2830-LB

A Single Injection of Ultra-Long-Acting GLP-1 Receptor Agonist AM-710 Produces Durable >20% Weight Loss in Obese Nonhuman Primates

Brian P. Kearney, Benson Edagwa, Tim Garnett, Alborz Yazdi

Aion Medicines, San Francisco CA USA

BACKGROUND

- Glucagon-like peptide-1 receptor agonists (GLP-1RA) & other incretins have redefined the treatment of diabetes & obesity, but poor adherence to once-weekly peptide therapies (e.g. only ~5-6 months avg. duration of therapy w/ semaglutide[1, 2]) limits real-world impact
- Pharmacokinetic (PK) enhancement (i.e. longer half-life and "flatter" profile) can improve adherence, tolerability, & effectiveness of incretins as evidenced by class evolution from twice- & once-daily to weekly agents, and more recently emerging monthly agents[3]
- Small molecule prodrug strategies have enabled ultra-long-acting therapies (e.g. Q3M-Q6M duration) in other indications such as schizophrenia & HIV that have transformed outcomes & the standard of care (e.g. paliperidone palmitate and VH310, originally developed by the Aion Medicines team)
- AM-710 is a novel prodrug of orforglipron (OFG) designed to provide attenuated OFG peak-to-trough & achieve ultra-long-acting PK for sustained pharmacodynamic (PD) effects & improved clinical efficacy with infrequent administration
- Previously we reported ultra-long-acting PK in rats and ultra-long-acting PK/PD (reduced food intake, body weight, fat mass, FBG, & improved OGTT) with single doses of AM-710 compared to daily oral OFG in hGLP1 DIO mice (Obesity Week 2025; Poster #615)

METHODS

- Male diet-induced obese (DIO) cynomolgus monkeys maintained on a stable high-fat chow diet were screened for body weight and fat mass
  - Animals were housed in temperature & humidity-controlled room with 12-hr light/dark cycle
  - To establish baseline, body weights were taken at D-14, D-10, D-7 and D-3, and food intake measured at D-6, D-5, D-4, D-3, D-2 and D-1
  - DEXA (Medilink DR) was performed at D-7 to establish baseline body fat %
  - At baseline, animals were 15-18 years old with average body weight 13kg, representing BMI 55, and 57% body fat
- Enrolled animals (N=4) received a single 23mg/kg OFG-molar-equivalent dose of AM-710 as a 1.0 mL subcutaneous injection (interscapular) on Day 1
  - 23mg/kg OFG-equivalent dose is approximately 0.55mg/kg/day of OFG for the 42 day study duration, representing a substantially lower (~1/6th) dose than the 3mg/kg/day dose in GLP-toxicology studies of daily oral orforglipron in NHPs that are reported to be representative of clinical exposures for approved doses[4]
  - Food intake was measured daily post dose throughout the study. Body weight was measured daily for the first week, and then twice-weekly post dose
  - PK samples were taken on D1(pre-dose), D2, D3, D4, D5, D6, D7, D14, D21, D28, D35, & D42 & plasma OFG was quantified by LC-MS/MS

RESULTS

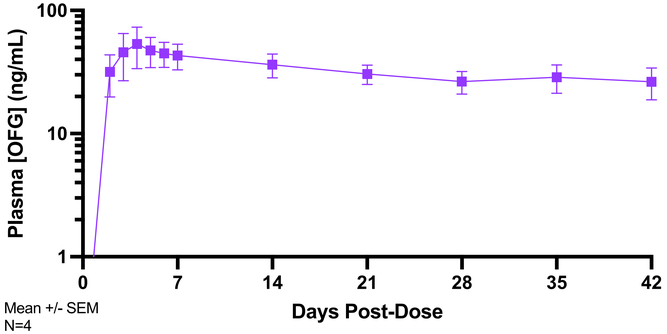
TOLERABILITY PROFILE OF SINGLE-DOSE AM-710

- AM-710 was well tolerated with no evidence of injection site reactions or notable systemic adverse events through Day 42
- Despite the lack of titration, few GI-related adverse events were observed
  - One animal experienced transient emesis in the first week post-dosing that resolved without intervention or negative sequalae
  - No animals experienced loose stools, which have been noted in studies of other oral and injectable GLP1s in obese NHPs

PHARMACOKINETIC PROFILE OF SINGLE-DOSE AM-710

- A single dose of AM-710 achieved sustained plasma orforglipron concentrations consistent with flip-flop PK over the 42 day study period
- Plasma orforglipron exhibited flat, near-zero-order kinetics over the 42 day study period; apparent half-life is indeterminate at this time (Figure 1). This contrasts to the reported half-life for plasma OFG of ~4 hours following oral OFG dosing in NHPs[5]
- AM-710 produced desirable improvements in orforglipron plasma PK parameters including gradual & sustained absorption, prolonged T_{max}, little peak-to-trough variability (near-zero day-to-day), & profoundly extended half-life relative to that established for oral orforglipron administration

