Safety, tolerability, and clinical effects of dapiglutide, a once-weekly GLP-1R/GLP-2R agonist

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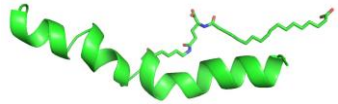
Disclosures

- Received **research funds** from Adocia, Afon Technology, Astra Zeneca, Altimmune, Betagenon, Biocon, Bioton, Cass Pharmaceuticals, Civica Foundation, Corteria, Cytoki, Eli Lilly, Enyo Pharma, Gan&Lee Pharmaceuticals, Genova, Nanexa, Neodyne, Novo Nordisk, SamChunDang Pharm. Co., Spiden, Sun Pharma and Zealand Pharma.
- Received **speaker honoraria** from Eli Lilly and Novo Nordisk.
- **Consultant** to Gan&Lee Pharmaceuticals.

Dapiglutide (GLP-1/GLP-2): Potential first-in-class targeting obesity and low-grade inflammation



Design of the molecule

Dapiglutide is derived from a 33-amino acid GLP-2 peptide backbone with amino acid substitutions to 'dial in' GLP-1R activity

GLP-1 component reduces body weight and **GLP-2** has potential for additional **anti-inflammatory effects**[1]

Designed with **higher potency towards the GLP-1R** while retaining activity on the GLP-2R[2]

Long-acting with a half-life (123–129 hours) that is suitable for **once-weekly administration**[3]

Strong scientific rationale to be validated in clinical trials

People with **obesity** have increased **low-grade inflammation**, which drives several comorbidities

Potential for complementary **anti-inflammatory effects** from GLP-1 agonism and GLP-2 agonism

Sources: 1. Drucker & Yusta. Annu Rev Physiol 2014;76:561–583; 2. Reiner et al. JPEN J Parenter Enteral Nutr 2022;46(5):1107–1118; 3. Data presented by Agersnap at the 82nd ADA Scientific Sessions, June 3–7, 2022. GLP-1=glucagon-like peptide-1; GLP-1R=glucagon-like peptide-1 receptor; GLP-2=glucagon-like peptide-2; GLP-2R=glucagon-like peptide-2 receptor; MASH=metabolic dysfunction-associated steatohepatitis (formerly, non-alcoholic steatohepatitis, or NASH). **Intellectual property**: Composition of matter, patent expiry in 2037. Patent-term extension up to 5 years, i.e. 2042. Potential rights beyond 2042 based on patent applications and additional elements.

Objectives: Dapiglutide Phase 1b MAD – part 1

1

Primary objective

- To evaluate the **safety and tolerability** of dapiglutide administered as multiple SC injections in overweight and obese, but otherwise healthy subjects in order to identify the maximum tolerated dose with the applied dose up-titration regimen

Primary endpoint

- Incidence of TEAEs

2

Secondary and exploratory objectives

- To **investigate the PK properties** of dapiglutide after multiple up-titrated SC doses
- To **assess the PD response** to SC administration of dapiglutide

Secondary and exploratory endpoints

- PK and PD parameters

Source: ClinicalTrials.gov (NCT06000891), accessed March 2025.
MAD=multiple ascending dose; PD=pharmacodynamic; PK=pharmacokinetic; SC=subcutaneous; TEAEs=treatment-emergent adverse events.

Trial design: Dapiglutide Phase 1b MAD – part 1

A randomized, double-blind, placebo-controlled, Phase 1b, MAD trial of dapiglutide[1]

No lifestyle modifications, such as counselling on diet and exercise

- Adults 18–64 years
- BMI 27.0–39.9 kg/m^2
- HbA1c <6.5%

Part 1
Dose escalation every 2 weeks

R **14:4 dapiglutide versus placebo (randomized within cohort)**

N **N=54, Part 1: 3 cohorts[a]**

- 2.5 → 5 → 7.5 → 10 → 13 mg (5 weeks)
- 2.5 → 5 → 7.5 → 10 mg (7 weeks)
- 2.5 → 5 → 7.5 mg (9 weeks)

13 weeks treatment + 6 weeks follow-up

Randomization — Time (weeks) — 13 — Safety follow-up — 19

Part 2
Dose escalation every 4 weeks

Up to 26 mg with 28 weeks treatment ▶▶▶

[a]Safety evaluation occurred after 2 weeks of treatment at the target dose for each cohort; initiation of the next, higher dose cohort only occurred following safety evaluation for the previous cohort.[2] Sources: 1. ClinicalTrials.gov (NCT06000891), accessed March 2025; 2. Data on file. BMI=body mass index; HbA1c=glycated hemoglobin; MAD=multiple ascending dose; SC=subcutaneous.

