ADO09, A Co-Formulation Of Pramlintide (Pram) and Insulin A21G improves Post-Prandial Glucose Vs Novolog® in Type 1 Diabetes (T1DM)

G.Meiffren[1], G.Andersen[2], R.Eloy[1], C.Seroussi[1], C.Mégret[1], S.Famulla[2], Y.-P Chan[1], M.Gaudier[1], O.Soula[1], J.H. DeVries[2],T.Heise[2] ([1] Adocia, Lyon, France ; [2] Profil, Neuss, Germany)

Introduction & Background

- ADO09 (M1Pram) is a co-formulation of pramlintide and insulin A21G developed to leverage the beneficial effects of pramlintide on post-prandial glucose without additional injections

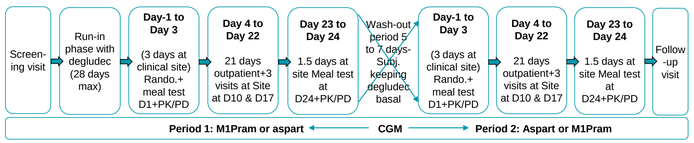
Objective and design

- To compare the effect of M1Pram and insulin aspart (Novolog®, Novo Nordisk) on post-prandial glucose control, glycemic control assessed by CGM and safety/tolerability
- Double-blind, single center, randomized, 2 period cross-over trial comparing pre-meal M1Pram vs aspart over 24 days
- Key endpoints: Mixed meal tolerance test (MMTTs) at day 24 and CGM metrics of 21 T1DM subjects

Methods

- Basal insulin: insulin degludec (Tresiba®, Novo Nordisk) optimized during a run-in phase of 28 days
- Dosing period: 3 inpatient days and 21 outpatient days with 2 interim visits (Figure 1)
- CGM: Dexcom® G6 CGM unblinded to patients from the start of the run-in phase to the end of the trial
- IMP titration: done by subjects, supported by study physicians and a titration guidance
- Statistical Analyses: Comparisons were done with a linear mixed-effect model with treatment, period, and sequence as fixed effects and subject within sequence as random effect, with a significance level of 5%. For endpoints not normally or log-normally distributed, comparisons were done non-parametrically with the Wilcoxon Signed Rank Test

Figure 1: Trial overview



Demographic data

- 34 T1D subjects were screened, 28 randomized, 26 exposed and 22 completed the trial (6 discontinued) (Table 1)

Table 1: Patients' Characteristics (n=28; mean ± SD, unless stated otherwise)

Female/Male (n)	8/20	White race (%)	100
Age (years)	40.4 ± 11.70	HbA1c (%)	7.3 ± 0.77
Weight (kg)	76.7 ± 9.49	C-peptide (nmol/L)	0.06 ± 0.050
Height (cm)	176.7 ± 9.50	Diabetes duration (years)	20.4 ± 12.53

Overall safety

- Both treatments were well tolerated without any treatment-related serious adverse events (Table 2). As expected M1Pram had numerically more, mostly gastrointestinal adverse events than insulin aspart
- No severe hypoglycemia were seen, slightly more hypoglycemic events occurred with M1Pram than with aspart (Table 3)

Table 2: Incidence of adverse events throughout the trial

	M1Pram (N=25)	Aspart (N=23)
	Number of Subjects (%) / Number of Events	
Adverse Events	20 (80 %) / 47	10 (43 %) / 23
Moderate and Severe Adverse Events	7 (28 %) / 8	2 (8 %) / 3
Drug Related* Adverse Events **Possible or probable, as assessed by the Investigator*	14 (56 %) / 34	4 (17 %) / 9
Serious Adverse Event (unlikely related)	1 (4%) / 1	0
Drug Related Adverse Events leading to permanent Discontinuation of Study Drug	2 (8 %)	0

