DA-1241 a novel GPR119 Agonist: Data on Safety, Tolerability and Pharmacokinetics (PK), from Part 1 of a Phase 1b Multiple Ascending Dose (MAD) Study in Healthy Volunteers (HV)

Mi-Kyung Kim[1], Dae Young Lee[1], Jiyoon Jeong[1], Bridgette Franey[2], Michael Grimm[2], Marcus Hompesch[2]

1.Dong-A ST, Seoul, Republic of Korea 2. ProSciento, Chula Vista, CA, USA

81st Scientific Sessions of American Diabetes Association,
Jun 25-29, 2021: 766-P

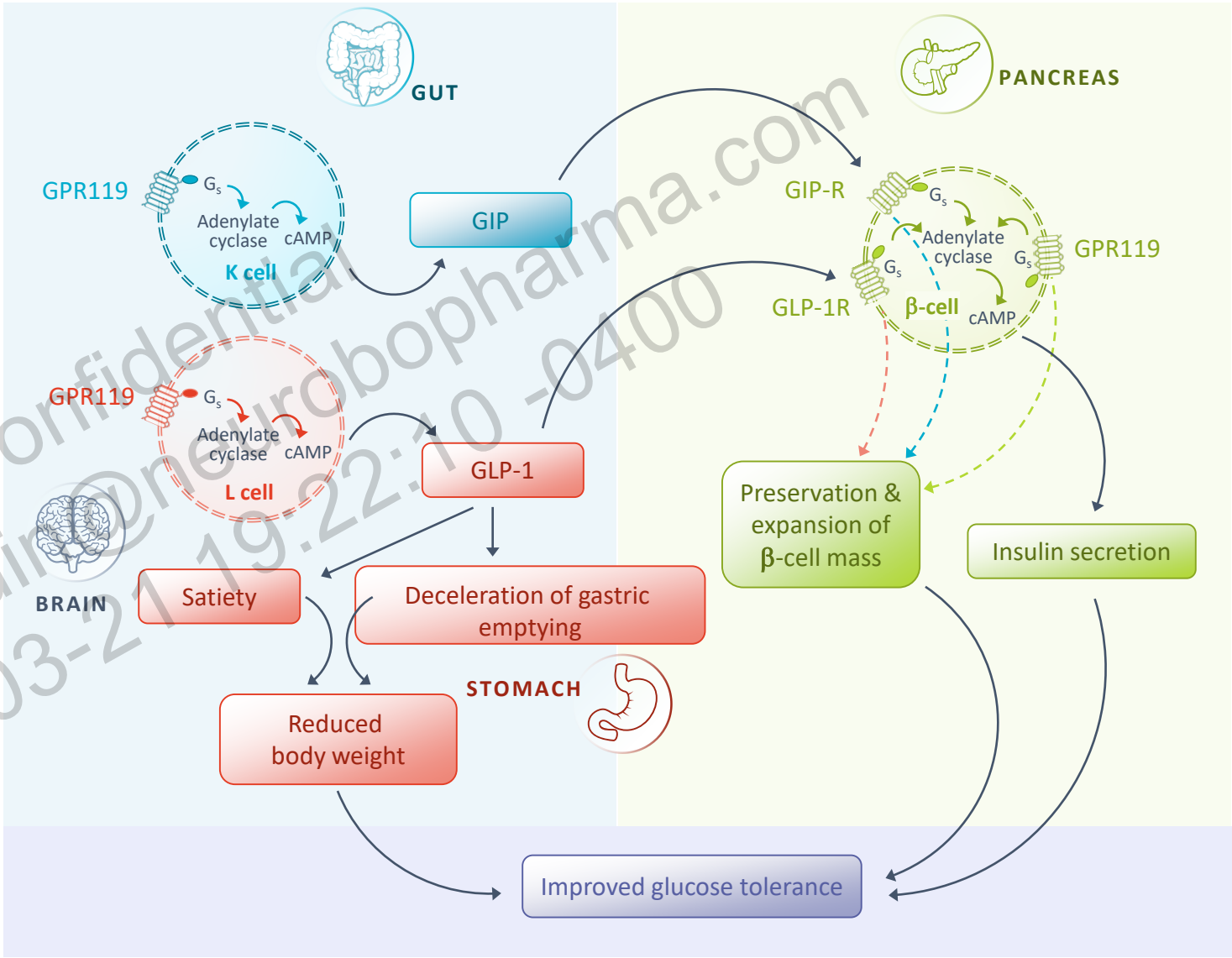
DONG-A ST prosciento ADVISE • ADVANCE • ACHIEVE

