Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Drs. Hong Jiang, Jason Gaglia and Tuochuan Dong, with the help of Karen Segal, Ph.D. organized and wrote the first draft of the manuscript. All authors reviewed, revised and approved the manuscript, and had access to the data and made the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

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1. EFFICACY ASSESSED BY C-PEPTIDE AUC

For changes from baseline in C-peptide AUC, after the backward stepwise variable selection process, the final model is change from baseline of C-peptide AUC (nmol/L) as the dependent variable, its baseline value (nmol/L) as covariate, and treatment group, visit, BMI (kg/m^2), the CD8+ T cell Inhibition Assay and the treatment group-by-visit interaction as fixed effects.

The treatment effects assessed by the differences of least square means of AVT001 vs. placebo were 0.154 nmol/L (95% CI: 0.056, 0.251) at D150 and 0.146 nmol/L (95% CI: 0.049, 0.242) at D360 respectively (Figure S1), which were consistent with the results for ln[C-peptide AUC + 1] (Figure 2A).

2. ADDITIONAL EXPLORATORY ANALYSES FOR C-PEPTIDE AUC

To evaluate the robustness of the findings, the following exploratory analyses were performed for C-peptide AUC:

1. Fit the mixed model without any additional covariates and rely on the randomization to balance baseline characteristics
2. Make comparisons between the two groups at D150 and D360 with t-tests

2.1. Exploratory Analysis 1

The model Change from baseline of ln[C-peptide AUC + 1] = Treatment + Visit + Treatment x Visit was fitted, and the results are compared with C-peptide AUC=Treatment + Visit + Treatment x Visit and, and the corresponding results were reported in Table S7.

The treatment effects assessed by the differences of least square means for C-peptide AUC of AVT001 vs. placebo estimated from this model were 0.135 nmol/L (95% CI: 0.013,0.258) at D150 and 0.147 nmol/L (95% CI: 0.023, 0.271) at D360 respectively**.** The treatment effects assessed by the differences of least square means for ln[C-peptide AUC + 1] of AVT001 vs. placebo estimated from this model were 0.0**77** nmol/L (95% CI: 0.005, 0.149) at D150 and 0.091 nmol/L (95% CI: 0.019, 0.164) at D360 respectively (Table S7), which are very similar to the corresponding results reported in the Efficacy Section of the manuscript (Figure 2A and S1).

2.2. Exploratory Analysis 2

The Change from baseline of C-peptide AUC at D150 and D360 in AVT001 and Placebo were compared with two sample t-test. The corresponding estimates and its 95% confidence intervals were shown in Table S8.

The mean differences between AVT001 and Placebo were 0.126 nmol/L (95% CI: 0.005, 0.247) at D150, and 0.154 nmol/L (95% CI: 0.006, 0.302) at D360. These results are consistent with the ones from MMRM (Table S8)**.**

3. SUPPLEMENTARY METHODS

C-peptide was measured from frozen plasma using a two-site immunoenzymometric assay (Tosoh Bioscience, South San Francisco, CA) at Medpace, Cincinnati OH[1].

Autoantibodies GADA and IA-2A[2], ZnT8A[3] and IAA[4] were measured from frozen serum using radio immunobinding assays at the Barbara Davis Diabetes Center, Aurora CO.

Overview of the CD8+ T cell Inhibition Assay

It is well known that while the autoimmune destruction of beta cells has long been known to cause T1D, the specific mechanism remained unelucidated. In this regard, we have identified a Q/E CD8+ Treg pathway that **keeps self-reactive T cells in check and its dysfunction has been found in a majority of T1D patients we have tested**.