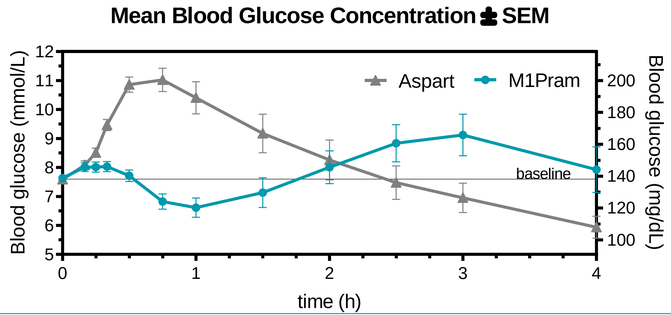
Table 3: Incidence of hypoglycemic events during the outpatient period

Category	M1Pram (N=25)	Aspart (N=23)
	Number of Subjects (%) / Number of Events	
Overall	21 (84 %) / 142	18 (78 %) / 115
Daytime (6:00 am to 11:59 pm)	19 (76 %) / 117	18 (79 %) / 109
At night (midnight to 05:59 am)	15 (60 %) / 25	5 (21 %) / 6

Meal Test - Plasma Glucose

- Incremental plasma glucose AUCs on day 24 were reduced by >100% after 1h and 2h (both p<0.001) and by 39% after 4h with M1Pram vs aspart (Figure 2)
- Similarly, ΔPGmax was reduced by 19 mg/dL (p=0.01) and ΔPG_1h by 70 mg/dL (p<0.001) (Figure 2)

Figure 2: M1Pram improves post prandial glucose control



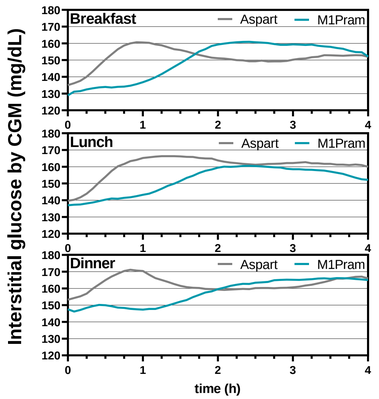
Outpatient period results - CGM metrics

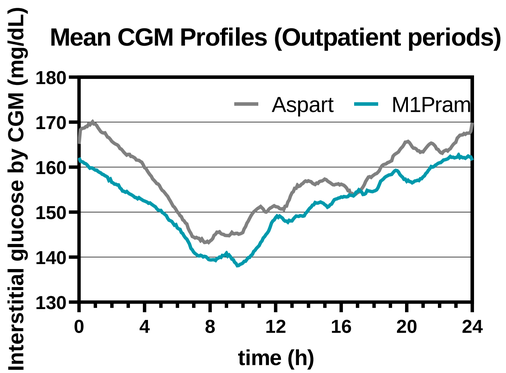
- Most of the CGM metrics (TiR [70-180], TiR [80-140], mean blood glucose per day), were significantly improved with M1Pram (Table 4). Postprandial and mean 24-hour glucose profiles were improved with M1Pram (Fig. 3)

Table 4: CGM metrics, all days. Significant differences are marked in bold

Parameter	Treatment	LS Mean	Ratio of LSMean* M1Pram / Aspart (95% CI)	Difference (M1Pram-Aspart)	P-value
TIR [70-180 mg/dL] (h)	M1Pram (N=24)	16.50	1.05 (1.01;1.10)	**+51 mins**	**0.0134**
	Aspart (N=22)	15.65			
TIR [80-140 mg/dL] (h)	M1Pram (N=24)	9.66	1.14 (1.06;1.22)	**+70 mins**	**0.0017**
	Aspart (N=22)	8.50			
Time < 70 mg/dL (h)	M1Pram (N=24)	0.69	1.31 (1.00;1.72)	**+10 mins**	**0.0464**
	Aspart (N=22)	0.53			
Time < 54 mg/dL (h)	M1Pram (N=24)	0.15	1.06 (0.65;2.15)	<1 min	0.8045
	Aspart (N=22)	0.14			
Mean BG per Day (mg/dL)	M1Pram (N=24)	149.98	0.95 (0.93;0.97)	**-8.19 mg/dL**	**0.0001**
	Aspart (N=22)	158.17			