Demographics and clinical characteristics

Dapiglutide Phase 1b MAD trial – baseline characteristics[1,2]

	Placebo (N=12)	Dapiglutide 7.5 mg (N=14)	Dapiglutide 10 mg (N=14)	Dapiglutide 13 mg (N=14)	Total (N=54)
Male sex, n (%)	10 (83%)	13 (93%)	10 (71%)	13 (93%)	**46 (85%)**
Age (years), mean (min–max)	54 (26–61)	46 (21–63)	45 (27–59)	43 (24–62)	**46 (21–63)**
Body weight (kg), mean (min–max)	91 (80–128)	103 (81–119)	87 (66–122)	101 (72–123)	**95 (66–128)**
BMI (kg/m^2), mean (min–max)	29.1 (27.7–36.5)	29.6 (27.2–35.6)	29.1 (27.2–32.5)	29.4 (27.7–33.0)	**30.0 (27.1–36.5)**

Sources: 1. Zealand Pharma. Press release 09-SEP-2024. Available from: https://www.globenewswire.com/news-release/2024/09/09/2943004/0/en/Zealand-Pharma-announces-positive-topline-results-from-13-week-Phase-1b-multiple-ascending-dose-clinical-trial-with-GLP-1-GLP-2-receptor-dual-agonist-dapiglutide.html, accessed June 2025; 2. Data on file.
BMI=body mass index; MAD=multiple ascending dose; N=number of participants.

Safety summary of TEAEs

13-weeks dose escalation cohorts – dose escalation every 2nd week

Adverse events	Placebo (N=12)		Dapiglutide 7.5 mg (N=14)		Dapiglutide 10 mg (N=14)		Dapiglutide 13 mg (N=14)	
	N (%)	E	N (%)	E	N (%)	E	N (%)	E
Total	8 (66.7%)	17	14 (100%)	52	14 (100%)	135	13 (92.9%)	103
▶ Mild	8 (66.7%)	15	14 (100%)	48	14 (100%)	123	13 (92.9%)	91
▶ Moderate	1 (8.3%)	1	4 (28.6%)	4	7 (50.0%)	11	5 (35.7%)	12
▶ Severe	1 (8.3%)	1	-	-	-	-	-	-
Serious	1 (8.3%)	1	-	-	1 (7.1%)	1	-	-

Serious adverse event details: For one male participant in the 10 mg dose group, his female partner had a miscarriage. This SAE was considered unrelated to treatment by investigator. One participant on placebo reported Diverticulitis Intestinal Perforated (severe AE).
E=number of events; N=number of participants; TEAE=treatment-emergent adverse event.

Most common TEAEs

13-weeks dose escalation cohorts – dose escalation every 2nd week

System Organ Class Preferred Term	Placebo (N=12)		Dapiglutide 7.5 mg (N=14)		Dapiglutide 10 mg (N=14)		Dapiglutide 13 mg (N=14)	
	N (%)	E	N (%)	E	N (%)	E	N (%)	E
Gastrointestinal disorders	**5 (41.7%)**	**8**	**10 (71.4%)**	**23**	**12 (85.7%)**	**80**	**12 (85.7%)**	**69**
Nausea	1 (8.3%)	1	3 (21.4%)	**5**	10 (71.4%)	**17**	10 (71.4%)	24
Vomiting	0		2 (14.3%)	2	7 (50.0%)	30	6 (42.9%)	16
Dyspepsia	1 (8.3%)	1	5 (35.7%)	5	4 (28.6%)	5	4 (28.6%)	7
Diarrhoea	0		1(7.1%)	2	4 (28.6%)	6	6 (42.9%)	11
Eructation	1 (8.3%)	1	2 (14.3%)	3	6 (42.9%)	8	3 (21.4%)	3
Metabolism and nutrition disorders	**0**		**3 (21.4%)**	**4**	**7 (50.0%)**	**8**	**10 (71.4%)**	**12**
▶ Decreased appetite	0		3 (21.4%)	3	7 (50.0%)	7	10 (71.4%)	11
Nervous system disorders	0		**6 (42.9%)**	**7**	**10 (71.4%)**	**12**	**1 (7.1%)**	**7**
Headache	0		6 (42.9%)	7	8 (57.1%)	9	1 (7.1%)	7
Respiratory, thoracic and mediastinal disorders	**4 (33.3%)**	**4**	**8 (57.1%)**	**9**	**4 (28.6%)**	**7**	**5 (35.7%)**	**5**
Nasopharyngitis	2 (16.7%)	2	7 (50.0%)	8	4 (28.6%)	5	2 (14.3%)	2