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

- G protein-coupled receptor 119 (GPR119) is expressed on intestinal L cells and pancreatic β-cells.
- In pancreatic β-cells, the activation of GPR119 by endogenous ligands causes the induction of glucose-dependent insulin secretion and stimulates the intestinal secretion of incretins (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic peptide [GIP]).
- The stimulation of GLP-1 and GIP causes inhibition of hepatic lipogenesis, which could potentially prevent hepatic steatosis.



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 no risk of hypoglycemia. Data from *pre-clinical studies showed* that *DA-1241 efficiently lowered both blood glucose and lipid levels*. These data suggest that DA-1241 has enhanced intrinsic efficacy in glycemic control compared to other GPR119 investigational drugs; DA-1241 may 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.

The present study generated safety, tolerability, pharmacokinetic, and pharmacodynamic data for DA-1241 in healthy volunteers. Data presented here support the further evaluation of DA-1241 in T2DM patients.

Data from DA-1241 Multiple Ascending Dose in T2DM patients is presented in poster 765-P

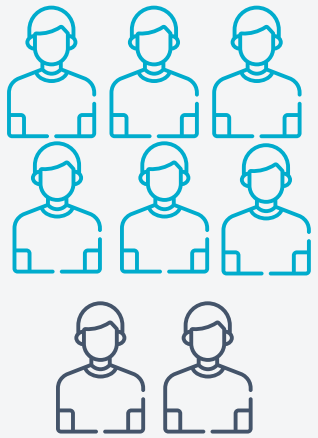
Objectives and Endpoints

- **To assess safety and tolerability of DA-1241 after Multiple Ascending Dose (MAD), in healthy male subjects.**
- **DA-1241 was to be assessed at three different dose levels: 50mg, 100mg, and 200mg.**
- **To assess the PK profile in plasma and urine after MADs of DA-1241.**
  - **C_{max}, t_{max}, C_{trough}, $AUC_{0\text{-}tau}$, k_e, $t_{1/2}$**, apparent clearance (**CL/F**), apparent volume of distribution at terminal phase (**V_z/F**), accumulation ratio (**AUC_{tau} Day 28/AUC_{tau} Day 1**).
  - Drug excreted into urine (**A_e**), cumulative A_e (**CumA_e**), fraction of drug excretion into urine (%) (**F_e**), cumulative F_e (**CumF_e**), renal clearance (**CL_R**).
- **To assess the PD profile after MADs of DA-1241.**
  - Fasting Plasma Glucose (**FPG**)
  - Total area under the glucose measurements versus (vs) time curve (**AUE**) over *24 hours after dosing* (i.e., **$AUE_{0\text{-}24h}$**)
  - Total and incremental AUE over *4 hours after lunch* (i.e., **$AUE_{0\text{-}4h}$**)
  - Total weighted mean glucose (**WMG**) over 24 hours after dosing (i.e., **24h-WMG**)
  - Total and incremental WMG over 4 hours after lunch (i.e., **4h-WMG**)

Methods: Cohorts and DA-1241 Doses

Double-blind, placebo-controlled, single-center study of DA-1241 in Healthy Male Volunteers.

COHORTS



In three sequential cohorts for each DA-1241 dose, 8 subjects in each cohort were randomized (3:1) to receive DA-1241 or placebo.

