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ADO09, A Co-Formulation of the Amylin-Analog Pramlintide and the A21G Human Insulin Analog, Lowers Postprandial Blood Glucose versus Insulin Lispro in Type 1 Diabetes (T1D)

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Introduction & Background

- Pramlintide, a prandial treatment used as an adjunct to intensive insulin therapy, improves postprandial blood glucose (ppBG) through delaying gastric emptying, reducing nutrient-stimulated glucagon secretion, and promoting satiety. So far, pramlintide and insulin had to be injected separately as combination in one pharmaceutical formulation has not been possible.
- ADO09 is the first co-formulation of pramlintide and a rapid-acting insulin analog (A21G human insulin analog) which is stable at pH 4.

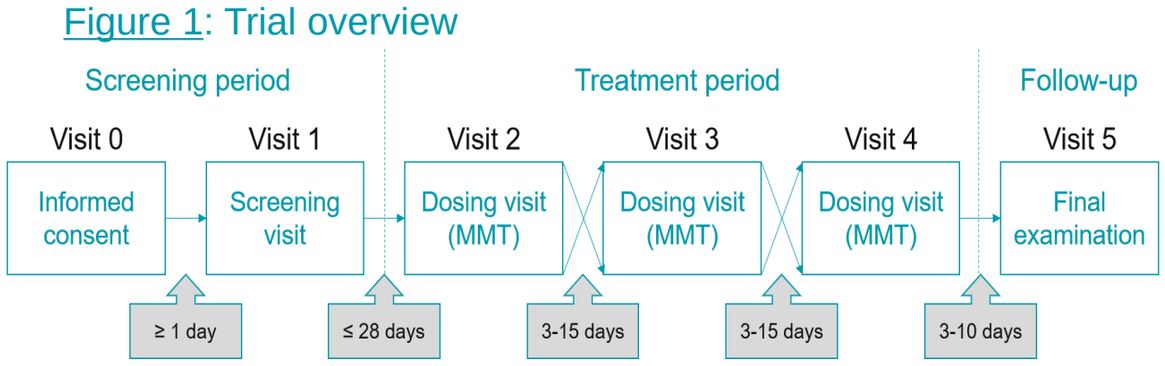
Aims of the study

- This randomized, double-blind, double-dummy, cross-over trial compared the safety, pharmacokinetics and pharmacodynamics of ADO09 with those of insulin lispro (LIS) and those of the separate injections of human insulin and pramlintide (Ins&Pram) in a meal test in 24 patients with T1D (Figure1).

Methods

- At three dosing visits, participants received ADO09, Ins&Pram and LIS immediately before eating a standardised mixed meal (618 kcal, 53% carbohydrate, 19% protein, 26% fat, 2% fibers) and 1g paracetamol to evaluate the kinetics of gastric emptying. The insulin dose was 7.5 U and the pramlintide dose 45µg.
- Prandial insulin was washed-out before dosing visits. Baseline glucose was controlled at 126mg/dL ± 10%. Meal ingestion started immediately after dosing and had to be completed in less than 15 mins.

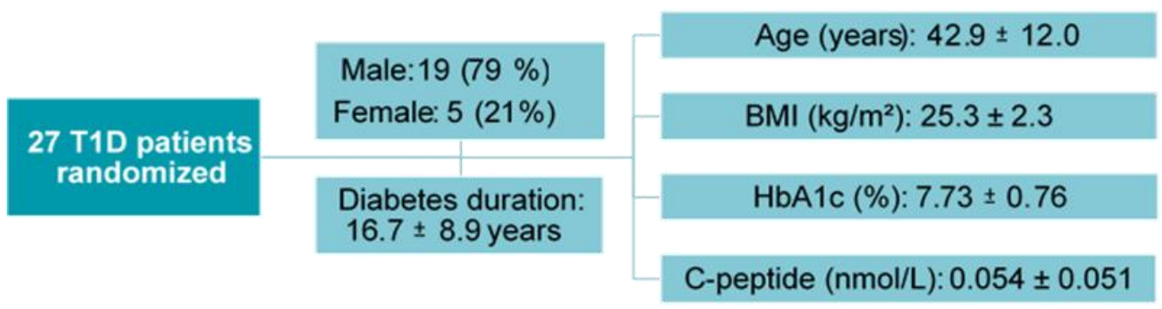
Figure 1: Trial overview



Demographic data

- Out of 27 subjects screened, 24 were randomised & exposed and 23 completed the trial (1 withdrawal) (Figure 2).

Figure 2: Characteristics of the study population (mean±SD)



Safety

- All treatments were well tolerated and both, adverse events (3 with ADO09, 2 with Ins&Pram) and hypoglycaemic events (2 each with ADO09 and Ins& Pram), were rare during the meal test procedures.

