Preclinical characterization of AM-710, a novel ultra-long-acting small-molecule GLP1R agonist

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BACKGROUND

- Glucagon-like peptide-1 receptor agonists (GLP1RA) & other incretins have transformed 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 on patient outcomes
- Pharmacokinetic (PK) enhancement (longer half-life, attenuated peak-to-trough) can improve adherence, tolerability, & effectiveness of incretin therapy as evidenced by class evolution from twice- & once-daily to weekly approved agents, and more recently with emerging longer-acting (e.g., monthly) agents[3]
- Ultra-long-acting therapies (e.g. Q3M-Q6M duration) developed for other indications such as schizophrenia & HIV using small molecule prodrugs have transformed therapeutic outcomes & standards of care (e.g. paliperidone palmitate, aripiprazole lauroxil, & VH310, originally developed by Aion Medicines team)
- Aion Medicines has generated a library of small molecule GLP1RA prodrugs capable of providing long-acting & ultra-long-acting duration of therapy—AM-710 is a novel prodrug of orforglipron (ORF) designed to provide substantial half-life extension, attenuated peak-to-trough PK & achieve deeper, more sustained pharmacodynamic (PD) effects & clinical efficacy via infrequent administration
- **Here, we characterize the PK & PD of AM-710, an ultra-long-acting small molecule prodrug of ORF**

METHODS

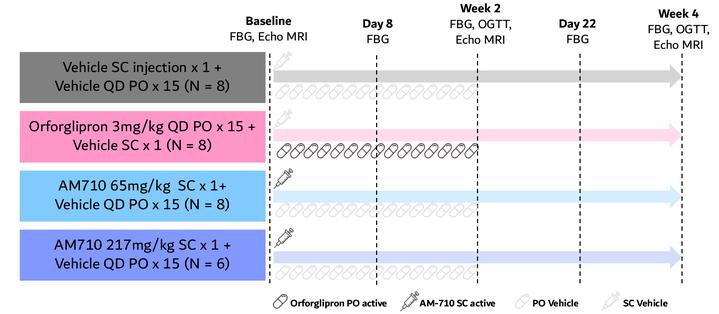
AM-710 Pharmacokinetics in Mice & Rats

- Single injections of AM-710 were administered to male C57BL/6NJ mice & S-D Rats (N=2-4/group) intramuscularly (IM) or subcutaneously (SC)
- PK parameters for orforglipron & general tolerability were characterized for several months post-dose
- Oral orforglipron was given to C57BL/6NJ mice by gavage (N=3) for comparative PK assessment

AM-710 Pharmacodynamics in Diet-Induced Obesity (DIO) humanized GLP1R (hGLP1R) mice

- Male humanized GLP1-R DIO mice (C57BL/6NJ background), required for assessing GLP1RA PD effects, received a high-fat diet (60% fat; D12492, Sniff) for 25 weeks before randomization to four groups (N = 6-8/cohort) stratified by weight & fat mass
- Double-dummy vehicle-controlled treatment groups consisted of a single dose of AM-710 (low dose of 65mg/kg ORF-eq. SC) a single dose of AM-710 (high dose 217mg/kg ORF-eq. SC), 15 days of daily oral orforglipron (3mg/kg suspension PO), or a single dose of SC vehicle + 15 days PO vehicle (Figure 1)
- Daily food intake & body weight measurements, as well as assessment of fat mass (Echo MRI), fasting blood glucose, and oral glucose tolerance testing were completed throughout the study period (Figure 1). PK samples were taken 2 hours post first dose on Day 1, pre-dose on Day 8, and at Day 31

Figure 1. Study Design: double-dummy vehicle-controlled PD study of AM-710 versus oral ORF



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.** Pratt E et al. *Diabetes Obesity and Metabolism*. 2023;25(9):2642-2649. doi:10.1111/dom.15150. **5.** Wharton S et al. *New England Journal of Medicine*. Published online September 16, 2025. doi:10.1056/nejmoa2511774. **6.** Kawai T, et al. *PNAS*. 2020;117(47):29959-29967. doi:10.1073/pnas.2014879117. **7.** Sonne N et al. *Diabetes*. 2025;74(Supplement_1). doi:10.2337/db25-2182-lb

