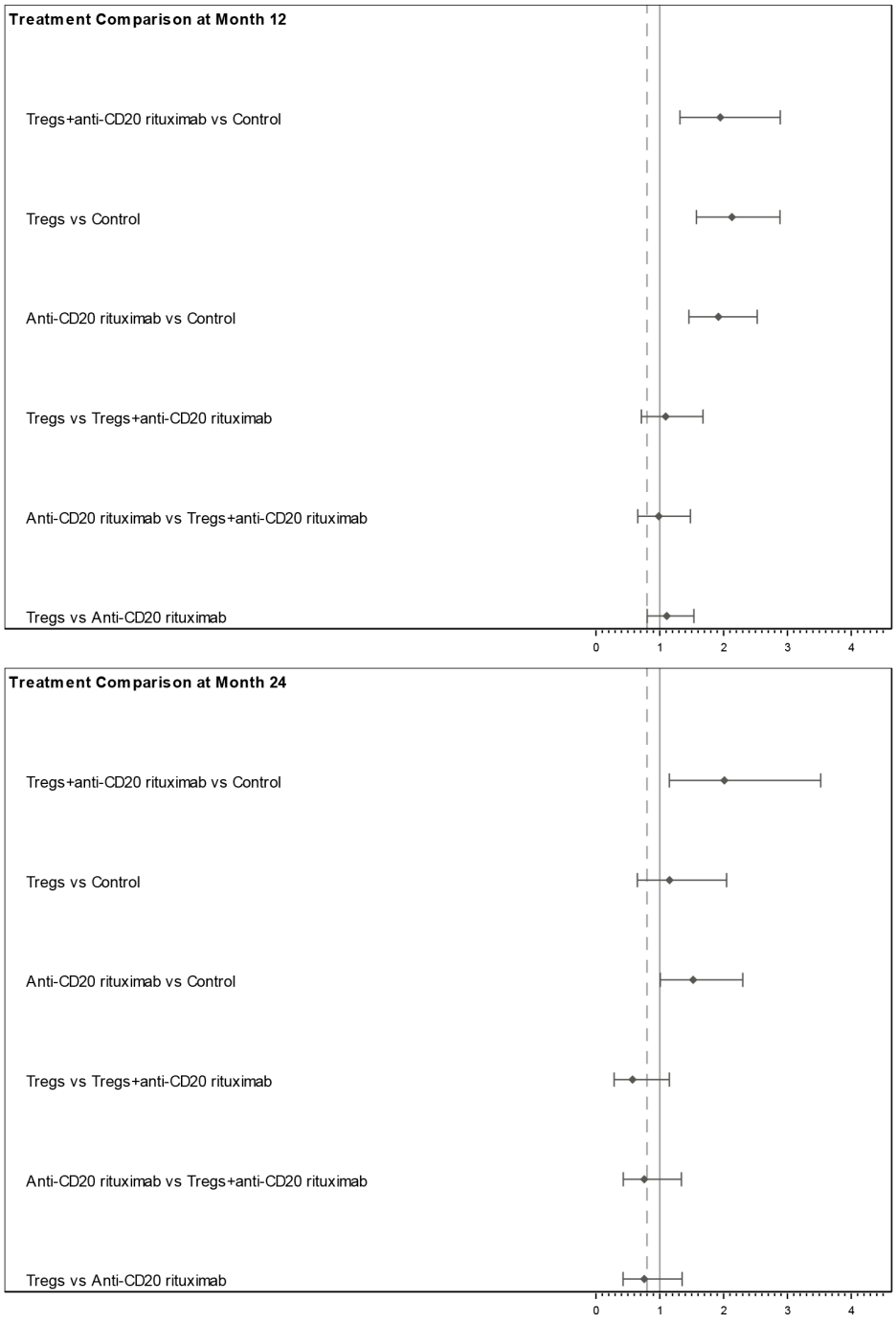
Note(s): Geometric mean ratios and 90 % confidence intervals are presented.

