SUPPLEMENTARY DATA

The DIA-AID 1 Writing Group

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Supplementary Table 1. Parameters of Patients Screened for Eligibility.

Parameter	Average ± SD (minimum - maximum)
Gender	457 Males / 222 Females
Age (years)	27.4 ± 7.92 (15 - 47)
Time from diagnosis (months)	1.87 ±1.27 (0 – 8.57)
BMI (kg/m^2)	22.9 ±3.43 (16 – 39.5)
Fasting C-peptide (nmol/l)	0.46 ±0.30 (0.07 – 2.46)
HbA1c (%)	7.52 ±1.88 (4 - 17)
Autoantibodies (% positive)	IA2A 51.2%, IAA 65.8%, GADA 75.4%

Supplementary Table 2. Inclusion / Exclusion Criteria that were Violated by Patients Excluded from ITT to Form the mITT Population Prior to Unmasking**.**

Inclusion / Exclusion Criteria Violated	Number of Subjects
No affirmation of T1D	12
Time from Diagnosis (not newly diagnosed)	5
Age at Randomization (either <16 or >45)	7
Ketonuria & proteinuria at visit 1; Use of Metformin	1
Repeated tests of ketonuria, proteinuria, hematuria	2
Ketones in urine and weight loss > 10%	1
No insulin taken for at least 2 months after diagnosis	3
Underlying disease	1
Received both allocations (treatment group cannot be determined for efficacy evaluation)	2

Calculations Used for Data Analysis

Change from baseline in AUC = $AUC_{24\ months} - AUC_{baseline}$

Relative treatment effect = (1-LS $mean_{DiaPep277}$® / LS $mean_{Placebo}$) x100.

Rate of hypoglycemic events/month was calculated as follows (based on 30 days per month):

Rate of Events/month at Baseline = Number of Events/{[(Month 3–Baseline)+1]/30}; Rate of Events/month at Study End = Number of Events/{[(Month 24–Month 3)+1]/30}.

Change of Hypoglycemic Event Rate = (Hypoglycemic event rate at Month 24-Hypoglycemic event rate at Month 3).

SUPPLEMENTARY DATA

Supplementary Table 3. Hypoglycemia Classification**.**

Severity	Symptoms	Plasma Glucose	Action Taken	Classification
Subject able to initiate self-treatment if necessary	Symptoms suggestive of hypoglycemia	< 70 mg/dL (3.9 mmol/L)	Enter in Glycemia Study Diary eCRF including the actions taken	Symptomatic Hypoglycemia*
	Symptoms suggestive of hypoglycemia	≥70 mg/dL (3.9 mmol/L)	Enter in Glycemia Study Diary eCRF including the actions taken	Relative Hypoglycemia*
	Symptoms suggestive of hypoglycemia	Not taken	Enter in Glycemia Study Diary eCRF including the actions taken	Probable symptomatic Hypoglycemia*
	Asymptomatic	< 70 mg/dL (3.9 mmol/L)	Enter in Glycemia Study Diary eCRF including the actions taken	Asymptomatic Hypoglycemia*
Subject is unable to initiate self-treatment and requires assistance of another person or hospitalization.	Symptoms suggestive of hypoglycemia	< 70 mg/dL (3.9 mmol/L)	Enter in Glycemia Study Diary eCRF Report as SAE if criteria are fulfilled including the actions taken	Severe Hypoglycemia* SAE, if applicable
	Symptoms suggestive of hypoglycemia	Clinical manifestation reversed by administration of oral carbohydrate, subcutaneous glucagon or intravenous glucose	Enter in Glycemia Study Diary eCRF Report as SAE if criteria are fulfilled including the actions taken	Severe Hypoglycemia* SAE, if applicable

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Supplementary Table 4. Reasons for Screen Failure.

	Number	Percentage
Autoantibodies negative	54	24.32
Low C-peptide	54	24.32
Withdrawal of Consent	40	18.02
Failed to comply with inclusion/exclusion criteria	21	9.46
Patient not compliant with requirements of the study	19	8.56
Aberrant lab results	10	4.50
Time from Diagnosis not applicable	8	3.60
Lost to follow-up	5	2.25
BMI out of range	4	1.80
Age	2	0.90
Unexplained weight loss	2	0.90
Allergy to penicillin	1	0.45
Worsening or complication of the underlying disease	1	0.45
Hyperglycemic Event	1	0.45
Total	222	100

Supplementary Table 5. Drop-out Patients: Breakdown by Reason and Allocation.