The interaction between Tregs and self-reactive T cells is restricted by a non-conventional, Human leukocyte antigen class Ib molecule, leukocyte antigen E (HLA-E). The mouse homologue of HLA-E is nonclassical Major histocompatibility complex (MHC) molecules of Class Ib (Qa-1), so this pathway is referred to as the Qa-1/HLA-E or Q/E pathway, mediated by Q/E-restricted CD8+ Tregs. The common target structure specifically recognized by the T cell receptor (TCR) of the Q/E CD8+ Tregs is a complex of an oligo signal peptide of Heat Shock Protein 60 (Hsp60sp) presented by Qa-1/HLA-E molecule, preferentially expressed on the surface of self-reactive T cells. This complex is termed as **Q/E-Hsp60sp in general, or HLA-E/Hsp60sp in human studies**. The precise cognitive interaction between the Q/E CD8+ Treg cells and the self-reactive T cell leads to down-regulation of self-reactive T cell pool that activated by any self-antigens *in vivo* which are potential harmful to "self". It was demonstrated and determined that when the Q/E CD8+ Treg pathway is defective, self-reactive T cells are no longer under the control to be downregulated, resulting in beta cell destruction and the development of T1D.

A CD8+ T cell Inhibition Assay has also been developed to assess/measure the functional status of the Q/E CD8+ Treg pathway that controls peripheral autoimmunity. In our ongoing T1D Phase I/II clinical trial, this assay has been used to determine whether AVT001 corrects the defect of the dysfunctional Q/E CD8+ Treg pathway in T1D patients. More specifically, this

assay detects the specific recognition between the TCR on patient's Q/E CD8+Treg cells and the "common target structure", **the HLA-E/Hsp60sp complex,** expressed on the surface of the artificially established target cells.

Currently, CD8+ T cell Inhibition Assay is the only existing cellular/molecular assay that precisely detects the unique specificity of the Q/E CD8+ Treg pathway, by which the specific recognition by the TCR on the testing T cells of the "common target structure", in our human studies, **the HLA-E/Hsp60sp complex,** expressed on the artificially established specific "target TH1 cells" is assessed. The readout is the specific down-regulation of the specific TH1 cells (expressing the HLA-E/Hsp60sp complex) vs the control target TB1 cells (expressing the HLA-E/B7sp complex), measured by the "% of inhibition" (please see details in the Method in the Supplementary Appendix).

CD8+ T cell Inhibition Assay was performed on fresh PBMCs at Avotres Inc., Cedar Knolls NJ and is a modification of the previously described method[5-7]. CD8+ T cells were purified from PBMCs by positive selection with MACS magnetic beads (Miltenyi Biotec, Cat. # 130-045-201). Two stable transfectants, TH1 and TB1, served as the target cells in the assay. Both cell lines were made from the HLA-E-negative human B-lymphoblastoid cell line B721.221 (ATCC, Cat. # CRL-1855). The cell line TH1 was generated by co-transfection with the DNA constructs of HLA-E with Hsp60sp (QMRPVSRVL) and green fluorescent protein (GFP). These cells expressed the HLA-E/Hsp60sp complex on the cell surface and were labelled with GFP. The TB1 line was generated by co-transfection with the DNA constructs of HLA-E with the signal sequence of HLA-B*0701 (B7sp, VMAPRTVLL) and GFP. TB1 cells expressed the HLA-E/B7sp complex on the cell surface and served as a control.

Equal numbers of TH1 or TB1 cells were mixed with un-transfected B721 cells, which serves an internal control. The CD8+ T cells to be assayed were added to the targets at graded effector-to-target ratios, from 2.7:1 to 0.01:1. For the control cultures, no CD8+ T cells were added. The assay is set up in 48-well plates and following incubation at 37 ºC, 5% CO_2, for 5-7 days. The cell mixtures were assessed by flow cytometry with a CytoFLEX Flow Cytometer (Beckman Coulter, Indianapolis, IN). The CD8+ T cells were gated out during analysis and the numbers of TH1 or TB1 versus un-transfected B721 cells were assessed, differentiated by the GFP expression in the TH1 and TB1 cells. The ratio between TH1 or TB1 cells versus B721 cells (TH1/B721 or TB1/B721) were calculated accordingly. The read out of the CD8+ T cell Inhibition Assay was the percent of down-regulation (% inhibition) of the specific target cells (TH1), versus the control target cells (TB1).