Figure S3. Forest Plot (RMANCOVA) of Geometric Mean Ratios of AUC of C-peptide (MMTT, 0-240 min) (ITT Set).



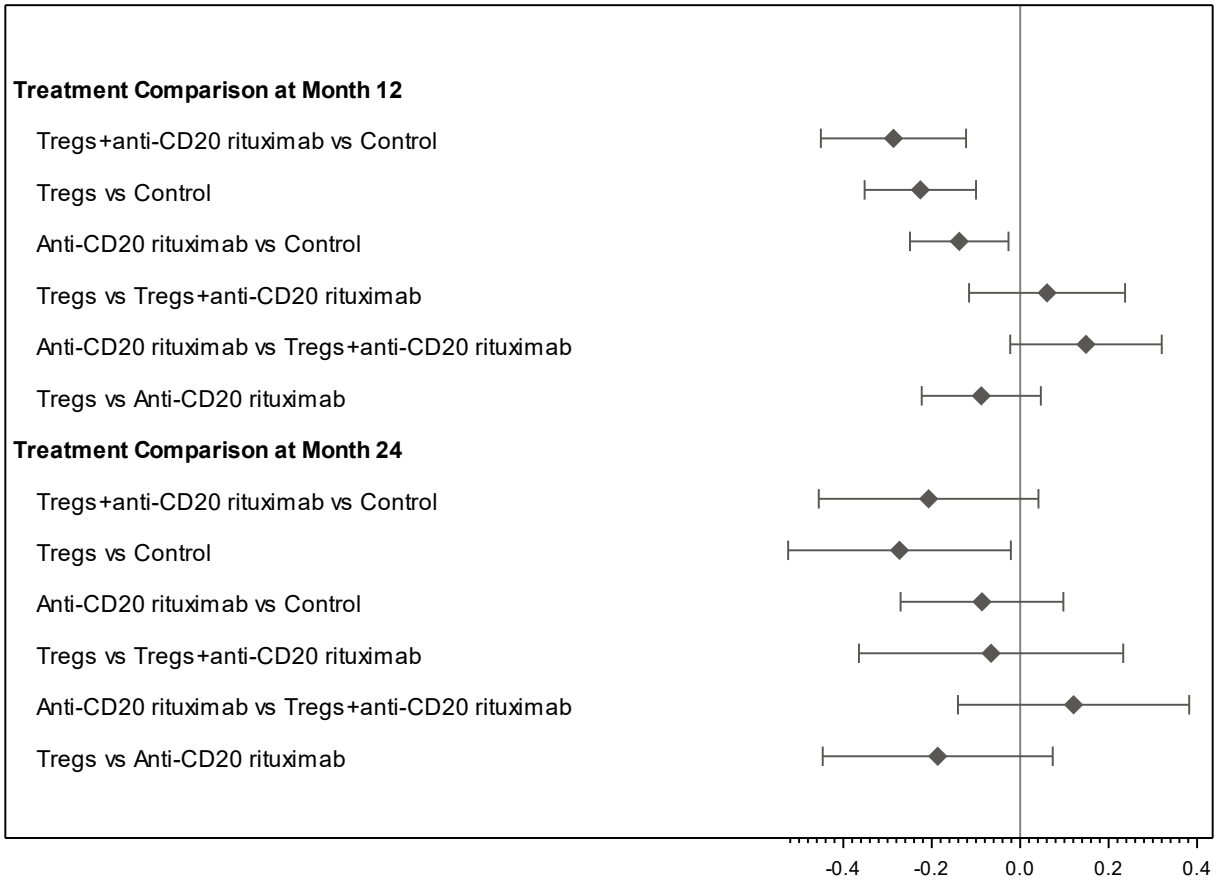
Note(s): Geometric mean ratios and 90 % confidence intervals are presented.

Figure S4. Forest Plot (ANCOVA) of Geometric Mean Ratios of C-peptide (Fasted) at Months 12 and 24 (ITT Set).



