DA-1241 a novel GPR119 Agonist: Data on Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) from Part 2 of a Phase 1b Multiple Ascending Dose (MAD) Study in Patients with Type 2 Diabetes Mellitus (T2DM)

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81st Scientific Sessions of American Diabetes Association, Jun 25-29, 2021: 765-P

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Disclosures

Mi-Kyung Kim, Dae Young Lee, and Jiyoon Jeong are employees of *Dong-A ST*, Seoul, Republic of Korea

Bridgette Franey, Michael Grimm, and Marcus Hompesch are employees of *ProSciento*, Chula Vista, CA, USA

Background

DA-1241 is a small, novel, chemically synthesized, potent molecule, and a selective agonist for GPR119. It has been reported that GPR119 *stimulates glucose-dependent insulin secretion* in the pancreatic beta cells which makes GPR119 a promising drug target for controlling glucose levels with little to no risk of hypoglycemia. Data from pre-clinical studies showed that DA-1241 efficiently lowered both blood glucose and lipid levels simultaneously. These data suggest that DA-1241 has enhanced intrinsic efficacy in glycemic control compared to other GPR119 investigational drugs; DA-1241 may therefore have therapeutic potential for patients with T2DM and dyslipidemia. DA-1241 in combination with other oral anti-diabetics may be more effective in glucose control relative to each treatment alone.

Part 1 of this study showed that DA-1241 is well-tolerated in healthy volunteers. It also generated a favorable pharmacokinetic profile. The present study (Part 2) extends the safety, tolerability, pharmacokinetic, and pharmacodynamic assessment of DA-1241 to T2DM patients.

DA-1241 Multiple Ascending Dose data in healthy volunteers is presented in poster 766-P

Objectives and Endpoints

PRIMARYY OBJECTIVE:

(a) The primary objective of this study was to assess safety and tolerability of multiple once daily oral doses of DA-1241 versus placebo and Sitagliptin in T2DM.

SECONDARY OBJECTIVES:

(b) To establish PK and characteristics in the target population.

- C_{max}, t_{max}, C_{trough}, AUC overdosing interval ($AUC_{0\text{-}tau}$), accumulation ratio (AUC_{tau} Day 56/AUC_{tau} Day 1).

(c) To assess PD characteristics after MADs of DA-1241, compared with sitagliptin and placebo.

- Glucose-stimulated metabolic biomarkers*, as assessed by a Mixed Meal Tolerance Test (MMTT) with total and incremental areas under the effect (AUEs; e.g., AUE0-240 min, AUE0-30 min, and AUE0-60 min) for the following parameters:

*Plasma glucose, Insulin, Glucagon (GCG), C-peptide, total and active GLP-1, GIP, Free fatty acids (FFA), Peptide tyrosine-tyrosine (PYY).

Methods: Cohorts, Doses and Schedule of Events

COHORTS

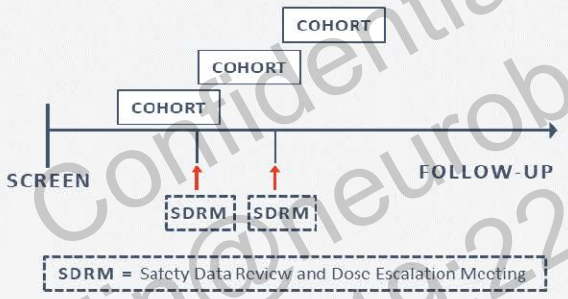
DA-1241
n=15

PLACEBO
n=5

SITAGLIPTIN
n=5

In three sequential cohorts for each DA-1241 dose, 25 subjects in each cohort were randomized (3:1:1) to receive DA-1241, placebo or Sitagliptin.

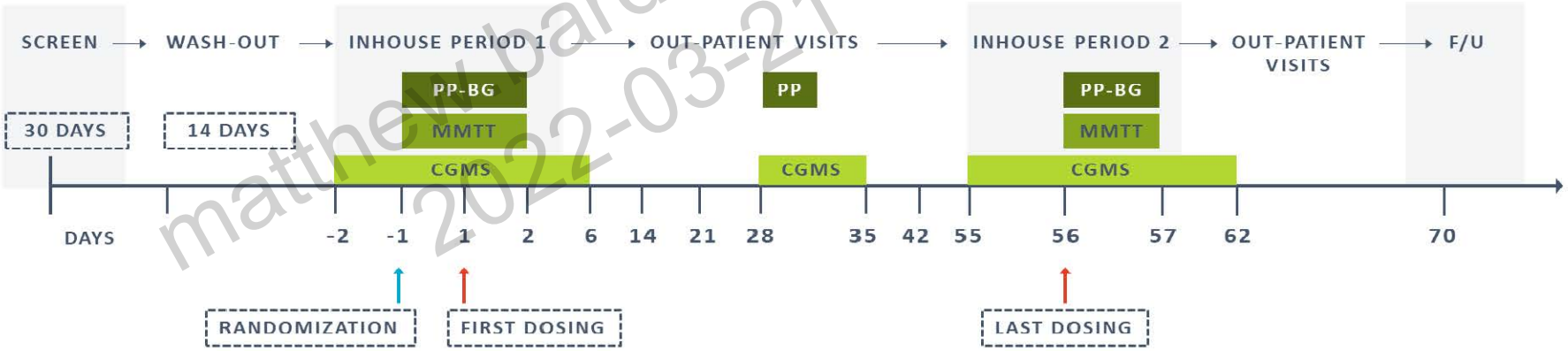
Safety data reviews and dose escalation decisions between cohorts took place after at least of 16 subjects of an ongoing cohort had completed procedures through day 14.



