SUN-680. First-in-Class Oral Dual GLP-1/Glucagon Agonist for Patients with Obesity and Metabolic Disorders: In Vivo Pharmacokinetic and Pharmacodynamic Results

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BACKGROUND

Entera Bio Ltd. and OPKO Health Inc. are collaborating to advance a first-in-class novel oxyntomodulin tablet therapy for patients with obesity, metabolic and fibrotic disorders.

Oxyntomodulin is a naturally occurring peptide hormone secreted by the intestinal L-cells in response to food intake. Acting as a dual agonist of GLP-1 and glucagon receptors, oxyntomodulin plays a critical role in regulating appetite, energy expenditure, and glucose metabolism. However, due to its short plasma half-life, the therapeutic potential of the native hormone is limited. OPK-88006 is an analog of oxyntomodulin linked with an acylated long-chain fatty acid to increase its circulating half-life and is suitable for a once-a-week subcutaneous administration.

Oral bioavailability of peptide drugs is typically negligible due to the large molecular size, polarity and enzymatic degradation in the gastrointestinal tract. Entera's proprietary N-Tab™ platform minimizes enzymatic degradation while facilitating transcellular permeability, enabling oral bioavailability of peptide drugs. The N-Tab™ platform was validated with EB613, the first osteoanabolic tablet treatment in clinical development (Phase 3 ready) for postmenopausal women with osteoporosis.

Oral OPK-88006 is currently undergoing preclinical studies, and a Phase 1 trial is planned. Here we report on the experimental data obtained in preclinical pharmacokinetic (PK) and pharmacodynamic (PD) studies conducted to assess the technical feasibility of an oral OPK-88006 treatment.

METHODS

I) The biologic half-life of OPK-88006 was evaluated in male Sprague-Dawley rats (n=8) and minipigs (n=2/2 males/females) following intravenous administration and blood sampling for 48 hours and 120 hours, respectively.

II) A PK/PD study was conducted in rats with oral OPK-88006 (4 mg/rat; n=12 PK, of those n=6 PD) and placebo (n=6 PD) tablets. Tablets were intra-gastrically administered to fasted animals and PK blood samples were withdrawn for 7 hours post-dose. The PD effect was assessed by Glucose Tolerance Test (GTT). Glucose injection (2 gr/kg) was administered intraperitoneally 1 hour post tablet administration. Blood glucose was measured just prior to tablets administration, then just prior to the glucose injection, and then monitored for 2 hours.

III) A clinically relevant dose (50 mg) and dosage form of oral OPK-88006 was tested in minipigs (n=2/2 males/females) weighing 48 +/-2 kg (mean +/-SD). Tablets were administered intra-gastrically to sedated animals. Minipigs were fasted prior to the dosing. Stomach content and pH were monitored.

OPK-88006 in rat and minipig plasma were measured by a qualified LC/MS method.

RESULTS

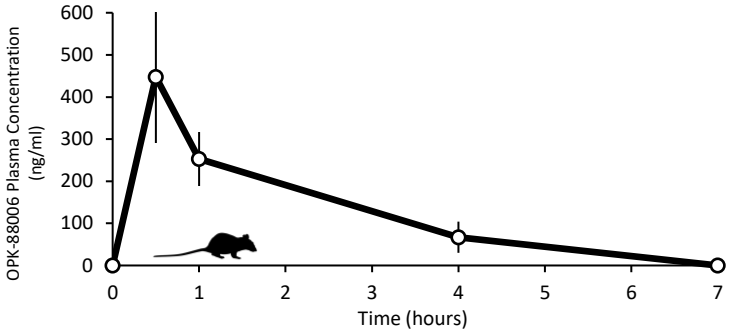

Figure 1. Mean (+/-SE) OPK-88006 plasma levels following oral administration of 4 mg OPK-88006 tablets in 12 male Sprague-Dawley rats of 355 +/-8 gr weight.

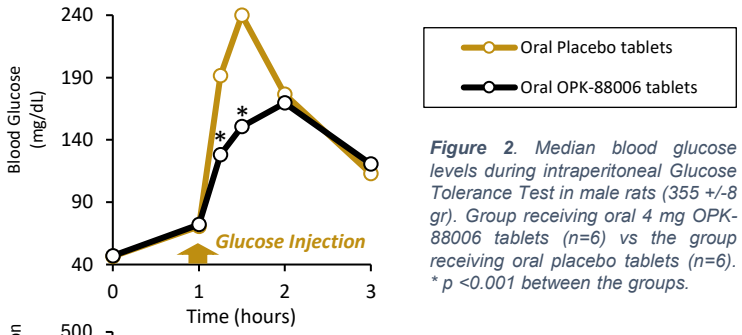

***Figure 2.** Median blood glucose levels during intraperitoneal Glucose Tolerance Test in male rats (355 +/-8 gr). Group receiving oral 4 mg OPK-88006 tablets (n=6) vs the group receiving oral placebo tablets (n=6). * p <0.001 between the groups.*

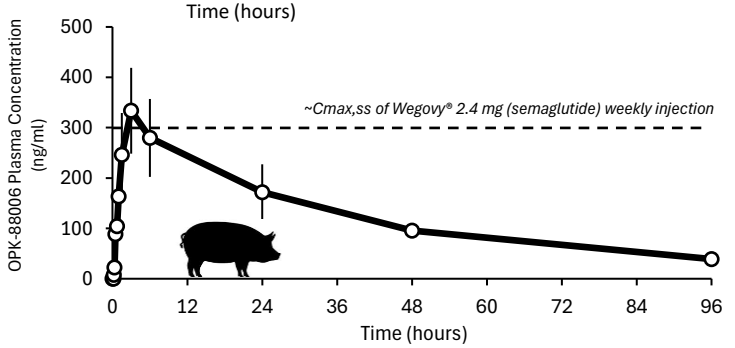

***Figure 3.** Mean (+/-SE) OPK-88006 plasma levels following oral administration of OPK-88006 tablets (50 mg) in 2 male and 2 female minipigs of 48 +/-2 kg weight.*

I) Plasma half-lives of OPK-88006 following intravenous administration in rats and minipigs were ~4 and ~35 hours, respectively.

II) PK/PD study in rats showed substantial and prolonged systemic exposure along with a significantly ($p<0.001$) lower blood glucose levels vs placebo group (in GTT) (Figures 1 and 2).

III) Cmax of ~0.3 µg/ml, and systemic exposure for more than 96 hours with relatively low variability were shown with OPK-88006 tablets in minipigs (Figure 3).

DISCUSSION

- The observed biological half-lives of OPK-88006 in rats and minipigs were found to be comparable to the reported half-lives of semaglutide, in the same animal models, thereby supporting a once-daily oral OPK-88006 treatment regimen.
- The pharmacologic action of oral OPK-88006 was shown in rats.
- Following administration of OPK-88006 tablets to minipigs, plasma levels of the drug were consistent with those reported for 2.4 mg subcutaneous dose of Wegovy (semaglutide), indicated for obesity treatment. These levels also exceeded those reported in humans for other oxyntomodulin analogs developed as once-daily and once-weekly injections. OPK-88006 was still detectable in plasma at the last measured time point of 96 hours. Therefore, doses of oral OPK-88006 may be lower than the 50 mg dose tested in minipigs.
- No toxic effects were observed in animals.

CONCLUSIONS

In conclusion, *in vivo* PK/PD data support development of OPK-88006 as a potential first-in-class oral dual GLP-1/glucagon agonist for the treatment of obesity and metabolic and fibrotic disorders. A Phase 1 clinical trial of this novel oral peptide candidate is currently being planned.

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