Figure 1. Mean OFG concentration-time profile following single-dose AM-710

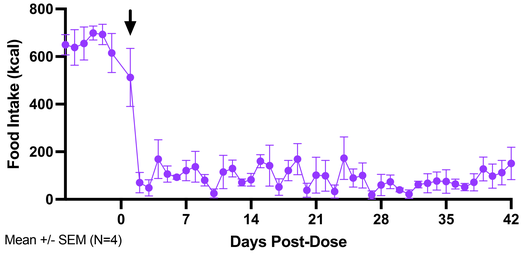


Mean +/- SEM
N=4

PHARMACODYNAMIC EFFECTS OF SINGLE-DOSE AM-710 ON FOOD INTAKE AND BODY WEIGHT

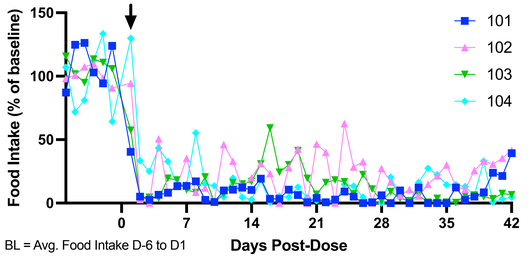
- A single subcutaneous dose of AM-710 resulted in >80% reduction from baseline in daily eating that was sustained with minimal rebound observed throughout the six-week study period
- A single subcutaneous dose of AM-710 produced rapid and sustained weight-loss of >25% in all four animals that showed continued decline with no plateau observed throughout the six-week study period
- At Day 42, animals maintained a mean 77% reduction in food intake and mean weight loss of 26.4% from baseline
- To our knowledge, this represents the greatest weight loss published to date of any six-week study in obese monkeys, with greater weight loss observed than daily oral GLP-1RAs or weekly dosing with GLP-1/GIP dual agonist, GLP1-GIPRa antibody-peptide conjugate, and even with GLP-1/GIP/GCG triple agonist incretins[6,7,8]

Figure 2. Mean food intake following single-dose AM-710



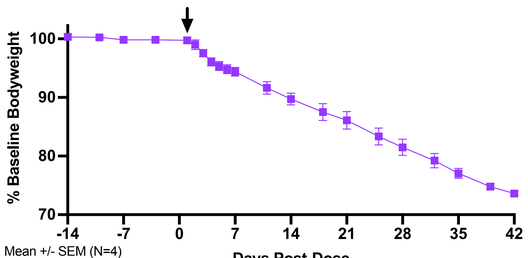
Mean +/- SEM (N=4)

Figure 3. Individual food intake following single-dose AM-710



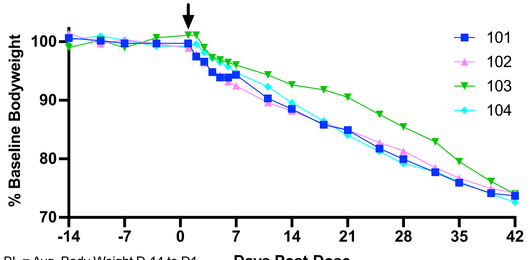
BL = Avg. Food Intake D-6 to D1

Figure 4. Mean weight loss following single-dose AM-710



Mean +/- SEM (N=4)
BL = Avg. Body Weight D-14 to D1

Figure 5. Individual weight loss following single-dose AM-710



BL = Avg. Body Weight D-14 to D1

CONCLUSIONS

- **AM-710 is a novel prodrug of orforglipron and the longest-acting incretin agent identified to date. AM-710 produces ultra-long-acting PK & PD after a single dose in DIO NHPs**
- **To our knowledge, these data represent the longest-acting PK profile in any reported NHP study, and the greatest weight-loss in any reported obese NHP study at 6 weeks, with prolonged duration of action and depth of pharmacodynamic effect that exceed reports for GLP-1/GIP targeted agents, and even triple-G agonists**
- **These data support continued development and clinical investigation of AM-710 as a "best and longest in class" incretin with the potential to achieve improved tolerability and efficacy with infrequent, ultra-long dosing intervals (e.g. QM, Q3M, Q6M+)**

References: 1. Rodriguez PJ et al. *JAMA Network Open.* 2025;8(1):e2457349. doi:10.1001/jamanetworkopen.2024.57349. **2.** Reuters. US patients take Wegovy obesity drug for around six months. August 7, 2024. **3.** Huthmacher JA et al. *Diabetes Care.* 2020;43(9):2303-2312. doi:10.2337/dc20-0498. **4.** FOUNDAYO (orforglipron) US FDA Multi-Disciplinary NDA Review. **5.** Kawai et al. *PNAS*. 2020;117(47):29959-29967. doi:10.1073/pnas.2014879117. **6.** Luo et. al *Diabetes.* 2024;73(Supplement_1). doi:10.2337/db24-771-p. **7.** Veniant et al. Nature Metabolism. 2024;6(2):290-303. doi:10.1038/s42255-023-00966-w. **8.** Song *Diabetes.* 2025;74(Supplement_1). doi:10.2337/db25-1967-lb

Contact Alborz Yazdi at alborz@aionmedicines.com for additional information

Presented at the 86th American Diabetes Association Scientific Sessions. June 5–8, 2026, New Orleans, Louisiana