DA-1241 DOSE

25 mg
or
50 mg
or
100 mg

single daily oral doses
(56 days)



Abbreviations: BG: Blood Glucose; CGMS: Continuous Glucose Measurement System; MMTT: Mixed Meal Tolerance Test; PP: Post-Prandial; F/U: Follow-Up Visit

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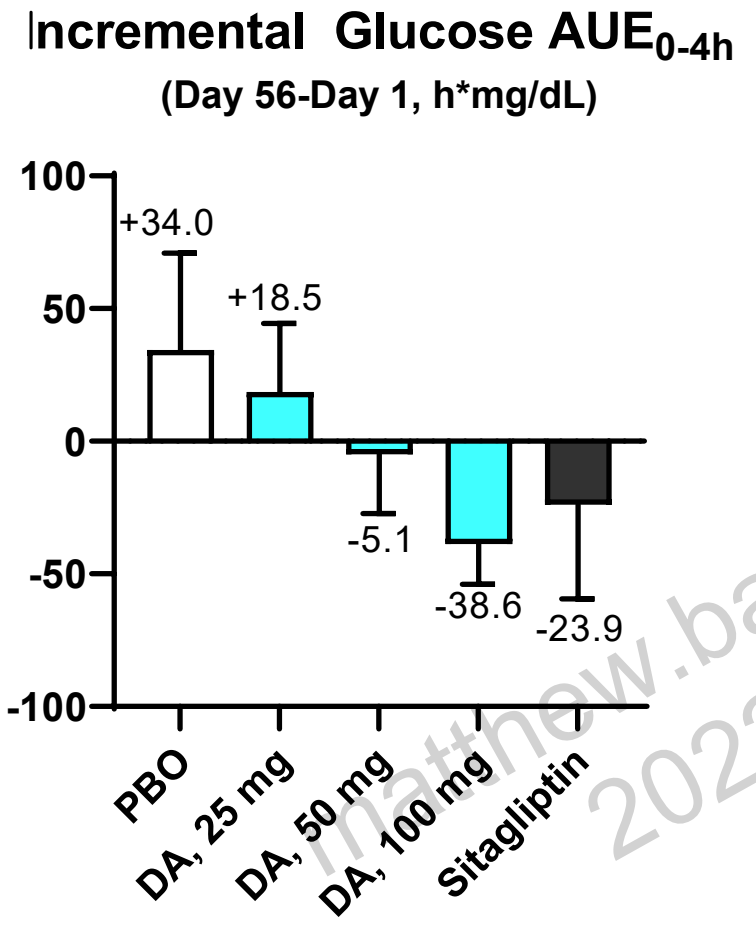
Results: Tolerability & PK

83	PBO	DA-1241			Sitagliptin
		25 mg	50 mg	100 mg	
N	19	13	19	15	17

- 84 subjects were enrolled, and 83 subjects were dosed in Part 2, 3 subjects were withdrawn due to TEAEs (1 active, 2 placebo), 72 subjects completed the study.
- There were no relevant demographic imbalances. In the overall study population, 44 (53%) subjects were male, and mean (SD) age was 56.8 (7.27) years.
- Most of the subjects (63 subjects, 75.9%) identified as White. Subjects predominantly identified as Hispanic or Latino (59 subjects, 71.1%).
- Mean (SD) BMI was 29.40 (3.269) kg/m^2.
- Doses tested were generally safe and well tolerated. The most frequent TEAEs were mild GI side effects (nausea, diarrhea, abdominal pain), all resolved spontaneously.
- Day 56 PK C_{max} and $AUC_{0\text{-}tau}$ parameters were dose proportional.