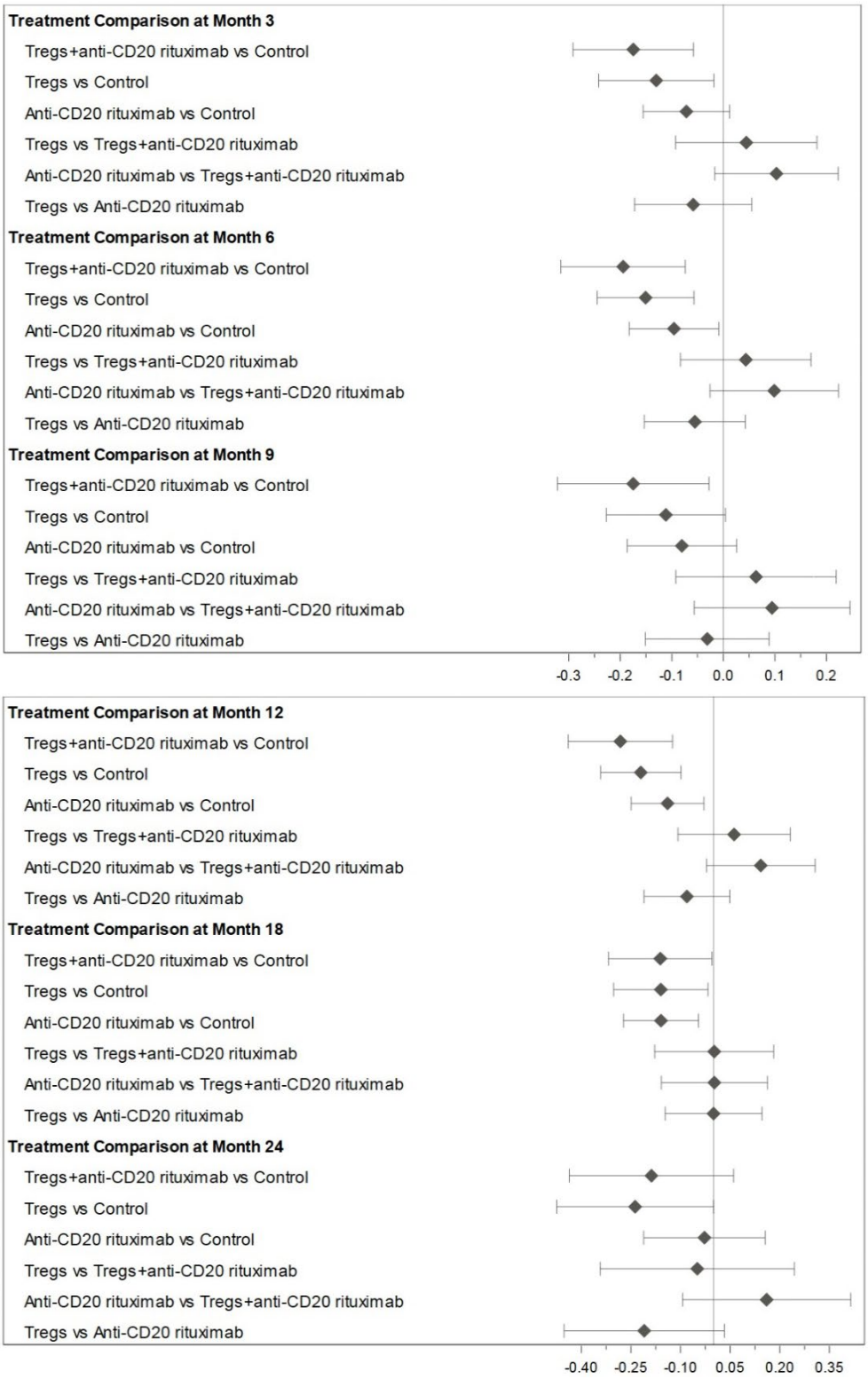
Note(s): Geometric mean ratios and 90 % confidence intervals are presented.