The percent inhibition was calculated as:

$\text{Ratio}_{\text{control}} = \frac{\text{Number of TH1 or TB1 cells}}{\text{Number of B721 cells}}$, in the control cultures (without CD8+ T cells)

$\text{Ratio}_{\text{exp}} = \frac{\text{Number of TH1 or TB1 cells}}{\text{Number of B721 cells}}$, in the experimental cultures (with CD8+ T cells)

$$\%\ \text{inhibition} = \left(\left[\frac{\text{Ratio}_{\text{control}} - \text{Ratio}_{\text{exp}}}{\text{Ratio}_{\text{control}}} \right]_{\text{TH1}} - \left[\frac{\text{Ratio}_{\text{control}} - \text{Ratio}_{\text{exp}}}{\text{Ratio}_{\text{control}}} \right]_{\text{TB1}} \right) \times 100\%$$

The % inhibition measures the function of down-regulation by Q/E CD8+ Tregs via comparing the % of inhibition of TH1 cells versus TB1 cells.

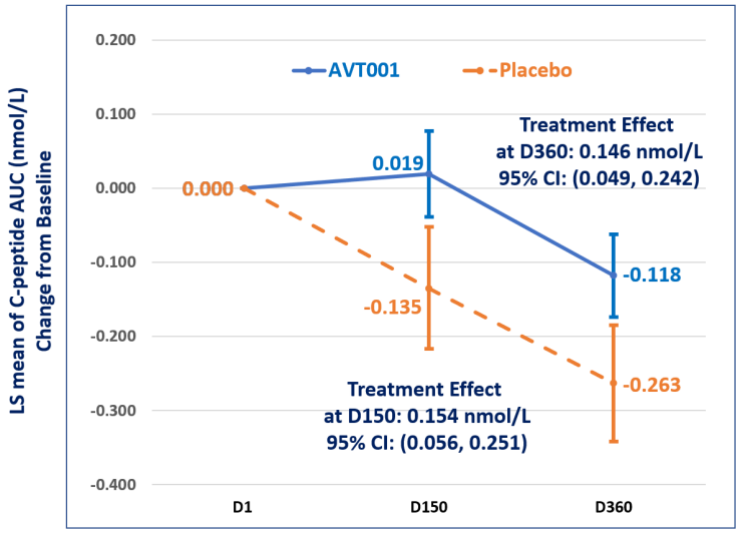
By assessing the % inhibition of the TH1 cells of the patient's CD8+ T cells, the CD8+ T cell Inhibition Assay detects the specific recognition of the common target structure (HLA-E/Hsp60sp) on TH1 cells by the TCR on the patient's T cells to be tested.

Samples from 185 healthy controls have been used in the validation of the performance of this assay. Based on the 185 healthy controls tested, the normal mean % of inhibition was 29% with a standard deviation of 25%.

The TH1 and TB1 cell lines have been deposited to ATCC under the following patent deposit numbers:
TH1: PTA-127256
TB1: PTA-127257