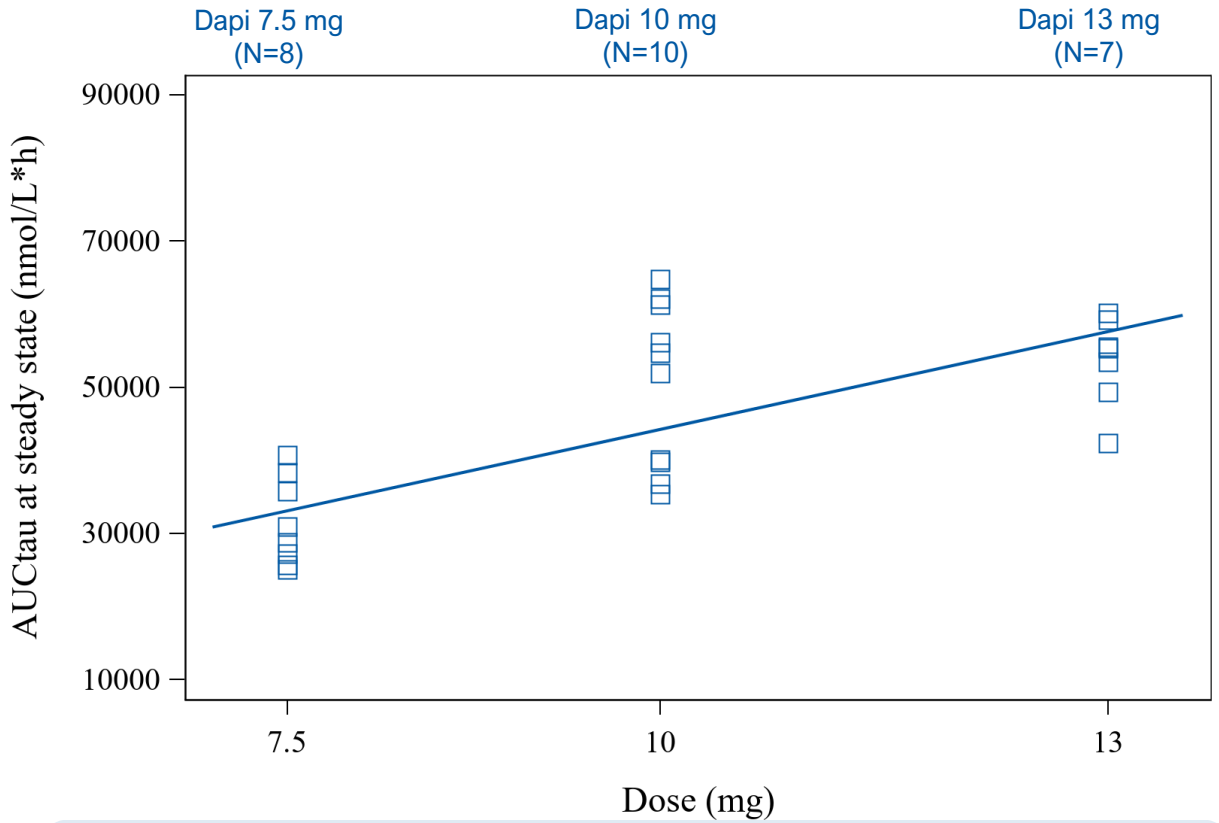
Most frequently reported TEAEs by dapiglutide treated participants (≥10 subjects overall).
E=number of events; N=number of participants; TEAE=treatment-emergent adverse event.