Figure S5. Forest Plot (ANCOVA) of Arithmetic Mean Differences of Daily Insulin Dose Per Kg Body Weight (ITT Set).



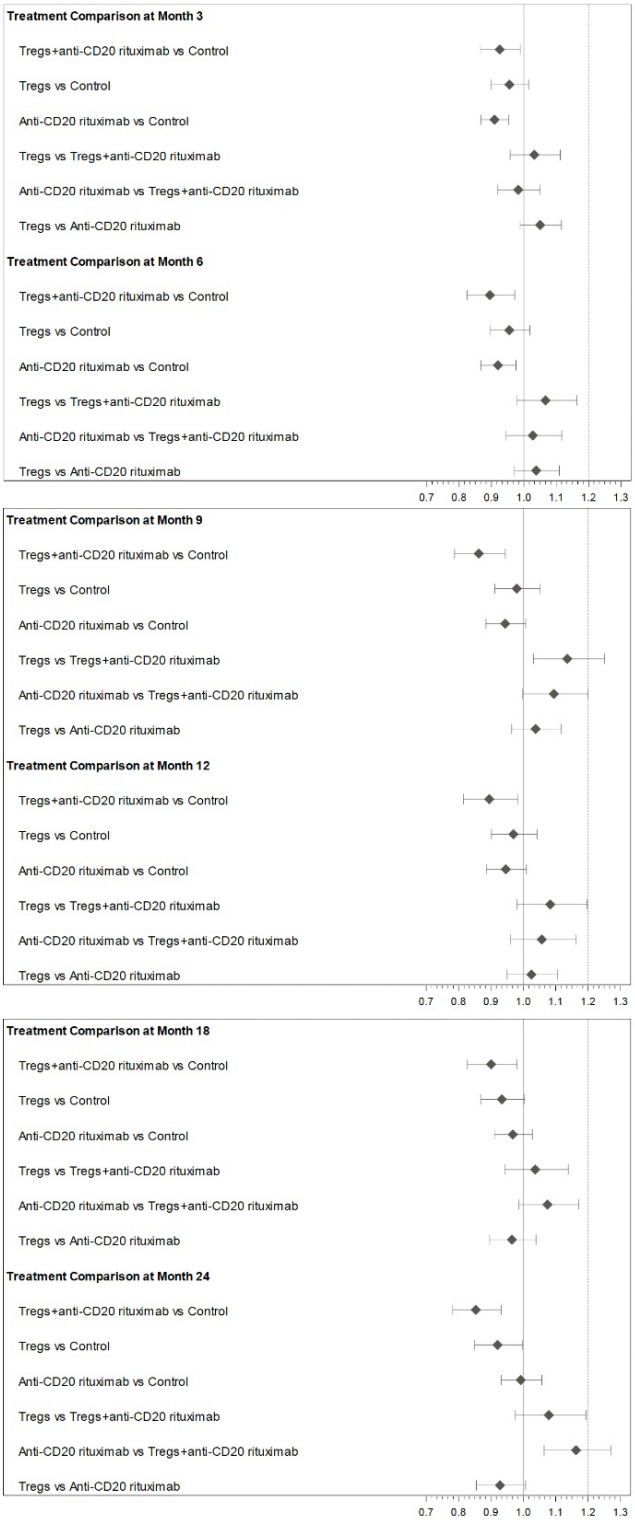
Note(s): Differences of the treatment means and 90 % confidence intervals are presented.

Figure S6. Forest Plot (RMANCOVA) of Arithmetic Mean Differences of Daily Insulin Dose Per Kg Body Weight at Months 3, 6, 9, 12, 18, and 24 (ITT Set).