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RESULTS

PHARMACOKINETIC PROFILE OF AM-710 IN MICE & RATS

- In both mice & rats, single doses of AM-710 administered IM or SC were well tolerated and provided continuous plasma orforglipron exposure that was sustained over several months within clinically relevant concentrations associated with oral orforglipron doses utilized in successful Phase 3 studies in diabetes and obesity[4,5] (Figures 2 & 3)
- AM-710 produced desirable improvements in orforglipron plasma PK parameters including a profoundly extended half-life, gradual absorption and prolonged T_{max}, and reduced C_{max} below that observed with 3mg/kg oral orforglipron administration (Table 1)
- Apparent half-life of plasma orforglipron from AM-710 administration was >75 days in both species, representing a greater than 150-fold improvement from the measured oral orforglipron half-life of 6 hours in mice observed in this study and 10-12 hours half-life in rats reported for oral orforglipron in previous studies[6]

Figure 2. ORF concentration-time profile in rats

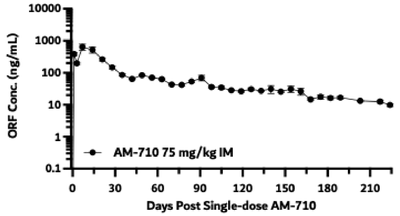


Figure 3. ORF concentration-time profile in mice

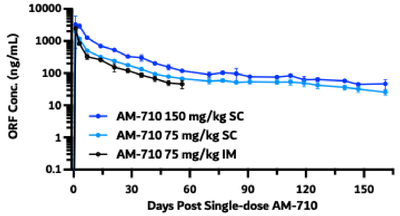


Table 1. PK parameters of AM-710 & orforglipron

Species	Dose (mg/kg)	$AUC_{0->T\text{-}last}$ (ug*day/mL)	C_{max} (ug)	T_{max}	$T_{1/2}$
Parenteral AM-710					
Rat	75 IM x 1	18.1	0.642	7 days	76 days
Mouse	75 IM x 1	13.3	2.47	1 day	NC
	75 SC x 1	22.0	2.03	1 day	91 days
	150 SC x 1	44.5	3.27	1 day	83 days
Oral Orforglipron					
Mouse	3 PO x 1	2.04	4.26	1 hours	6 hours

Data presented as mean +/- SEM; N=2-4/group. AM-710 doses are in ORF molar equivalent. Plasma drug levels were quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS).

PHARMACODYNAMIC EFFECTS OF AM-710 ON FOOD INTAKE, BODY WEIGHT, & FAT MASS IN DIO MICE

- A single subcutaneous dose of AM-710 in both low dose & high dose groups provided deep & sustained reductions in food intake, body weight, & fat mass at Day 15 & Day 31 versus vehicle control (Figure 4, 5, 6), with greater effect size than previously reported results with 30nmol/kg daily semaglutide administration in the same mouse strain & model[7]
- At Day 15, low dose AM-710 produced similar body weight reduction to daily oral orforglipron PO, but low dose AM-710 produced greater fat mass reduction than orforglipron PO, indicating a possible beneficial effect of sustained target engagement on body composition associated with AM-710 versus oral orforglipron (Figure 6)
- Cessation of orforglipron PO led to rebound in food intake, body weight & fat mass, with comparable results to that of vehicle control by the end of recovery period, whereas animals treated with a single dose of AM-710 in both low & high dose groups experienced little to no rebound & maintained weight loss versus vehicle control and oral orforglipron at Day 31
- PK samples showed lower C_{max} for AM-710 low dose versus the orforglipron PO group, similar C_{max} for orforglipron PO and AM-710 high dose groups, prolonged T_{max} associated with both AM-710 groups, and persistent plasma drug concentrations for both AM-710 groups throughout the duration of the study