Summary of additional safety parameters

- **No clinically significant findings** for vital signs, ECG, physical examinations, or clinical laboratory assessments
- Mean **pulse rate** increased for all cohorts compared to placebo and was approximately 5–10 bpm higher than baseline towards the end of treatment
- Trend for decrease for all cohorts in mean systolic **blood pressure** compared to placebo and was approximately 5 mmHg lower than baseline towards the end of the treatment (No apparent treatment trend for diastolic blood pressure)
- **Anti-drug antibody** incidence was 14.3% Incidence of cross-reaction with endogenous GLP-2 was 2.4% and no cross-reaction with endogenous GLP-1 detected
- Six participants on dapiglutide reported **injection site reactions** compared to one on placebo

Source: Data on file.
Bpm=beats per minute; ECG=electrocardiogram; GLP-1=glucagon-like peptide-1; GLP-2=glucagon-like peptide-2.

Summary of pharmacokinetics



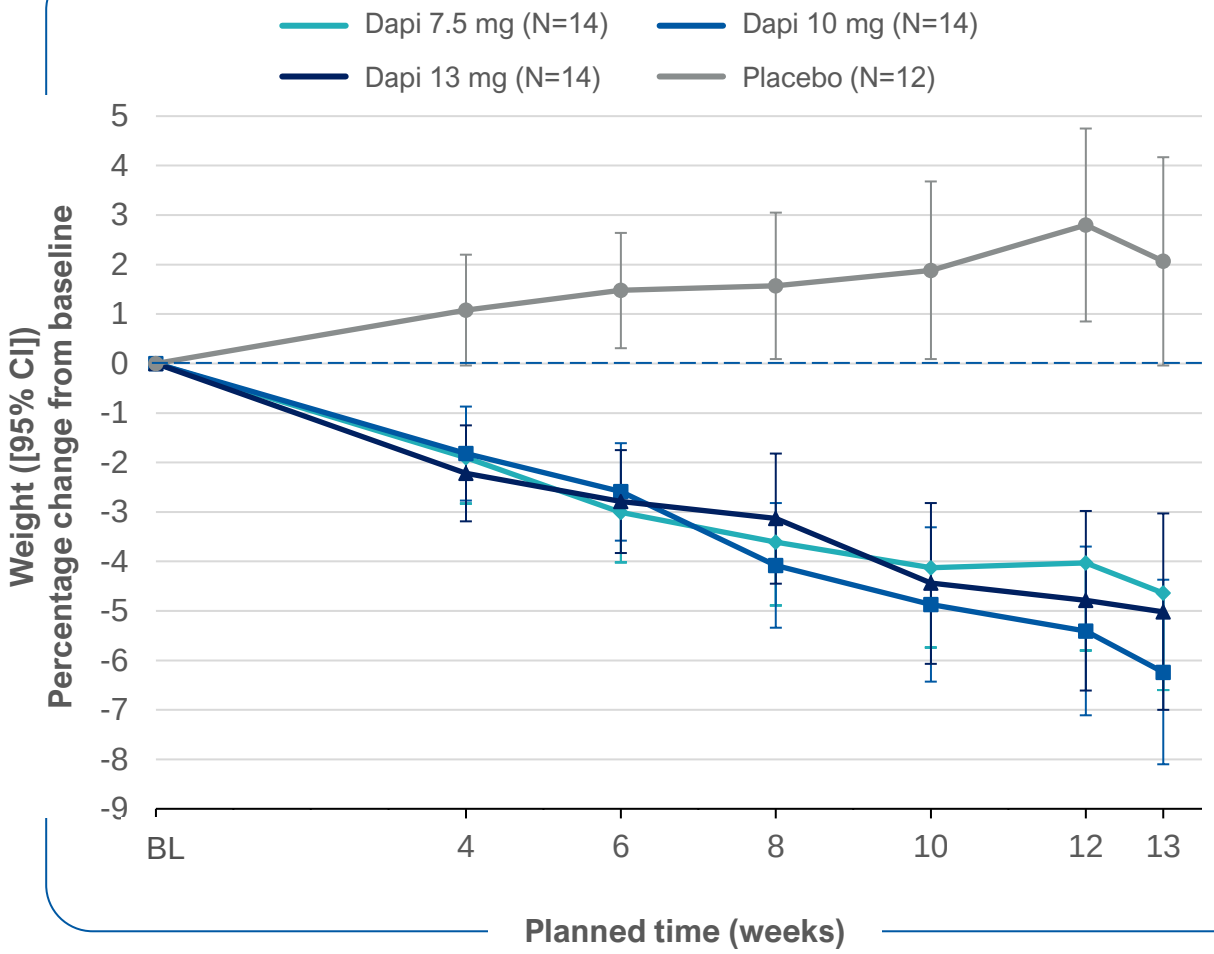
Steady state dose range of 7.5 mg to 13 mg