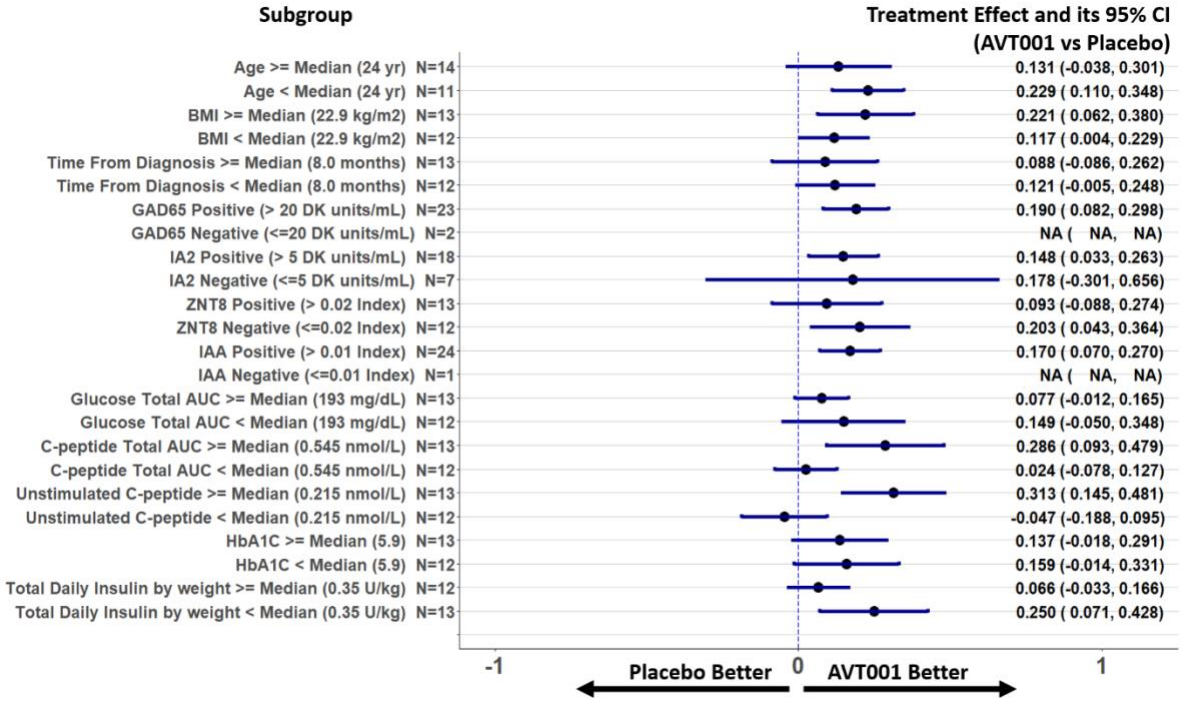
4. SUPPLEMENTARY TABLES AND FIGURES

Figure S1. Least square mean of C-peptide AUC (nmol/L) change from baseline, its 95% confidence interval, and treatment effects of AVT001 vs. placebo at Visit D150 and D360, estimated by MMRM



Change from baseline (D1) for C-peptide AUC is set as 0 per definition. The widths of all the above confidence intervals have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing. AUC: Area Under the Curve, MMRM: Mixed-effect Model for Repeated Measurements.

Figure S2. Forest plots of MMRM least square treatment effect estimates and 95% confidence interval of C-peptide AUC on D150 by subgroups at Baseline.



Positive treatment effects of C-peptide AUC evaluated by MMRM favoring AVT001 have been observed in several subgroups including participants who had higher baseline C-peptide (measured by either AUC or unstimulated C-peptide), lower insulin requirements, or younger age. The widths of all the above confidence intervals have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing. AUC: Area Under the Curve, MMRM: Mixed-effect Model for Repeated Measurements.

Table S1. Supplementary Table on the Representativeness of Study Participants

Category	Considerations
Disease, problem, or condition under investigation	Type 1 Diabetes (T1D)
Special considerations related to	
Sex and gender	On average male and female individuals are similarly affected. However, there can be age and regional differences. In regions of higher incidence (populations of European origin) there is a male predominance, whereas regions with lower incidence (populations of non-European origin) female predominance has been reported.
Age	May occur at any age
Race or ethnic group	In the US, T1D is more common in non-Hispanic whites than other racial or ethnic groups.
Geography	Europe has the highest incidence of T1D among all the continents, with Finland and Sardinia (Italy) reporting the most cases.
Other considerations	There are likely both genetic and environmental factors contributing to the onset of T1D.
Overall representativeness of this trial	This small size of this early-phase trial limits the ability to extrapolate to make firm comment about overall representativeness.

