SAT-758

Phase 1 Study Results of EB612, a First-in-Class Oral PTH(1-34) Tablet for the Treatment of Hypoparathyroidism

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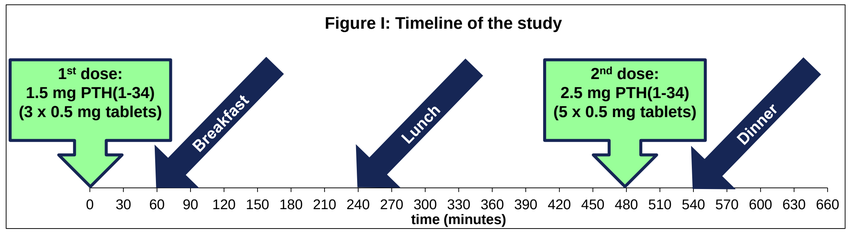
BACKGROUND

The EB612 program is being developed by Entera Bio to provide the first PTH replacement therapy for patients suffering from hypoparathyroidism in a form of oral tablet. Hypoparathyroidism is characterized by deficient PTH production, hypocalcemia, and hyperphosphatemia. Standard treatments include several daily administrations of high dose oral calcium supplements and calcitriol (or analogs). Raising serum calcium to normal physiological levels frequently leads to elevated urinary calcium in the absence of PTH and is often associated with ectopic calcification, including nephrocalcinosis and renal failure. Late stage investigational PTH replacement treatments include TransCon PTH (palopegteriparatide) by Ascendis Pharma A/S and eneboparatide (AZP-3601) by Amolyt Pharma. Both these modalities require patients to administer injections every day. Entera's proprietary N-Tab™ peptide delivery platform enables development of oral PTH(1-34) (teriparatide) tablets which potentially overcomes the limitations of parenteral delivery. These tablets are designed to provide hypoparathyroid patients with a more convenient and flexible treatment of hypocalcemia and hyperphosphatemia. Entera previously published positive Phase 2a study results in 19 hypoparathyroid patients using a QID regimen (Ish-Shalom, JBMR 2021). The data from the current Phase 1 study include PK and early PD results of the novel PTH(1-34) formulation based on the second generation of Entera's N-Tab technology platform. One of the objectives of this study was to test the new formulation's ability to reduce the frequency of daily administration of EB612.

STUDY DESIGN

In this Phase 1 (NCT05965167), open-label study, conducted at the Hadassah Clinical Research Center in Jerusalem, Israel, 15 healthy young male subjects [mean age 22 years (range 19-24)] received, with 100 ml water, 1.5 mg EB612 (3 tablets of 0.5 mg) orally in the morning after an overnight fast, followed by a second dose of 2.5 mg EB612 (5 tablets of 0.5mg) four hours after lunch. Blood samples were withdrawn over a period of 14 hours to evaluate the pharmacokinetics (PK) of PTH(1-34) and pharmacodynamics (PD) of the drug. Serum calcium, phosphate, 1,25(OH)$_2$-Vitamin D, and endogenous PTH(1-84) were measured as PD markers. Safety was assessed by clinical inspection of the subjects as well as by biochemistry, hematology, urinalysis, and vital signs measurement.