Figure 4. Cumulative Food Intake

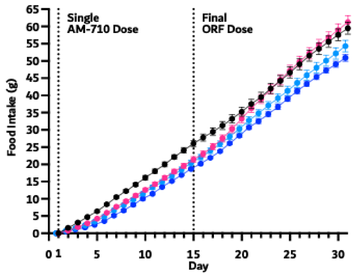


Figure 5 Body Weight Change

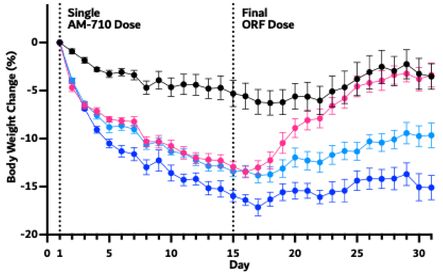
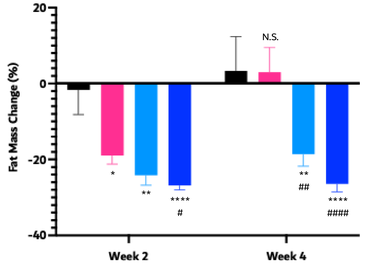
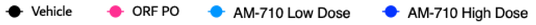


Figure 6. Fat Mass Change





Data presented as mean +/- SEM; N = 6-8/group
Fat mass change at each timepoint was analyzed by one-way ANOVA and Fisher's LSD test
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs vehicle group
#p<0.05, ##p<0.01, ###p<0.001, ####p<0.0001 vs ORF PO group

EFFECTS OF AM-710 ON GLYCEMIC CONTROL

Figure 7. Fasting Blood Glucose (FBG)

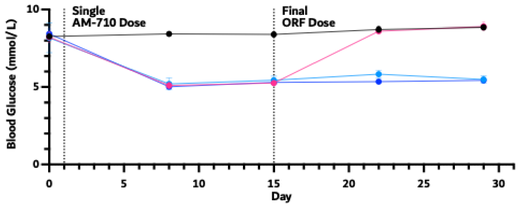
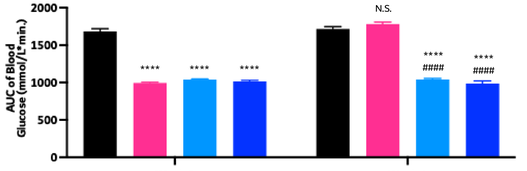


Figure 8. Oral Glucose Tolerance Testing (OGTT)



Data presented as mean +/- SEM; N=6-8/group. Glucose AUC at each timepoint was analyzed by one-way ANOVA and Fisher's LSD test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs vehicle group
#p<0.05, ##p<0.01, ###p<0.001, ####p<0.0001 vs ORF PO group

- At Day 8 & 15, FBG and Week 2 OGTT results were similar between both AM-710 arms and orforglipron PO, which were improved over vehicle control
- At Week 4, two weeks after the end of oral dosing, animals treated with orforglipron PO had no improvement in FBG or OGTT vs. vehicle control
- A single SC dose of AM-710 at both dose levels produced improved FBG & OGTT that were sustained throughout the four-week study period compared to orforglipron PO & vehicle control

CONCLUSIONS

- AM-710 is a novel prodrug of orforglipron that produces ultra-long-acting PK & deep, sustained PD effects with a single dose
  - AM-710 demonstrates dose-proportional PK with profound half-life extension & attenuated peak-to-trough concentration-time profile
  - AM-710 achieves sustained PD effects on food intake, body weight, fat mass, FBG, & OGTT with a single dose compared to oral ORF which rebounded rapidly following cessation of QD dosing
- Infrequent SC administration of AM-710 has the potential to offer favorable PK & PD versus available agents to facilitate long-term adherence & an improved therapeutic profile for incretin therapy
- These data support continued development of AM-710 and clinical investigation of ultra-long-acting dosing (e.g. Q3M-Q6M intervals)
- **AM-710 is a potential best-in-class GLP1RA and the longest-acting incretin agent in development identified to date**

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