Table S2. Hematology Laboratory Shift from Baseline to Worst Post-Baseline based on CTCAE v4.03 Toxicity Grade

Table S2-1

Hemoglobin (g/L): Anemia							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	10 (62.5)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	13 (81.3)
	Grade 1	0 (0.0)	2 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	3 (18.8)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	10 (62.5)	5 (31.3)	1 (6.3)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	8 (88.9)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	8 (88.9)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S2-2

Hemoglobin (g/L): Hemoglobin increased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Hemoglobin (g/L): Hemoglobin increased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
	Total	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S2-3

Lymphocytes (10^9/L): Lymphocyte count decreased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	14 (87.5)	0 (0.0)	2 (12.5)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	14 (87.5)	0 (0.0)	2 (12.5)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S2-4

Lymphocytes (10^9/L): Lymphocyte count increased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/Normal	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/Normal	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Lymphocytes (10^9/L): Lymphocyte count increased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S2-5

Neutrophils (10^9/L): Neutrophil count decreased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/Normal	11 (68.8)	2 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	14 (87.5)
	Grade 1	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (12.5)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	12 (75.0)	2 (12.5)	1 (6.3)	1 (6.3)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/Normal	5 (55.6)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	8 (88.9)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	5 (55.6)	3 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)	9 (100.0)

Table S2-6

Platelets (10^9/L): Platelet count decreased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	15 (93.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (93.8)
	Grade 1	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Platelets (10^9/L): Platelet count decreased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
	Total	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S2-7

Leukocytes (10^9/L): White blood cell decreased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	7 (43.8)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	10 (62.5)
	Grade 1	0 (0.0)	4 (25.0)	2 (12.5)	0 (0.0)	0 (0.0)	6 (37.5)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	7 (43.8)	7 (43.8)	2 (12.5)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	2 (22.2)	4 (44.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
	Grade 1	0 (0.0)	2 (22.2)	1 (11.1)	0 (0.0)	0 (0.0)	3 (33.3)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	2 (22.2)	6 (66.7)	1 (11.1)	0 (0.0)	0 (0.0)	9 (100.0)

Table S2-8

Leukocytes (10^9/L): Leukocytosis							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Abbreviations: Abbreviations: CTCAE = Common Toxicity Grading Adverse Event; n = Number of participants; N' = Number of participants with both baseline and post-baseline results; % = Based on N'.

Note: Baseline is defined as the last non-missing measurement taken prior to the first dose of study drug.

Note: Categories of Grades 1 to 4 are based on the CTCAE Grading System, version 4.03. Observations with non-missing values that are not graded between 1 and 4 are assigned Grade 0.

Note: Percentages are based on the number of participants in the population with data at both the baseline and the worst post-baseline visit by treatment group.

Table S3. Chemistry Laboratory Shift from Baseline to Worst Post-Baseline based on CTCAE v4.03 Toxicity Grade
Table S3-1

Albumin (g/L): Hypoalbuminemia							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/Normal	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/Normal	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-2

Alkaline Phosphatase (U/L): Alkaline phosphatase increased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	13 (81.3)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	13 (81.3)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	8 (88.9)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	8 (88.9)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-3

Alanine Aminotransferase (U/L): Alanine aminotransferase increased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-4

Aspartate Aminotransferase (U/L): Aspartate aminotransferase increased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	11 (68.8)	5 (31.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	11 (68.8)	5 (31.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-5

Bilirubin (umol/L): Blood bilirubin increased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	13 (81.3)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	15 (93.8)
	Grade 1	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	13 (81.3)	2 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	4 (44.4)	2 (22.2)	1 (11.1)	0 (0.0)	0 (0.0)	7 (77.8)
	Grade 1	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
	Grade 2	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (11.1)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	4 (44.4)	3 (33.3)	2 (22.2)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-6

Calcium (mmol/L): Hypocalcemia							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	11 (68.8)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	14 (87.5)
	Grade 1	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	2 (12.5)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	8 (88.9)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Calcium (mmol/L): Hypocalcemia							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
	Total	8 (88.9)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-7