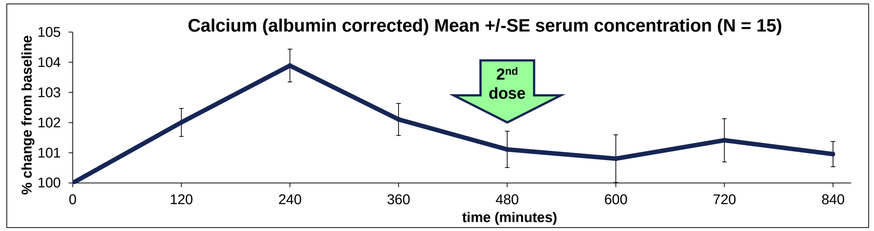
Figure I: Timeline of the study

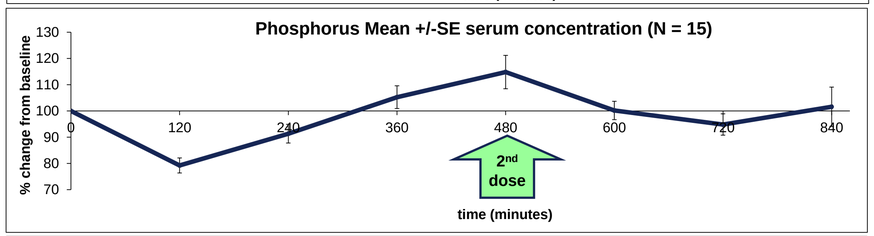


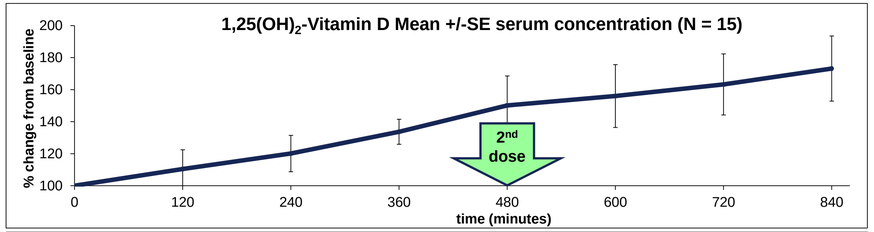
RESULTS

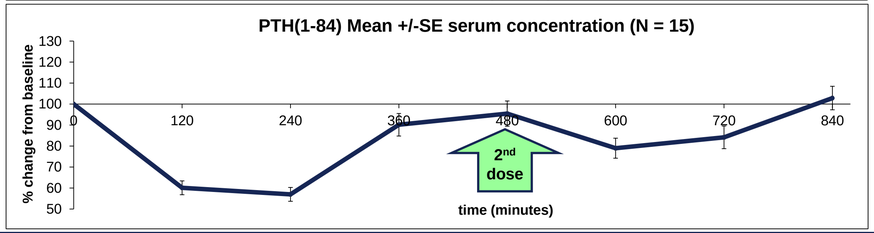
Serum Pharmacodynamic Endpoints

The desired biological effect on serum levels of calcium (albumin corrected), phosphate, and 1,25(OH)$_2$-Vitamin D was shown (reaching +3.9%, -20.8%, and +73.2% change on average from baseline, respectively). Endogenous serum PTH(1-84) was decreased in response to oral administration of PTH(1-34) (reaching -43.0% change on average from baseline). Changes in PD parameters were observed over the 14-hour study period. Mean profiles of serum calcium, phosphate, 1,25(OH)$_2$D, and PTH(1-84) are presented in the Figure II below.









RESULTS

Pharmacokinetics

Pharmacokinetic parameters are presented in Table I. Significant systemic exposure was achieved with EB612 tablets following both administrations.

Table I. *Pharmacokinetic parameters.*

Treatment	Cmax Mean (+/-SE) (pg/ml)	Tmax Median (range) (minutes)	AUClast Mean (+/-SE) (min*pg/ml)
1st dose: 1.5 mg	219 (72)	15 (10-30)	3808 (1492)
2nd dose: 2.5 mg	110 (35)	20 (15-40)	2483 (924)

Safety

There were no treatment-emergent Adverse Events of hypercalcemia reported. There were no treatment-emergent Serious AEs. The only Study Drug-Related AE was mild headache, reported in two subjects. No significant findings were observed in blood and urine lab tests. All vital signs were within the normal range. Change in vital signs from pre-dose is presented in Table II.

Table II. *Mean (+/-SD) change in vital signs from pre-dose measured at 30 +/-5 min post-dose.*

Treatment	Standing (orthostatic)			Supine			Sitting		
	Diastolic BP mmHg	Heart rate beat/min	Systolic BP mmHg	Diastolic BP mmHg	Heart rate beat/min	Systolic BP mmHg	Diastolic BP mmHg	Heart rate beat/min	Systolic BP mmHg
1st dose: 1.5 mg	-0.13 (9.96)	1.4 (8.61)	2.13 (12.94)	-2.20 (11.70)	-1.67 (10.03)	-4.40 (13.79)	---	---	---
2nd dose: 2.5 mg	---	---	---	---	---	---	2.13 (6.33)	4.40 (9.12)	1.93 (7.89)

CONCLUSIONS

In this Phase 1 study in healthy volunteers, BID dosing with oral PTH(1-34) tablets based on the 2nd generation N-Tab™ technology, affected serum chemistries directionally as intended with increases in calcium and 1,25(OH)$_2$-Vitamin D and decreases in phosphate. The sustained increase in serum 1,25(OH)$_2$D levels observed in this study may be indicative of a potential accumulation with chronic treatment that could enhance increased absorption of exogenous Ca over time.

In summary, these data suggest that BID administration of EB612 PTH(1-34) tablets may offer a convenient route of administration and dosing schedule that is attractive to patients with mild to severe hypoparathyroidism. Further research will evaluate the ability of EB612 to reduce daily supplementation with high doses of calcium and calcitriol analogs to mitigate associated adverse effects.

Poster Session P106: Late-Breaking Poster Presentations: Day 1, Sat., Jun. 1st, 2024, 12:15–1:45 pm