Reasons for not Completing the Study	Total	Breakdown by Allocation	
		DiaPep277®	Placebo
Withdrawal of Consent	36	17	19
Lost to follow-up	19	6	13
Patient not compliant with requirements of the study	10	6	4
Adverse Event	9	6	3
HbA1c withdrawal criteria	8	5	3
Serious Adverse Event	4	2	2
Dermal Hypersensitivity	3	0	3
Other	3	2	1
Patient's findings or conduct failed to meet protocol entry criteria	3	2	1
Patient requires use of an unacceptable medication	2	0	2
Death	1	1	0
Other: Occurrence of a concomitant disease	1	0	1
Pregnancy	1	1	0
Protocol Violation	1	1	0
Termination by sponsor	1	1	0
Total	102	50	52
Patients included in the primary efficacy endpoint analysis	35	18	17

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Supplementary Table 6. Exploratory Analysis, The Proportion of Patients in Partial Remission at Study End (HbA1c ≤ 7% and Insulin Dose ≤ 0·5 U/kg/day).

	% of Patients		p value
mITT Population			
	DiaPep277® (N = 159)	Placebo (N = 167)	
HbA1c ≤7% & Insulin Dose ≤0.5 U/kg/day	38.4	29.3	0.085
HbA1c >7% & Insulin Dose >0.5 U/kg/day	27	37.7	0.04
PP Population			
	DiaPep277® (N = 146)	Placebo (N = 162)	
HbA1c ≤7% & Insulin Dose ≤0.5 U/kg/day	41.8	30.2	0.035
HbA1c >7% & Insulin Dose >0.5 U/kg/day	23.3	37.7	0.006

Supplementary Table 7. Overall Summary of Treatment Emergent Adverse Events.

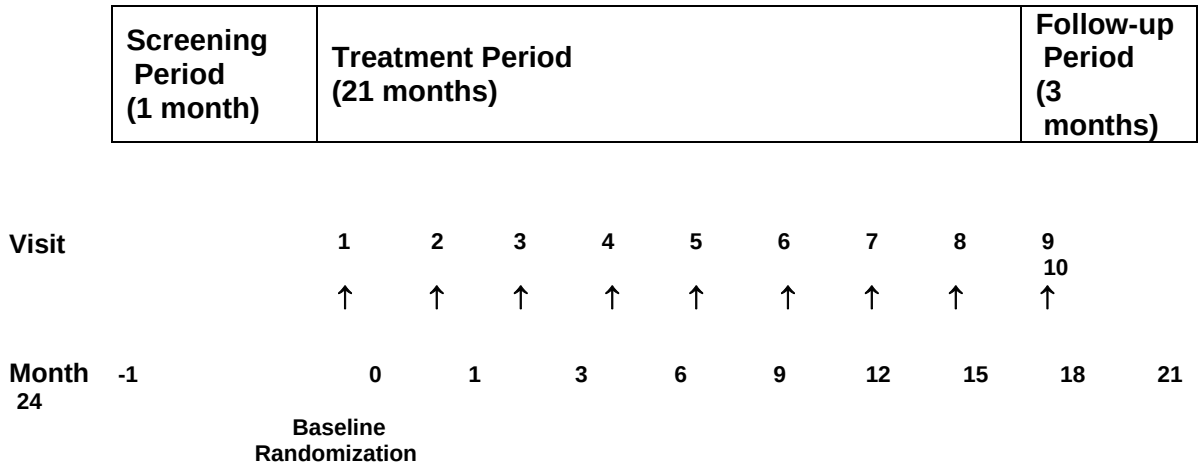
	DiaPep277® (N=225)	Placebo (N=231)	Total (N=456)
Number of Patients with at Least One TEAE	173 (76·9%)	164 (71%)	337 (73·9%)
Number of Patients with at Least One Serious TEAE Not Considered to be Drug Related	23 (10·2%)	13 (5·6%)	36 (7·9%)
Number of Patients with at Least One Suspected Drug-Related Serious TEAE	3 (1·3%)	1 (0·4%)	4 (0·9%)
Number of Patients with at Least One Life threatening TEAE	2 (0·9%)	2 (0·9%)	4 (0·9%)
Number of Patients with at Least One Severe TEAE	20 (8·9%)	13 (5·6%)	33 (7·2%)
Number of Patients with at Least One Suspected Drug-Related AE	31 (13·8%)	34 (14·7%)	65 (14·3%)
Number of Subject Deaths	1 (0·4%)	1 (0·4%)[1]	2 (0·4%)