Calcium (mmol/L): Hypercalcemia							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-8

Creatinine (umol/L): Creatinine increased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	3 (18.8)	13 (81.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	3 (18.8)	13 (81.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)

Creatinine (umol/L): Creatinine increased							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Placebo (N'=9)	Grade 0/ Normal	1 (11.1)	8 (88.9)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	1 (11.1)	8 (88.9)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-9

Glucose (mmol/L): Hypoglycemia							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	7 (77.8)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	7 (77.8)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-10

Glucose (mmol/L): Hyperglycemia							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	3 (18.8)	5 (31.3)	1 (6.3)	1 (6.3)	0 (0.0)	10 (62.5)

Glucose (mmol/L): Hyperglycemia							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
	Grade 1	2 (12.5)	0 (0.0)	3 (18.8)	1 (6.3)	0 (0.0)	6 (37.5)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	5 (31.3)	5 (31.3)	4 (25.0)	2 (12.5)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	4 (44.4)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
	Grade 1	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	4 (44.4)	4 (44.4)	0 (0.0)	1 (11.1)	0 (0.0)	9 (100.0)

Table S3-11

Potassium (mmol/L): Hypokalemia							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	6 (66.7)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	8 (88.9)
	Grade 1	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	7 (77.8)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-12

Potassium (mmol/L): Hyperkalemia							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	13 (81.3)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	14 (87.5)
	Grade 1	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-13

Sodium (mmol/L): Hyponatremia							
		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	11 (68.8)	4 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (93.8)
	Grade 1	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	12 (75.0)	4 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	7 (77.8)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	8 (88.9)
	Grade 1	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	7 (77.8)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Table S3-14

		Worst Post-Baseline Grade					
Treatment Group	Baseline CTCAE Grade	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
AVT001 (N'=16)	Grade 0/ Normal	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100.0)
Placebo (N'=9)	Grade 0/ Normal	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)

Abbreviations: Abbreviations: CTCAE = Common Toxicity Grading Adverse Event; n = Number of participants; N' = Number of participants with both baseline and post-baseline results; % = Based on N'.

Note: Baseline is defined as the last non-missing measurement taken prior to the first dose of study drug.

Note: Categories of Grades 1 to 4 are based on the CTCAE Grading System, version 4.03. Observations with non-missing values that are not graded between 1 and 4 are assigned Grade 0.

Note: Percentages are based on the number of participants in the population with data at both the baseline and the worst post-baseline visit by treatment group.

Table S4. Number and Percentage of Participants with at Least One Markedly Abnormal Post-Baseline Observed Value/Change from Baseline in Vital Signs

Vital Sign (unit) Markedly Abnormal Criterion, n(%)	AVT001 (N=16)	Placebo (N=9)
SBP (mmHg)		
Observed value ≤ 90 mmHg and Change from baseline ≤ -20 mmHg	0 (0.0)	0 (0.0)
Observed value ≥ 180 mmHg and Change from baseline ≥ 20 mmHg	0 (0.0)	0 (0.0)
DBP (mmHg)		
Observed value ≤ 50 mmHg and Change from baseline ≤ -15 mmHg	0 (0.0)	0 (0.0)
Observed value ≥ 105 mmHg and Change from baseline ≥ 15 mmHg	0 (0.0)	0 (0.0)
Pulse (bpm)		
Observed value ≤ 50 bpm and Change from baseline ≤ -15 bpm	0 (0.0)	1 (11.1)
Observed value ≥ 120 bpm and Change from baseline ≥ 15 bpm	0 (0.0)	0 (0.0)
Oxygen Saturation (%)		
Observed value ≤ 94%	0 (0.0)	0 (0.0)
Body Temperature (°C)		
Observed value ≥ 38.3 °C and Change from baseline ≥ 1.1 °C	0 (0.0)	0 (0.0)
Weight (kg)		
Percent change from baseline ≤ -7.0%	1 (6.3)	1 (11.1)
Percent change from baseline ≥ 7.0%	6 (37.5)	4 (44.4)

Abbreviations: SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; bpm = beats per minute.

