A FIRST- IN-CLASS ORAL GLP-2 ANALOG FOR TREATMENT OF SHORT BOWEL SYNDROME

LB055

Gregory Burshtein[1], Constantin Itin[1], Daniel Pery[1], Eli Reichman[1], Hillel Galitzer[1], Michal Kushnir[1], Ahuva Bar-Ilan[2], Moran Golan[2], Laura Moschcovich[2], Miri Zakar[2], Amit Rivkin[2], Moran Levy[2], Miranda Toledano[1], Jane Hsiao[3]

[1] Entera Bio Ltd., Jerusalem, Israel, [2] OPKO Biologics Ltd. Kiryat Gat, Israel, [3] OPKO Health Inc. Miami, FL, USA

BACKGROUND

Entera Bio Ltd. and OPKO Health Inc. are collaborating to advance a first-in-class novel Glucagon-like peptide-2 (GLP-2) tablet therapy for patients with Short Bowel Syndrome (SBS).

GLP-2 is a naturally occurring peptide hormone secreted by the intestinal L-cells in response to nutrient ingestion, that plays a critical role in regulating gastrointestinal (GI) physiology and nutrient absorption. However, due to its short plasma half-life, the therapeutic potential of the native hormone is limited. OPK-8801003 is an analog of GLP-2 with substantially increased 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 GI 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. Given the challenging compliance rates attributed to daily injectable GLP-2 therapy and heterogeneity of SBS patients, a tablet format may address a significant unmet need in treating and titrating patients more effectively.

Here we report a pharmacokinetic (PK) study in minipigs conducted to assess the technical feasibility of an oral OPK-8801003 treatment.

METHODS

I) The biological half-life of OPK-8801003 was evaluated in male Sprague-Dawley rats (n=8) and minipigs (n=2/2 males/females) following intravenous administration and blood sampling for 24 hours and 96 hours, respectively.

II) A clinically relevant dose (50 mg) and dosage form of oral OPK-8801003 was tested in minipigs (n=2/2 males/females) weighing 53 +/-4 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-8801003 in rat and minipig plasma were measured by a qualified LC/MS method.

RESULTS

I) Plasma half-life of OPK-8801003 following intravenous administration in rats and minipigs is ~3 and ~15 hours, respectively (Table).

II) Cmax of ~0.2 µg/ml, and systemic exposure for more than 24 hours (AUC ~2 h*µg/ml) with relatively low variability were shown with OPK-8801003 tablets in minipigs (Figure).

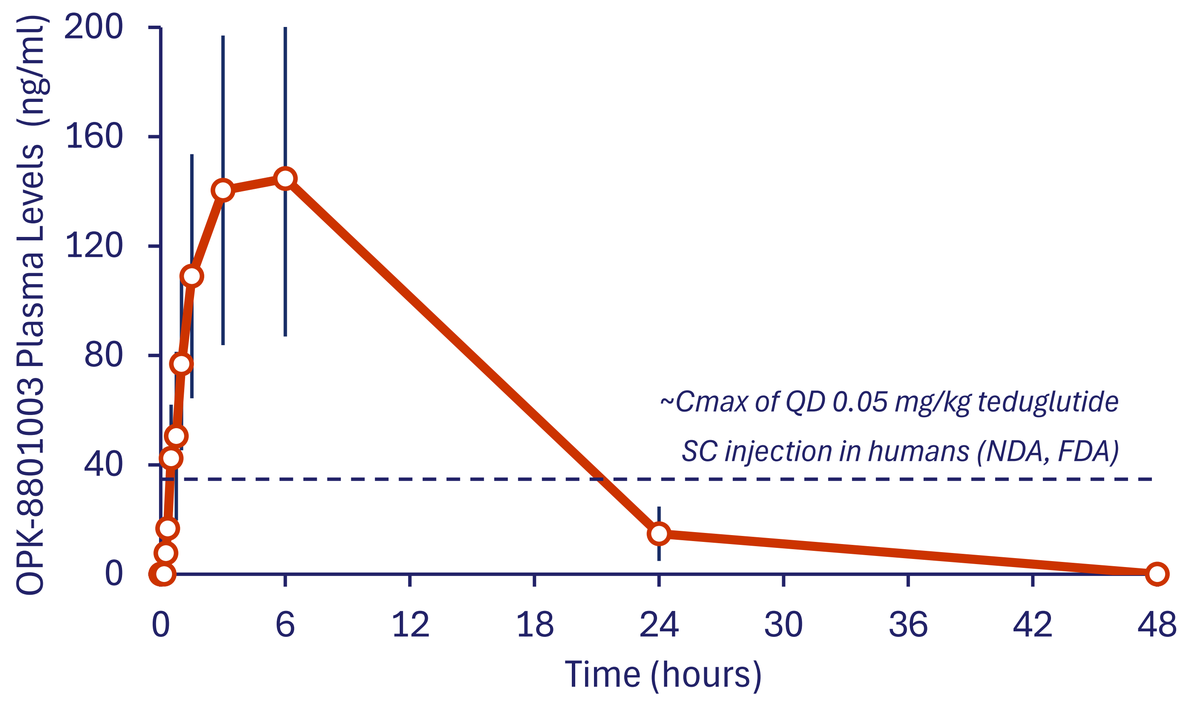

***Figure**. Mean (+/-SE) plasma levels following oral administration of OPK-8801003 in 2 male and 2 female minipigs 53 +/-4 kg weight*

DISCUSSION

➢ The observed biological half-lives of OPK-8801003 in rats and minipigs were found to be substantially longer than those reported for teduglutide (a SC injectable GLP-2 analog, and currently the only approved GLP-2 receptor agonist for SBS treatment, Gattex®) in the same animal models, thereby supporting a once-daily oral OPK-8801003 treatment regimen (Table).

	Half-life (hours)		
	Rat	**Pig**	**Human**
OPK-8801003	~3	~15	---
Teduglutide *	~0.3	~0.85	~2

***Table**. Biological half-life of OPK-8801003 vs teduglutide in different species*

** Values extracted from Gattex® NDA, FDA*

➢ Following administration of OPK-8801003 tablets to minipigs, the obtained plasma levels substantially exceeded the Cmax and systemic exposure reported in humans for QD 0.05 mg/kg teduglutide SC injection (Cmax = 36.8 ng/ml, AUC = 0.15 h*µg/ml; Gattex NDA, FDA).

➢ Based on the obtained results, clinical dose of oral GLP-2 tablets is expected to be substantially lower than the dose tested in minipigs in the current study.

➢ No signs of toxicity were observed in animals.

CONCLUSION

In conclusion, *in vivo* PK data support development of OPK-8801003 as a potential first-in-class oral GLP-2 analog for the treatment of Short Bowel Syndrome.

Contact details: Miranda Toledano, Chief Executive Officer, Entera Bio Ltd. Miranda@enterabio.com; www.enterabio.com