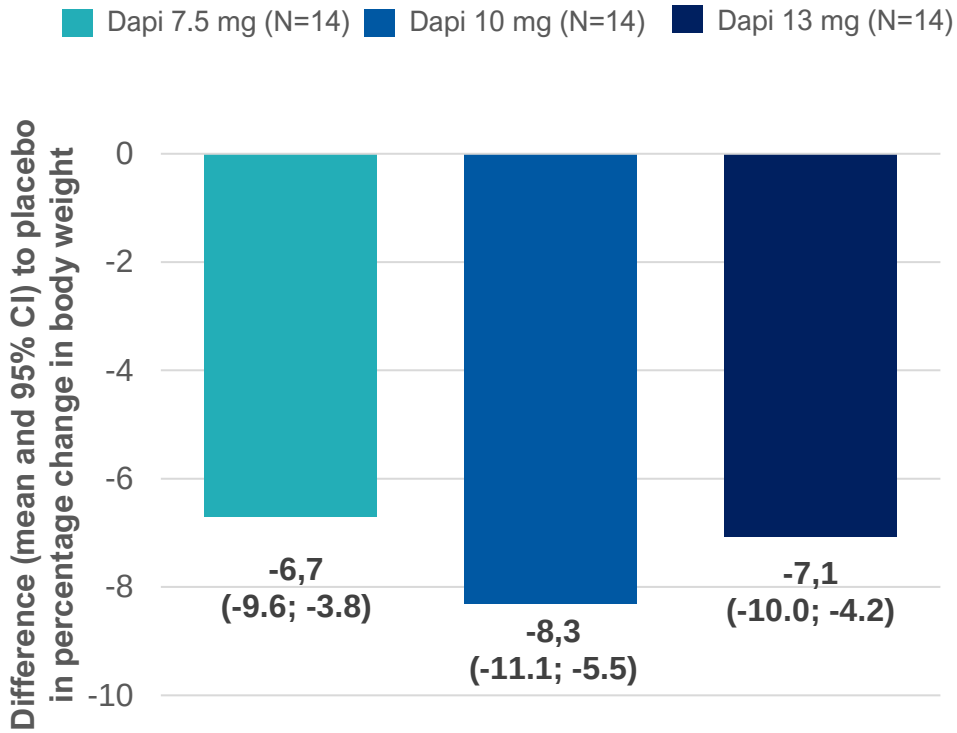
- Dapiglutide shows **dose proportional pharmacokinetics** from 7.5 mg to 13 mg
  - Both for **C_{max} and AUC_{tau}**
- **T_{max}** was observed at **24 hours**
- **Terminal half-life** of approximately **120 hours (5 days)** was confirmed
- Dapiglutide has pharmacokinetic profile suitable for **once-weekly dosing**

Source: Data on file.
AUC=area under the concentration–time curve; AUC_{tau}=area under the concentration–time curve for a dosing interval; C_{max}=peak concentration; T_{max}=time to peak concentration.

Relative body weight change from baseline to week 13

Estimated mean percent change in body weight





Estimated based on the hypothetical estimand = treatment effect if all participants adhered to treatment (also known as the efficacy estimand).
Source: Data on file. Full analysis set: all randomised participants with a post-baseline measurement (N=14, N=14, N=13, N=10). BL=Baseline; CI=Confidence interval; ETD=Estimated treatment difference.

Conclusions

- Dapiglutide treatment appeared safe and well-tolerated with an AE profile similar to other incretin-based therapies
- Dapiglutide displayed dose proportional pharmacokinetics and is suitable for once-weekly dosing
- Placebo-adjusted reductions in body weight were up to a mean of 8.3% with dapiglutide after 13 weekly doses
- Higher doses of dapiglutide with dose escalation every 4 weeks have been evaluated in Part 2

Source: Data on file.
AE=adverse event; GI=gastrointestinal; PK=pharmacokinetics; TEAE=treatment-emergent adverse event.

Data from part 2 to be presented at future scientific conference

Thank you !!