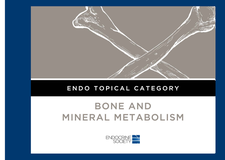

MON-768. PRE-CLINICAL RESULTS FOR EB612: FIRST-IN-CLASS ORAL LONG-ACTING PTH(1-34) ANALOG AS HORMONE REPLACEMENT TABLET FOR PATIENTS WITH HYPOPARATHYROIDISM

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BACKGROUND

Parathyroid hormone (PTH) plays a critical role in regulating calcium and phosphate homeostasis. Hypoparathyroidism is a chronic, rare endocrine disorder characterized by insufficient PTH levels in the blood. PTH insufficiency results in hypocalcemia and hyperphosphatemia, and a spectrum of debilitating symptoms, including muscle cramps, fatigue, and cognitive impairment.

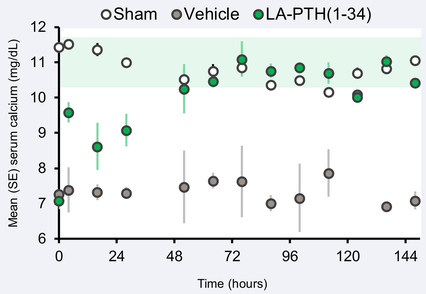
The currently approved PTH analogs require daily injections. There remains an unmet need for more treatment options for patients and an oral route of administration is generally preferred for chronic management.

EB612 [oral LA-PTH(1-34)] is being developed by Entera Bio and OPKO Health as the first once-daily PTH replacement tablet for patients with chronic hypoparathyroidism. The program combines OPK-8801004, a novel, proprietary long-acting PTH(1-34) [LA-PTH(1-34)] analog with Entera's proprietary N-Tab® platform.

METHODS

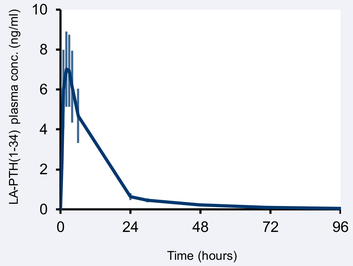
- The Thyroparathyroidectomized (TPTx) rodent model of hypoparathyroidism was utilized to evaluate the pharmacological effect of the LA-PTH(1-34) analog. The drug was administered intravenously to TPTx male SD rats on a daily basis for one week. Serum calcium (Ca) and phosphate (P) levels were measured to assess efficacy vs sham and vehicle arms (n=9 in each arm).
- PK/PD study with a single, clinically relevant dose of oral EB612 tablet was conducted in minipigs (n=5, males/females of 65-80 kg body weight). Plasma concentrations of LA-PTH(1-34) and serum Ca levels were evaluated to characterize the exposure and PD response.
- A pharmacologic study was conducted in non-human primates (NHP; Cynomolgus Macaque). A single, EB612 tablet of clinically relevant dose and size was administered to 4 males (4-6 kg body weight). Serum Ca and endogenous PTH levels were evaluated.

LA-PTH(1-34) Restored Serum Ca Levels in TPTx Rats

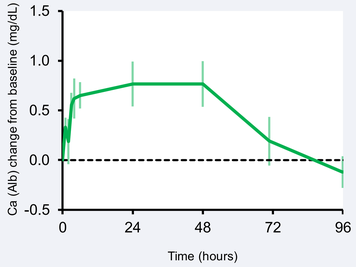


During the treatment phase of the TPTx study, serum Ca levels increased, and serum P levels decreased, reaching comparable levels to those of the sham control animals, for both parameters. *Green area: sham animals' range of Ca*

EB612 Tablet Produced a Rapid and Long-lasting Serum Ca Increase in Minipigs

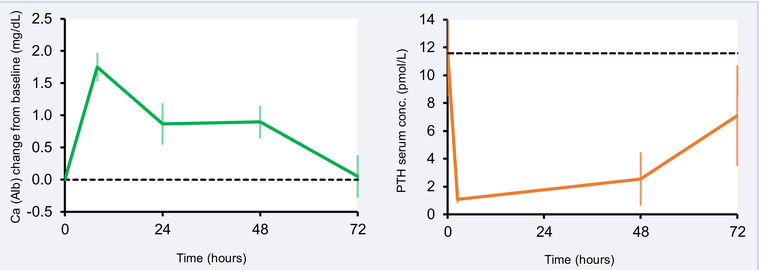


In the minipig model, following oral EB612 tablet dosing, LA-PTH(1-34) reached max plasma levels 2-3 hours post-dose, and the drug remained detectable in the plasma for more than 3 days [Mean (SE)]



The single oral EB612 tablet produced a rapid and long-lasting increase in serum Ca in all study animals. The max increase from baseline was 0.8 mg/dL [Mean (SE)], with effect sustaining for ~3 days

Sustained Pharmacodynamic Effects were Shown in NHP



Similar to minipigs long-lasting calcemic effect was observed in NHP study, with correlating decrease in serum endogenous PTH [Mean (SE)]

Calcemic effects observed in healthy animals with EB612 are consistent with those reported in similar studies with other clinically validated PTH-replacement injection therapies for hypoparathyroidism (Shimizu, JBMR 2016; Holten-Andersen, JBMR 2019).

EB612 was well tolerated and no safety concerns were identified in the animal studies.

CONCLUSIONS

The robust pharmacologic response in the TPTx rodent model along with the prolonged PK profile and sustained calcemic effect observed in the minipig and NHP models support further development of EB612 as a differentiated oral PTH replacement candidate for the treatment of hypoparathyroidism.

Ongoing studies are advancing oral EB612 tablet toward first-in-human clinical evaluation.

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