Results: Glucose Control



- On day 56 MMTTs Glucose $AUE_{0\text{-}4h}$ had decreased in a dose-dependently compared to baseline.
- MMTTs Glucose $AUE_{0\text{-}4h}$ correlated positively with CGMS $AUE_{0\text{-}4h}$ ($r=0.6854$, $p<0.05$) and HbA1c ($r=0.6260$, $p<0.05$).
- Based on the relatively small sample size of this exploratory study the differences observed did not reach statistical significance.

Results: Glucose Control

- Fasting plasma glucose trended towards improvement for all DA-1241 doses.
- Multiple parameters from continuous glucose monitoring (CGM), trended towards improvement for all DA-1241 doses; especially time spent at BG < 180 mg/dL and glucose $AUE_{0\text{-}24h}$.
- After 8-week treatment, HbA1c trended towards improvement across dosing groups, as did body weight.
- Based on the small sample size of this exploratory study the observed differences did not reach statistical significance.

Analysis Visit, Mean (SD)	DA-1241 25 mg	DA-1241 50 mg	DA-1241 100 mg	Sitagliptin 100 mg	Placebo
Fasting Plasma Glucose (mg/dL)					
Baseline	153.2 (19.63)	157.4 (38.95)	150.9 (33.95)	158.8 (23.12)	142.6 (28.53)
Change from Baseline to Day 56	**-3.6** (27.13)	**-21.1** (42.93)	**-3.8** (28.10)	**-10.7** (20.53)	**5.8** (34.17)
Hemoglobin A1C/Hemoglobin (%)					
Baseline	7.96 (0.840)	7.79 (1.123)	7.61 (1.060)	7.81 (0.735)	7.75 (0.728)
Change from Baseline to Day 56	**-0.59** (0.672)	**-0.32** (0.865)	**-0.39** (0.302)	**-0.62** (0.458)	**-0.26** (0.608)
Time at BG > 180 mg/dL (%)					
Baseline	55.82 (28.668)	44.91 (36.360)	35.62 (31.542)	51.36 (28.764)	41.51 (24.986)
Change from Baseline to Day 56	**-13.33** (29.597)	**-10.78** (21.646)	**-7.35** (18.491)	**-12.38** (27.920)	**6.96** (30.519)
Weight (kg)					
Baseline	79.004(11.6125)	81.772 (10.3253)	75.009 (14.5580)	82.565 (15.5437)	84.061 (15.4321)
Change from Baseline to Day 56	**-0.500** (1.1438)	**-0.417** (1.2022)	**-1.569** (1.5217)	**-0.237** (1.0775)	**-0.206** (1.9007)

Results: Target-Related Biomarkers

Hormone		AUE_{0-4h} (pmol h/L)	PBO	DA-1241			Sita
				25 mg	50 mg	100 mg	100 mg
N			16	12	15	15	14
tGLP-1	D-1	Mean	73.48	60.44	75.65	95.55	83.32
		SE	8.31	5.45	4.16	15.04	11.38
	D56	Mean	74.96	74.64	87.01	104.50	50.66
		SE	8.29	5.15	5.40	15.61	5.38
	CFB	**Mean**	**+0.43**	**+14.83**	**+11.44**	**+8.95**	**-17.29**
tGIP	D-1	Mean	278.05	329.47	319.03	406.96	389.34
		SE	18.65	37.10	25.28	35.44	43.86
	D56	Mean	275.50	372.33	352.29	437.84	262.75
		SE	21.71	36.64	26.86	32.38	24.91
	CFB	**Mean**	**+5.57**	**+60.88**	**+40.59**	**+30.88**	**-110.47**
tPYY	D-1	Mean	97.11	95.04	114.98	114.40	117.61
		SE	10.25	8.64	11.49	10.41	17.13
	D56	Mean	108.11	124.84	158.00	135.16	60.73
		SE	11.53	11.22	20.92	11.27	6.17
	CFB	**Mean**	**+8.38**	**+27.53**	**+38.14**	**+20.76**	**-34.75**

Abbreviations: CFB, change from baseline

- Secretion of GIP, GLP-1 and PYY were increased at day 56 in DA-1241-treated groups, consistent with the mechanism of action of DA-1241.
- Sitagliptin treatment lowered plasma total GIP, GLP-1 and PYY levels most likely due to a negative feedback loop.

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Conclusions

This phase 1b study in T2DM showed favorable safety, tolerability and PK profiles of DA-1241 administered daily over a period of 56 days, compared to placebo or sitagliptin in the target population of subjects with T2DM on metformin monotherapy.

Biomarkers and PD data support the hypothesized mechanism of action and showed favorable efficacy data trends.

Data presented here supports further progressing the DA-1241 clinical development program.

DA-1241 Multiple Ascending Dose data in healthy volunteers is presented in poster 766-P