The selective FXR agonist EYP001 is well tolerated in healthy male subjects and has additive anti-HBV effect with nucleoside analogues in HepaRG cells

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INTRODUCTION
- Nucleos(t)ide analogues (NAs) inhibiting Hepatitis B virus (HBV) polymerase are the main components of approved HBV therapies. New approaches to overcome the need for a life-long therapy are however needed.
- HBV interacts with the human nuclear farnesoid X receptor (FXR), an important regulator of bile acid metabolism. FXR agonists have been reported to inhibit HBV replication1.
- EYP001 is a selective, synthetic FXR agonist under development for the treatment of chronic HBV infection.

AIM
- To study in vitro (r) anti-HBV effect of EYP001 alone, and in combination with Tenofovir (TFV) or Entecavir (ETV), commonly used NAs.
- To assess safety, tolerance, pharmacokinetics (PK) and pharmacodynamics (PD) of oral EYP001 in healthy male subjects.

METHOD

In vitro assays
The HepaRG cell line can differentiate and retain phenotypic traits of human hepatocytes after 4 weeks of culture2. After differentiation, cells were infected for 24 hr with HBV (100 genome equivalent per cell), washed and cultured for 48 hr. Cells were then treated with EYP001 alone, or in combination with TFV or ETV. Treatment was replaced every 72 hrs. At day 14 post-infection, the effect on HBV infection and on FXR expression activity was evaluated: HBV DNA and antigen secretion in cell supernatant, and intracellular cccDNA, pgRNA, FXR mRNA, CYP7A1 mRNA and BSEP mRNA expression levels, were quantified as described3.

Phase I clinical study
EYP001 or placebo were administered to ten cohorts of young males (6 active & 2 placebo subjects per cohort): - Single dose part (SAD): six cohorts received single EYP001 doses of 30, 60, 120, 250 and 500 and 800 mg, respectively.
- Multiple dose part (MAD): four cohorts received EYP001 doses of 60, 120, 250 and 500 mg, respectively, once daily during 15 days.

Adverse events, clinical laboratory, ECG parameters and vital signs were recorded. Concentrations of EYP001 and PD markers (fibrinolysis growth factor 19 [FGF-19], FGF-19), 4-chololate-3-one (C4), Bile Acids) were assessed in plasma.

This paper presents preliminary results.

RESULTS

EYP001 and NA in vitro effects on HBV replication

When administered alone or combined with EYP001, ETV produced similar changes compared to TFV for HBV DNA, viral RNA, cccDNA, and pgRNA (data not shown).

Hepatocyte FXR pathway and in vitro effect of EYP001

EYP001 was well tolerated in all cohorts. No clinically relevant changes in vital signs, ECG, nor laboratory values (in particular liver enzymes, glucose and lipid profiles) occurred.

Overall 99 post-dosing mild and moderate AE occurred, mostly at the highest doses treated, and of which 28 were categorized as probably drug related. Those were reported up to 2 hours after dosing, short-lasting and mostly mild gastro-intestinal symptoms.

Safety and clinical tolerance of EYP001 in healthy subjects

EYP001 plasma-concentration (mean ± SD) in healthy subjects

- SAD cohorts
- MAD cohorts Day 1 and Day 15

No relevant changes of total bile acids in plasma in relation to EYP001 dose levels were identified in preliminary analysis.

EYP001 PK profiles MAD Day 15

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CONCLUSIONS

- EYP001 mono-treatment inhibited HBsAg and HBV DNA and reduced cccDNA and pgRNA expression in differentiated hepatic HepaRG cells, while TFV or ETV mono-treatment had negligible effect on these HBV markers.
- EYP001 mono-treatment inhibited HBV DNA similarity to TFV or ETV. The combination of EYP001 with NAs showed an additive effect.

- Single and multiple oral doses of EYP001 were well-tolerated in healthy male subjects. No clinical or biological relevant changes were identified.
- The PK profile of oral EYP001 doses showed dose linearity from 30 to 500 mg.
- PD marker revealed a dose and time-dependent engagement of bile-acid regulating FGF-19 in response to FXR stimulation by EYP001 and a time-dependent reduction of BA synthesis precursor C4 plasma levels.
- Overall, these results support further clinical testing in an ongoing study in chronically infected HBV subjects and exploration of efficacy in combination with NA.

REFERENCES


ACKNOWLEDGEMENTS

Thanks to Elsa Ray, Project Coordinator of ENYO Pharma for editorial assistance. This Clinical Phase I study is registered at ClinicalTrials.gov, identifier NCT02703076.

CONTACT INFORMATION

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