Table S5. Number and Percentage of Participants with at Least One Markedly Abnormal Post-Baseline Observed Value/Change from Baseline in ECG Parameters

Parameter Markedly Abnormal Criterion, n(%)	AVT001 (N=16)	Placebo (N=9)
QT Interval (uncorrected)[1]		
> 450 msec	2 (12.5)	1 (11.1)
> 480 msec	0 (0.0)	0 (0.0)
> 500 msec	0 (0.0)	0 (0.0)
> 30 msec increase from baseline	1 (6.3)	1 (11.1)
> 60 msec increase from baseline	0 (0.0)	0 (0.0)

Note: Baseline is defined as the last non-missing measurement taken prior to the first dose of study drug.

[1] Participants can be reported in more than one category.

Table S6. TEAE and PTAE by Preferred Term

TEAEs by Preferred Term	AVT001 (N=16)	Placebo (N=9)
Participants with Any TEAE	9 (56.3)	6 (66.7)
Neutrophil count decreased	4 (25.0)	1 (11.1)
Hyponatraemia	3 (18.8)	1 (11.1)
Cough	3 (18.8)	0 (0.0)
White blood cell count decreased	2 (12.5)	1 (11.1)
Ear pain	2 (12.5)	0 (0.0)
Lymphocyte count decreased	2 (12.5)	0 (0.0)
Dizziness	1 (6.3)	2 (22.2)
Anaemia	1 (6.3)	1 (11.1)
Blood bicarbonate decreased	1 (6.3)	1 (11.1)
Blood bilirubin increased	1 (6.3)	1 (11.1)
Corona virus infection	1 (6.3)	1 (11.1)
Fatigue	1 (6.3)	1 (11.1)
Hypocalcaemia	1 (6.3)	1 (11.1)
Pyrexia	1 (6.3)	1 (11.1)
Chills	1 (6.3)	0 (0.0)
Gastrooesophageal reflux disease	1 (6.3)	0 (0.0)
Joint dislocation	1 (6.3)	0 (0.0)
Nasal congestion	1 (6.3)	0 (0.0)
Non-cardiac chest pain	1 (6.3)	0 (0.0)
Oropharyngeal pain	1 (6.3)	0 (0.0)
Palpitations	1 (6.3)	0 (0.0)
Sinusitis	1 (6.3)	0 (0.0)
Headache	0 (0.0)	2 (22.2)
Blood potassium decreased	0 (0.0)	1 (11.1)
Gastroenteritis	0 (0.0)	1 (11.1)
Influenza like illness	0 (0.0)	1 (11.1)
Nausea	0 (0.0)	1 (11.1)
Oral papule	0 (0.0)	1 (11.1)
Upper-airway cough syndrome	0 (0.0)	1 (11.1)

PTAEs by Preferred Term	AVT001 (N=16)	Placebo (N=9)
Participants with Any PTAE	16 (100.0)	8 (88.9)
White blood cell count decreased	5 (31.3)	4 (44.4)
Neutrophil count decreased	4 (25.0)	1 (11.1)
Blood alkaline phosphatase increased	3 (18.8)	1 (11.1)
Blood bicarbonate decreased	3 (18.8)	0 (0.0)
Lymphocyte count decreased	3 (18.8)	0 (0.0)
Corona virus infection	2 (12.5)	1 (11.1)
Anaemia	2 (12.5)	0 (0.0)
Hypocalcaemia	2 (12.5)	0 (0.0)
Blood bilirubin increased	1 (6.3)	2 (22.2)
Alanine aminotransferase increased	1 (6.3)	0 (0.0)
Aspartate aminotransferase increased	1 (6.3)	0 (0.0)
Back pain	1 (6.3)	0 (0.0)
Cough	1 (6.3)	0 (0.0)
Dizziness	1 (6.3)	0 (0.0)
Headache	1 (6.3)	0 (0.0)
Hip fracture	1 (6.3)	0 (0.0)
Hyperkalaemia	1 (6.3)	0 (0.0)
Hyponatraemia	1 (6.3)	0 (0.0)
Monocyte count decreased	1 (6.3)	0 (0.0)
Otitis media	1 (6.3)	0 (0.0)
Pain in extremity	1 (6.3)	0 (0.0)
Pharyngitis	1 (6.3)	0 (0.0)
Proteinuria	1 (6.3)	0 (0.0)
Arthralgia	0 (0.0)	1 (11.1)
Attention deficit/hyperactivity disorder	0 (0.0)	1 (11.1)
Diarrhoea	0 (0.0)	1 (11.1)
Enterocolitis infectious	0 (0.0)	1 (11.1)
Rhinorrhoea	0 (0.0)	1 (11.1)