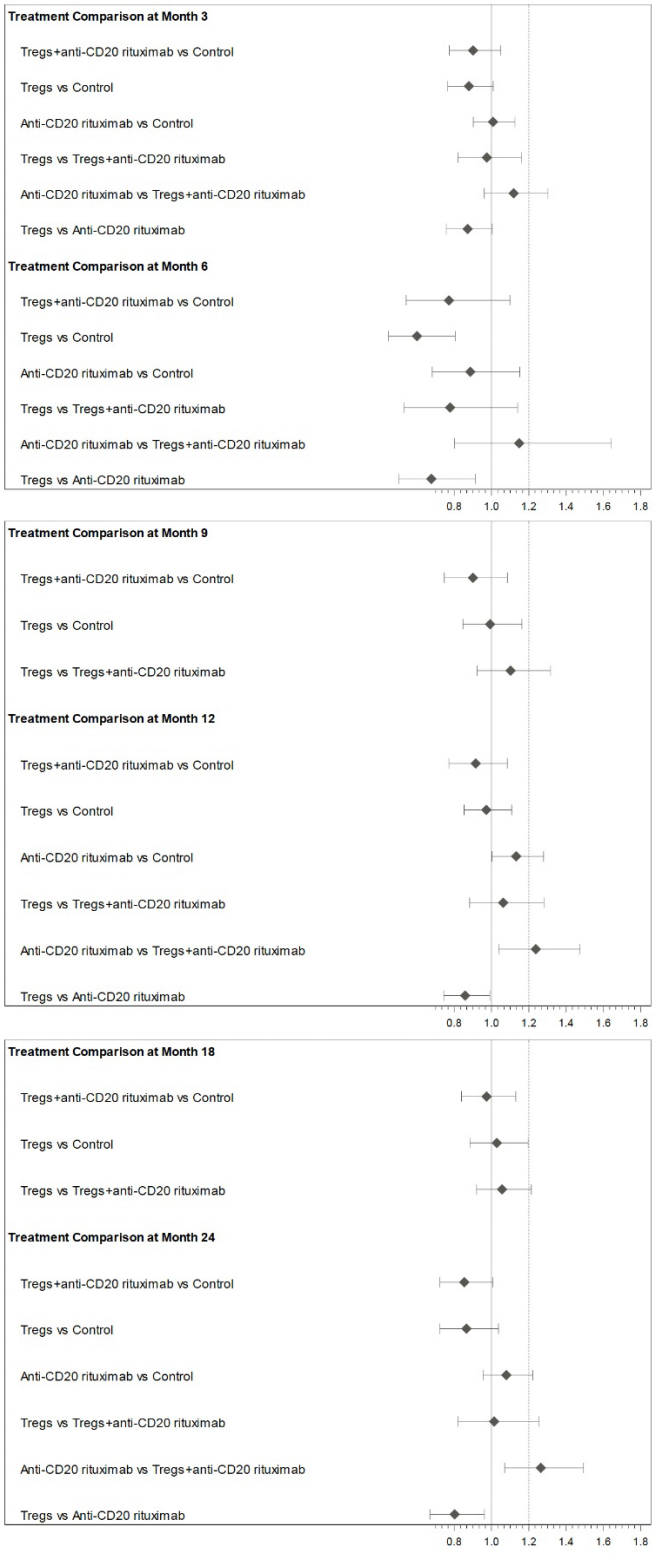
Note(s): Differences of the treatment means and 90 % confidence intervals are presented.

Figure S7. Forest Plot (RMANCOVA) of Geometric Mean Ratios of HbA1c at Months 3, 6, 9, 12, 18, and 24 (ITT Set).