Results

Postprandial Blood Glucose Response

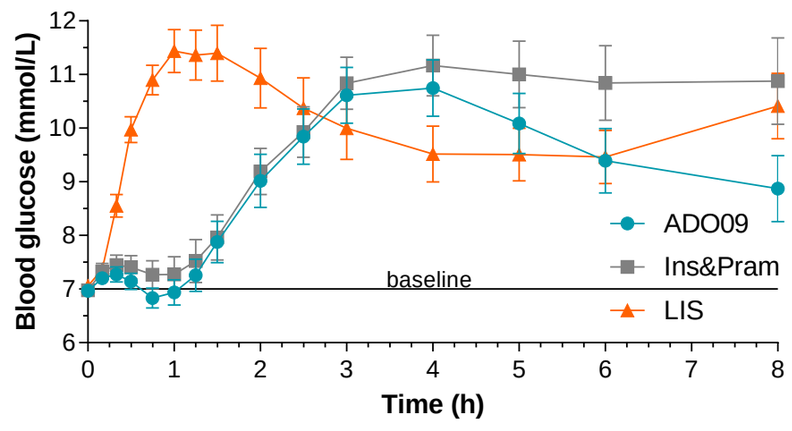
- Compared with LIS, ADO09 reduced ppBG excursions by more than 95% over the first hour ($p<0.0001$), by 85% over 2h ($p<0.0001$) and 41% over 4h ($p=0.0052$) (Table 1 & Figure 3)

Table 1: incremental AUC blood glucose least square means ratios

	ΔAUC 0-1h	ΔAUC 0-2h	ΔAUC 0-4h	ΔAUC 0-8h
Vs. Ins&Pram	NS	NS	NS	NS
Vs. LIS	0.033 p<0.0001	0.149 P<0.0001	0.589 p=0.0052	NS

LSM ratio and p-value for ADO09 vs. comparators

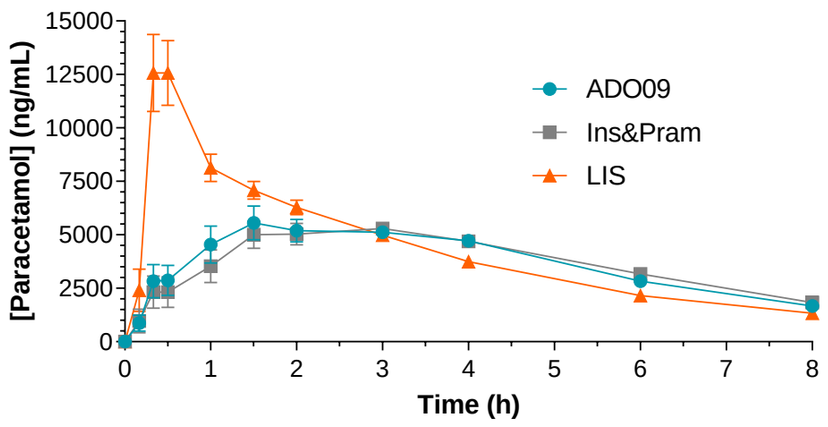
Figure 3: Mean ± SD blood glucose profiles



Gastric Emptying

Paracetamol oral absorption was used as a surrogate marker of gastric emptying kinetics. With ADO09, gastric emptying was significantly slower than with LIS ($t_{max\_paracetamol}$ 2.30±1.49 h vs 0.76±0.73 h, $p<0.0001$) (Figure 4).

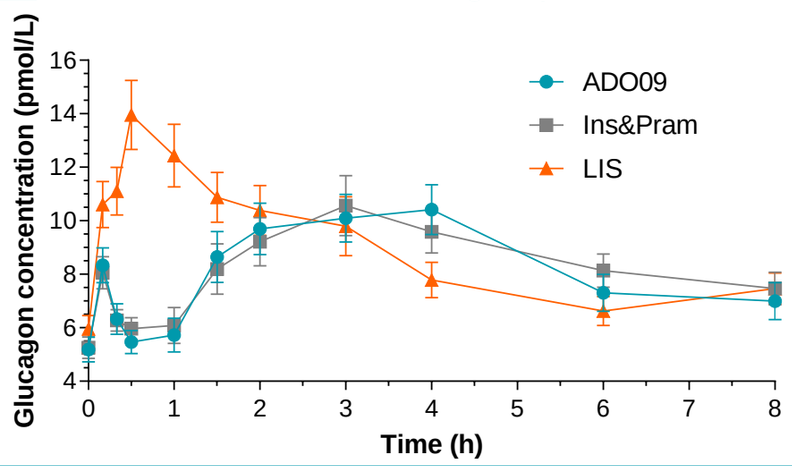
Figure 4: Mean ± SD Oral paracetamol PK profiles



Glucagonemia

Endogenous glucagon secretion was reduced with ADO09 compared to LIS ($\Delta AUC_{glucagon\_0\text{-}2h}$ 4.1±2.8 vs 11.8±6.2 pmol*h/L, $p<0.0001$) (Figure 5).

Figure 5: Mean ± SD blood Glucagon profiles



Conclusions

ADO09 was well tolerated, had similar effects on gastric emptying and glucagon secretion as separate injections of human insulin and pramlintide, and markedly reduced ppBG over 0-4 h compared to insulin lispro.

This study was sponsored by Adocia and performed by Profil
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