Figure 3: Mean CGM during outpatient days at mealtime (0-4h) and over 24h





Insulin dose & body weight

- On the last outpatient day, mean daily bolus doses were 4 U lower (-18%, p<0.0001) with M1Pram compared to aspart. No change in basal insulin dose was allowed after run-in period per protocol
- M1Pram induced a 0.7 kg weight loss from beginning to the end of the 23-day treatment period (p=0.01). No significant change was seen with aspart (p=0.96)

Conclusion: ADO09 (M1Pram) combines the established characteristics of pramlintide and insulin in one injection. In this short-term trial ADO09 was well-tolerated and significantly improved postprandial glucose in a test meal and CGM-metrics including TiR and mean glucose in an outpatient setting with lower prandial insulin doses compared to aspart and significant weight loss.

This study was sponsored by Adocia and performed by Profil

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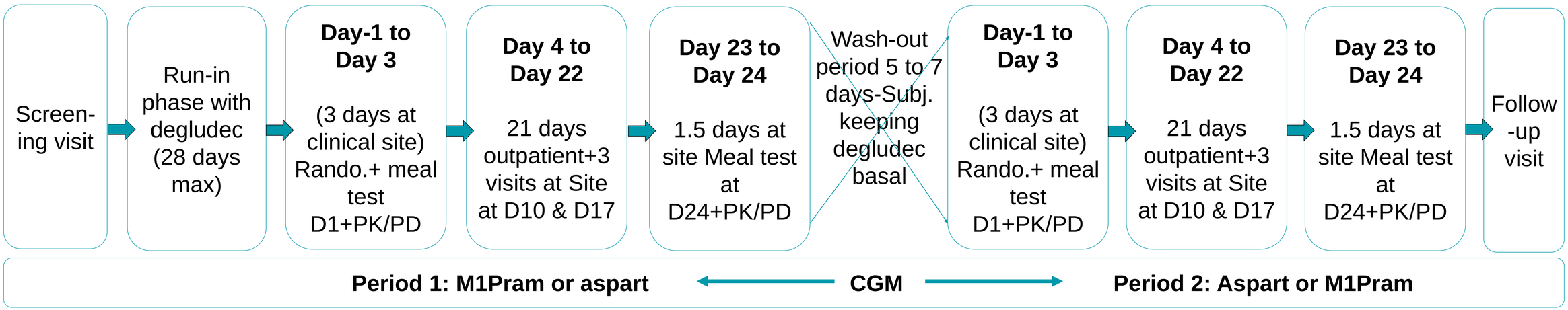