- Treatment-emergent AEs (TEAEs) are defined as any AE that started on or after the first dose of study medication through 30 days following the last dose.
- Post-treatment AEs (PTAEs) are defined as adverse events that started more than 30 days following the last dose through D360.

Table S7. Least square means of C-peptide AUC and ln[C-peptide AUC + 1] change from baseline (CHG), and treatment effect of AVT001 vs. placebo at Visit D150 and D360, estimated by MMRM

Two Analyses performed and compared	Visit	LS Mean of CHG in AVT001	LS Mean of CHG in placebo	Treatment Effect	95% Confidence interval for Treatment Effect
C-peptide AUC (nmol/L)	D150	-0.013	-0.149	0.135	(0.013,0.258)
	D360	-0.107	-0.254	0.147	(0.023,0.271)
ln[C-peptide AUC+1] (nmol/L)	D150	-0.019	-0.096	0.077	(0.005, 0.149)
	D360	-0.079	-0.170	0.091	(0.019, 0.164)

Change from baseline of C-peptide AUC/ln[C-peptide AUC + 1] = Treatment + Visit + Treatment x Visit were fitted. The widths of all the above confidence intervals have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing. AUC: Area Under the Curve, MMRM: Mixed-effect Model for Repeated Measurements.

Table S8. Point estimates and its 95% Confidence Interval for the difference of change from baseline of C-peptide AUC between AVT001 and Placebo, at D150 and D360

	Mean difference of Change from Baseline of C-peptide AUC, Between AVT001 and Placebo, estimated from two sample T-test	
Visit	Estimate (nmol/L)	95% CI (nmol/L)
D150	0.126	(0.005, 0.247)
D360	0.154	(0.006, 0.302)

The widths of all the above confidence intervals have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing. AUC: Area Under the Curve.

Table S9. Least square mean of GADA, IA-2A, ZnT8A and IAA change from baseline (CHG), and treatment effects of AVT001 vs. placebo at Visit D150 and D360, estimated by MMRM

Autoantibodies	Visit	LS Mean of CHG in AVT001	LS Mean of CHG in placebo	Treatment Effect	95% Confidence interval for Treatment Effect
GADA (DK units/ml)	D150	-32.814	-35.663	2.849	(-70.653, 76.352)
	D360	-30.613	-6.168	-24.444	(-94.631, 45.743)
IA-2A (DK units/ml)	D150	-19.231	6.890	-26.121	(-99.172, 46.930)
	D360	23.858	11.864	11.994	(-62.011, 85.998)
ZnT8A (1ndex)	D150	-0.039	-0.031	-0.007	(-0.084, 0.069)
	D360	-0.073	-0.048	-0.024	(-0.104, 0.055)
IAA (1ndex)	D150	0.189	0.016	0.173	(-0.215, 0.561)
	D360	0.327	0.350	-0.022	(-0.407, 0.362)

None of these antibody levels were statistically significant different between AVT001 and placebo, at either D150 or D360 visits. The widths of all the above confidence intervals have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing.

MMRM: Mixed-effect Model for Repeated Measurements.

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