DA-1241 DOSE

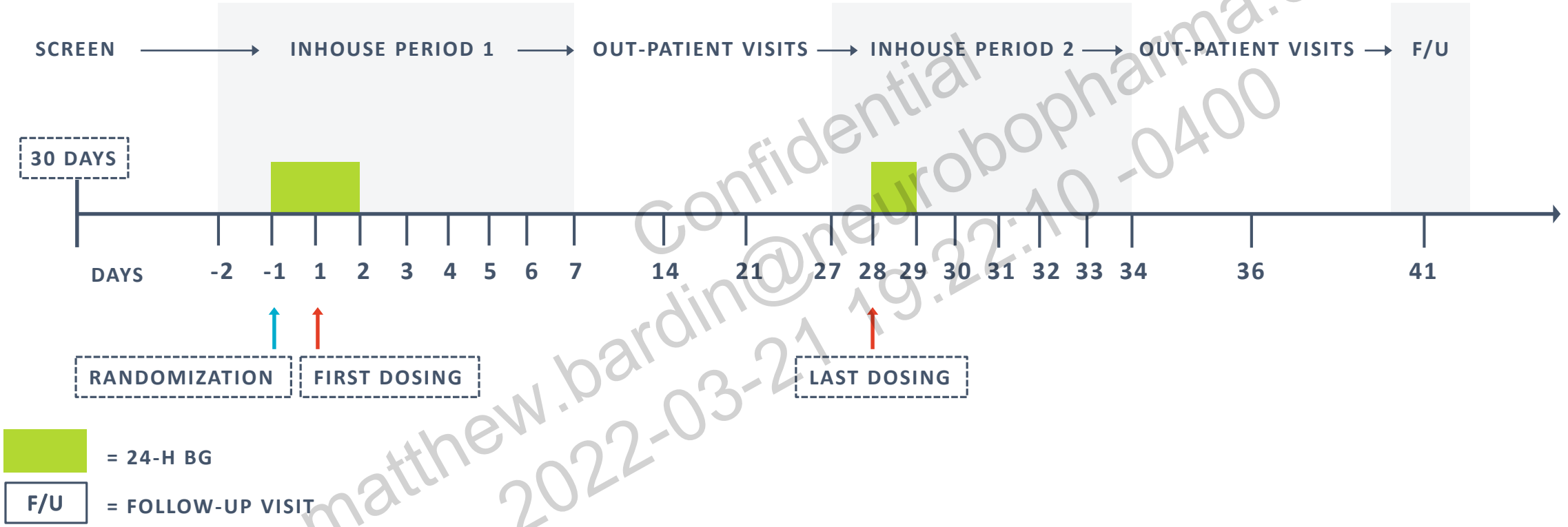
50 mg
or
100 mg
or
200 mg

single daily oral doses (28 days)

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

DA-1241 PLACEBO

Methods: Schedule



Abbreviations:
BG: Blood Glucose; F/U: Follow-Up Visit

DONG-A ST prosciento ADVISE • ADVANCE • ACHIEVE

Results

Safety and Tolerability

24 male subjects participated in this study.

Age 38.4 ± 10.7, BMI 26.0 ± 2.7

All doses tested were safe and well tolerated.

- No SAEs and no discontinuations due to AE
- TEAEs related to study drug per Investigator's assessment by System Organ Class: nervous system disorders (headache and somnolence), general disorders and administration site conditions (fatigue), metabolism and nutrition disorders (hypoglycemia), and skin and subcutaneous tissue disorders (cold sweat)
- No obvious relationship between frequency of TEAEs and dose of DA-1241
- Hypoglycemia was rare and not dose related
- All TEAE's were mild with no obvious dose relation and resolved spontaneously.

Pharmacokinetics Parameters on Day 28 in HVs

- C_{max} and $AUC_{0\text{-}tau}$ PK parameters showed dose proportional characteristics across the tested dose range.

DA-1241 Dose	C_{max} ng/mL	$AUC_{0\text{-}\tau}$ h*ng/mL	T_{max} hours	$t_{1/2}$ hours
50 mg	464.9 ± 284.1	5168.4 ± 1651.2	2.9 ± 1.8	590 ± 370
100 mg	569.3 ± 173.2	7620.0 ± 1837.7	2.3 ± 1.2	368 ± 355
200 mg	1653.2 ± 615.4	19167 ± 9088.8	1.9 ± 0.6	537 ± 395

Abbreviations: SAE: Serious Adverse Event; **AE**: Adverse Event

Conclusions

Data from this phase 1b study in Healthy Volunteers confirmed a favorable safety, tolerability and PK profile of DA-1241 administered daily over a period of 28 days.

Data supported a progression of the clinical development program into Type 2 Diabetes (T2DM) patients.

DA-1241 Multiple Ascending Dose in T2DM patients is presented in poster 765-P