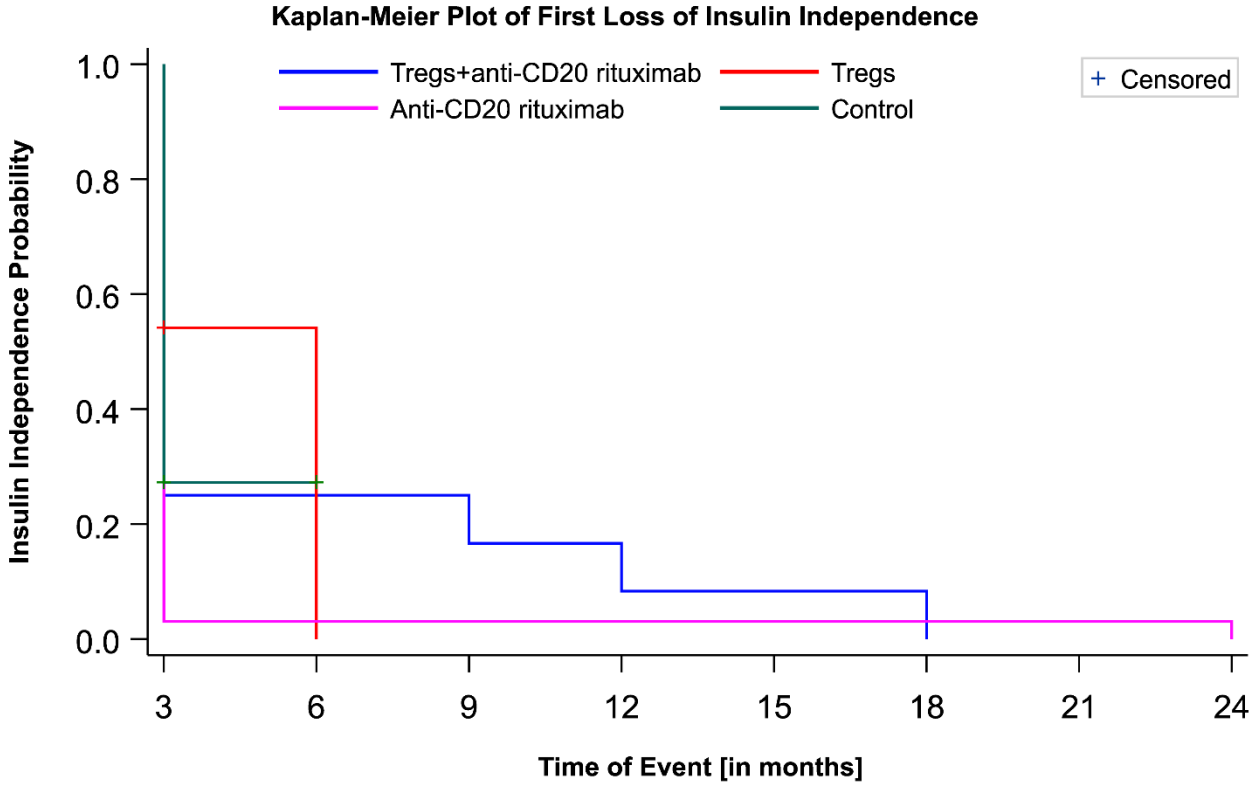
Note(s): Differences of the treatment means and 90 % confidence intervals are presented.

Figure S8. Forest Plot (RMANCOVA) of Geometric Mean Ratios of Glucose at months, 3, 6, 9, 12, 18, and 24 (ITT Set).