N= number of patients; TEAE= treatment emergent adverse event; AE= adverse event

[1]This life-threatening event and death documented in the Placebo group did not occur in a study patient, but in the neonate of a male patient (Patient 4309-002). The partner of the patient became pregnant during the study and gave birth to twins prematurely. One of the twin babies died during the study. The life-threatening event and death was recorded in the database under the Placebo group. There were no significant differences in the TEAEs between the Diapep277® treated and the Placebo treated groups by Fisher's exact test.

SUPPLEMENTARY DATA

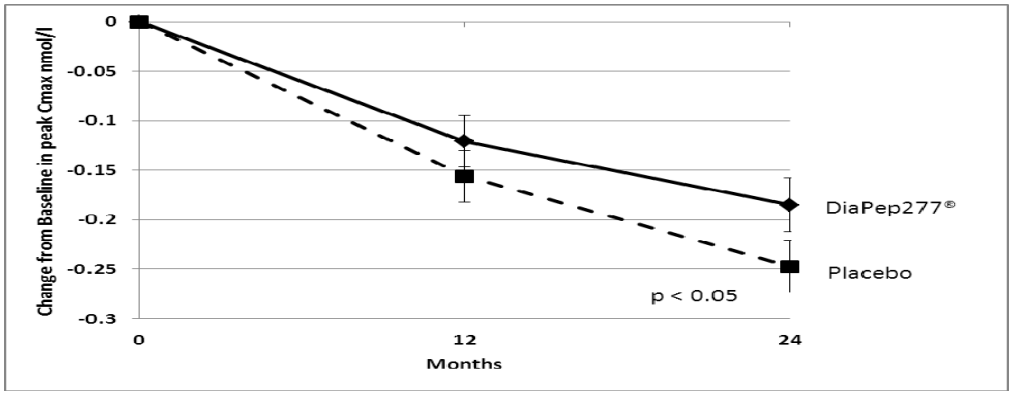
Supplementary Fig 1.



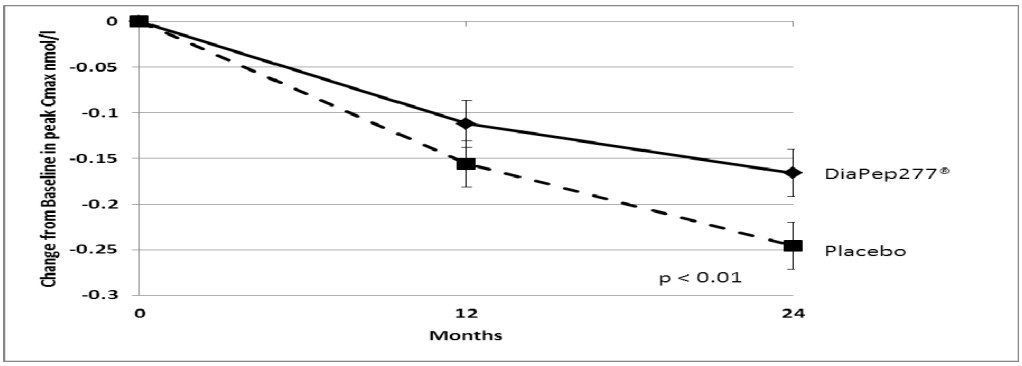
↑ **Application of blinded study medication**

Supplementary Figure 2. Change from Baseline in Glucagon-Stimulated Peak C_{max} Secretion**.**

A



B



Mean changes (± SE of means) in maximum C-peptide concentration (C_{max}) as determined using the 20 min glucagon stimulation test in (A) the mITT population and (B) the PP population. *$P < 0.05$.