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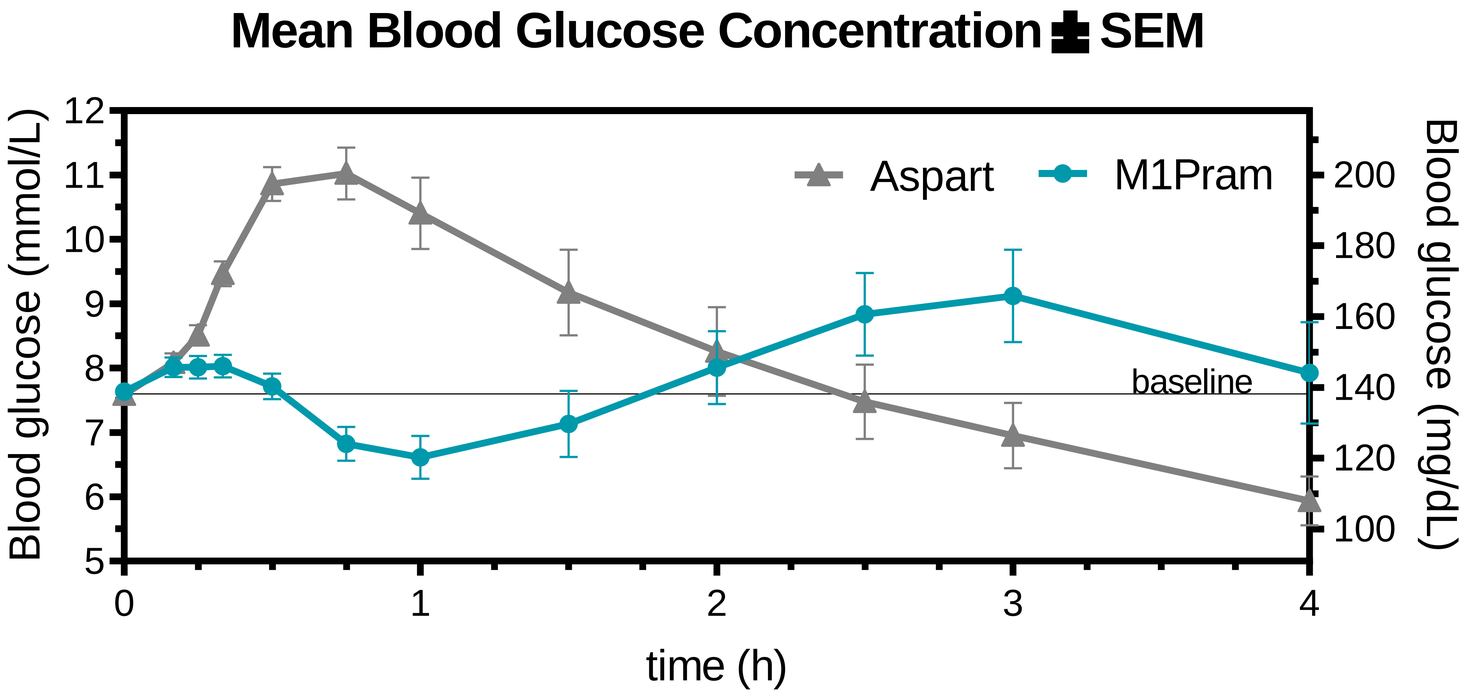

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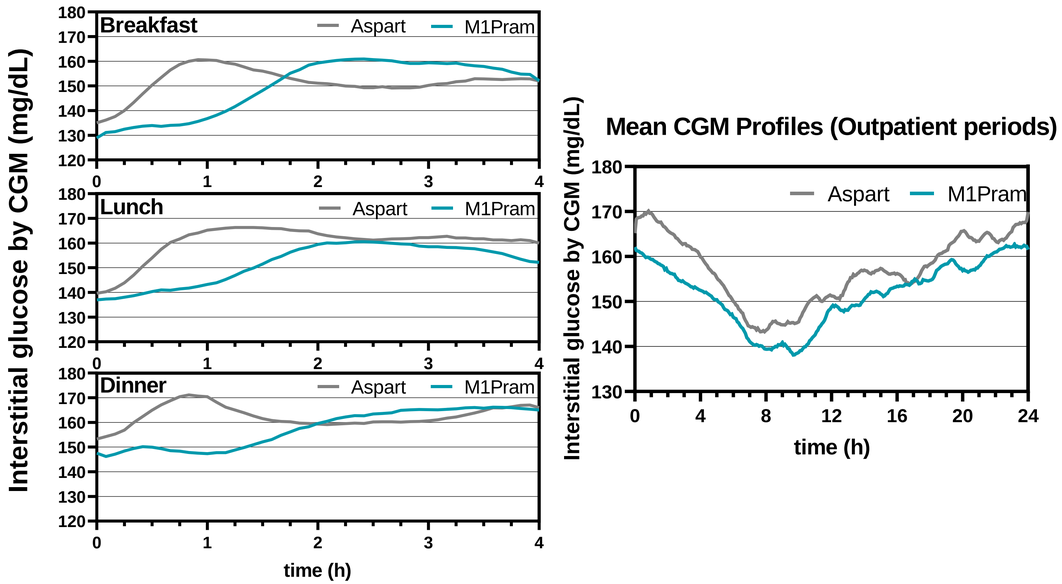

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