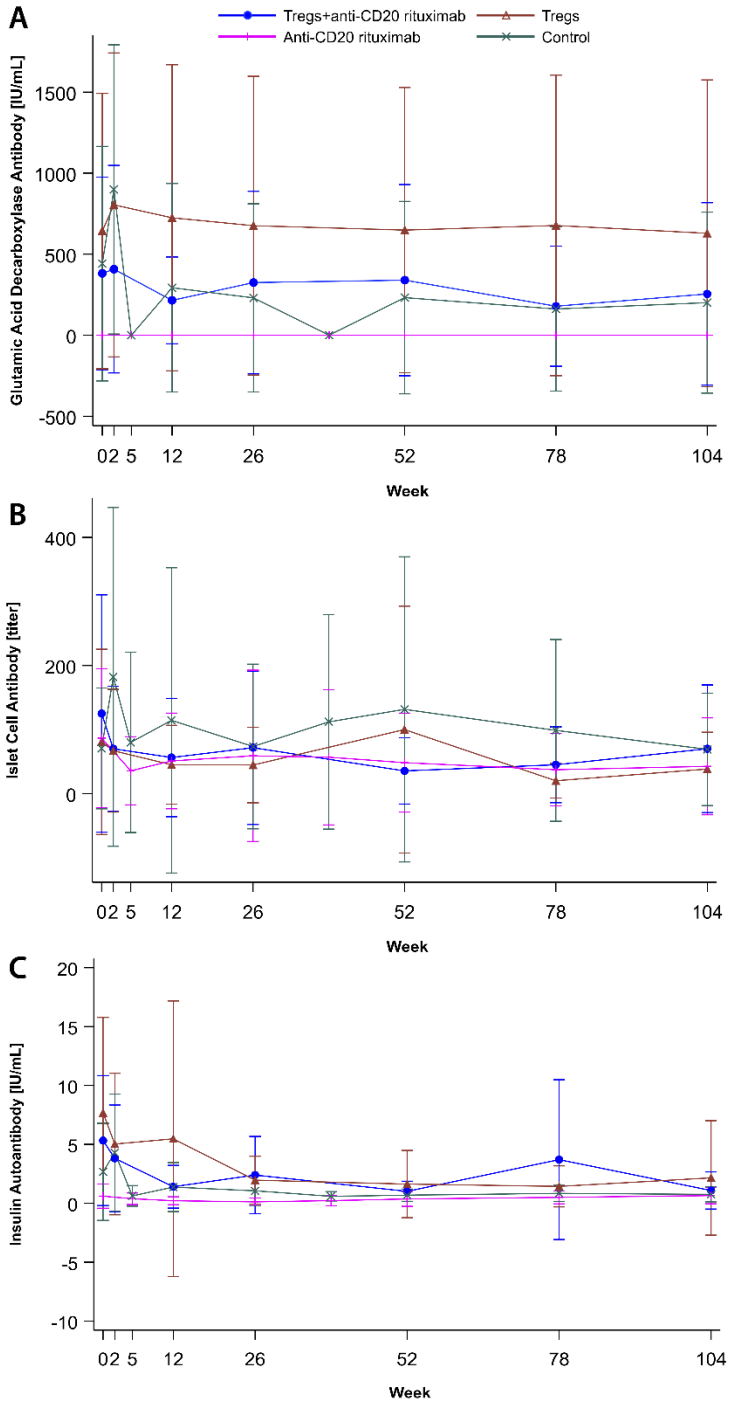
Note(s): Differences of the treatment means and 90 % confidence intervals are presented.

Figure S9. Kaplan-Meier-Plot of Time to First Loss of Insulin Independence (DDI = 0 IU/kg/day) (ITT Set).



Note(s): Survival - Duration of insulin independence until first loss.
This table shows the results of a survival analysis with the time to first loss of insulin independency status at the month 3 visit as the starting point.
Visits 3m, 6m, 9m, 12m, 18m and 24m are included in the analysis.
If the time to first loss of insulin independency status of a patient is not known for a scheduled visit, the patient will be censored from that visit onward.

Figure S10. Mean Concentration Time Plots of Autoantibodies (Safety Set). A, Glutamic acid decarboxylase antibody; B, islet cell antibody; C, insulin autoantibody.



Note(s): Means ± SD are presented.
If no data for Day 0 was available baseline as last value of assessment prior to first drug administration (Day 0) was used.

6. References

1. Marek-Trzonkowska N, Mysliwiec M, Dobyszuk A, et al. Administration of CD4+CD25highCD127- regulatory T cells preserves β-cell function in type 1 diabetes in children. Diabetes Care 2012;35:1817-20.
2. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. New England Journal of Medicine 2009;361:2143-52.
3. Lewis JA. Statistical principles for clinical trials (ICH E9): an introductory note on an international guideline. Statistics in medicine 1999;18:1903-42.
4. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. Bmj 2000;320:1240.
5. Gabir MM, Hanson RL, Dabelea D, et al. The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. Diabetes care 2000;23:1108-12.