First clinical evaluation in Chronic Hepatitis B patients of the synthetic Farnesoid X Receptor agonist EYP001

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BACKGROUND

- **EYP001** is a selective, synthetic FXR agonist being developed for liver diseases, in particular chronic Hepatitis B Virus (HBV) infection
- *Ex vivo* data showed that a EYP001 analogue inhibits HBV replication in hepatocytes derived from a mouse model of chronic HBV infection

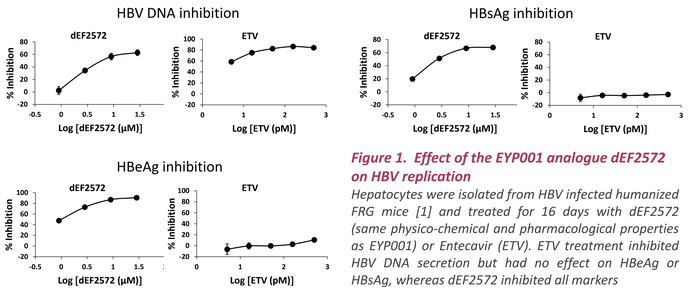

Figure 1. Effect of the EYP001 analogue dEF2572 on HBV replication

Hepatocytes were isolated from HBV infected humanized FRG mice [1] and treated for 16 days with dEF2572 (same physico-chemical and pharmacological properties as EYP001) or Entecavir (ETV). ETV treatment inhibited HBV DNA secretion but had no effect on HBeAg or HBsAg, whereas dEF2572 inhibited all markers

- EYP001 was safe and well tolerated in healthy subjects given as single and multiple doses over 15 days (*ClinicalTrials.gov, Identifier NCT03110276*)

AIM

- To assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of oral EYP001 in Chronic Hepatitis B (CHB) patients
- To determine the effect of food on PK and PD parameters

METHOD

- The study was designed as an in-house Phase 1, open-label, randomized, 4-way crossover study in CHB patients
- Patients received 4 single 300 mg oral doses of EYP001, either in the morning or in the evening, under fasted or fed conditions
- Patients were randomly assigned to 1 of the 4 treatment sequences

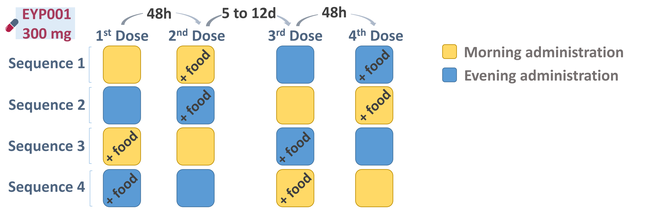

Figure 2. Representation of the treatment sequences

- **Safety**: Adverse events (AE), clinical laboratory, vital signs, ECG and liver ultrasound parameters were recorded
- **PK**: Plasma EYP001 concentrations were assessed
- **PD**: Plasma levels of FGF19 (fibroblast growth factor 19), the bile acid precursor C4 (7αhydroxy-4-cholesten-3-one), Total Bile Acids (TBA), and HBV virology markers were measured

RESULTS

Safety and tolerability

- EYP001 administration is safe and well tolerated, no serious AEs were observed
- 45 treatment-emergent AEs (TEAEs) occurred, of which 18 were categorized as possibly drug-related. All were of mild intensity except one moderate
- The most common AEs were gastrointestinal
- No clinically significant changes in liver enzymes nor lipids occurred

	Number of events *(Number of subjects exposed)*
Any TEAE	**45** *(11)*
Drug-related TEAE	**18** *(6)*
Gastrointestinal disorders	12 *(6)*
Dizziness	2 *(2)*
Fatigue	1 *(1)*
Menstruation delayed	1 *(1)*
Skin disorders	2 *(1)*

Table 1. Treatment-emergent adverse events

Pharmacokinetics

PK Parameter	Evening Fasted	Evening Fed	Morning Fasted	Morning Fed
C_{max} (ng/mL)	1699	1364	1911	1653
	[141 - 3257]	[476 - 2252]	[488 - 3334]	[295 - 3011]
t_{max} (h)	4.00	6.00	2.00	6.00
	[1.00 - 6.00]	[6.00 - 12.0]	[2.00 - 4.02]	[2.00 - 6.03]
$t_{1/2z}$ (h)	3.07	3.94	3.22	3.02
	[1.49 - 4.65]	[0.61 - 7.27]	[1.98 – 4.46]	[2.46 - 3.58]
AUC (ng*h/mL)	8286	8887	8191	9549
	[2016 - 14556]	[4579 - 13195]	[1388 - 14994]	[1872 - 17226]

Table 2. Pharmacokinetics parameters of EYP001

PK of a single oral dose of EYP001 when administered in the morning or in the evening in fasted or fed conditions was assessed. Mean and 95% confidence interval are shown. For T_{max} median and range are reported

- Food increased T_{max}, but did not change maximum and overall exposure (as expressed by C_{max} and AUC) or elimination ($t_{1/2z}$)

PD - HBV virology

HBV Viral Load (UI/mL)	Morning Fasted	Morning Fed	Evening Fasted	Evening Fed
Time 0h	1180 (1370)	1318 (1554)	1350 (1982)	1263 (1832
Time 12h	*1435 (1779)*	1463 (1762)	1611 (2435)	1542 (2093)
Time 48 h	*1467 (1681)*	1541 (1840)	1471 (2358)	1525 (2015)

Table 3. HBV Viral Load

Quantitative HBV DNA levels were measured from pre-dose up to 48 hours after a single oral dose of EYP001, when dosed in the morning or in the evening in fasted or fed conditions. Mean values are reported. SD is indicated in brackets

- HBV markers did not change significantly and were not affected by dosing condition

PD - biomarkers of the FXR-regulated pathway

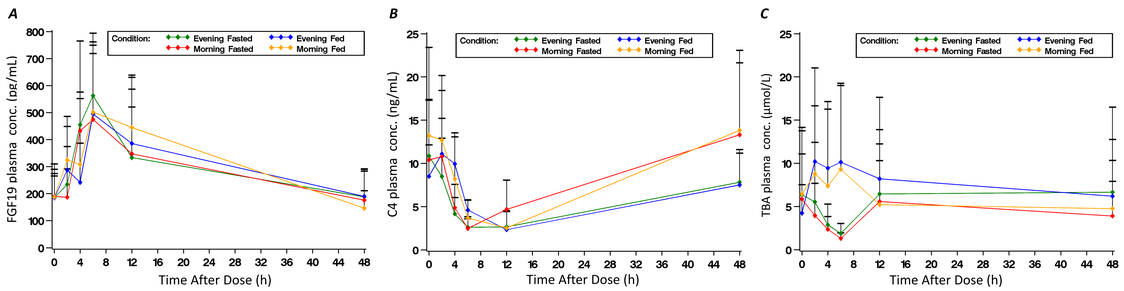

Figure 3. Concentration-time profile of FGF19 (A), C4 (B) and TBA (C) after EYP001 administration

PD of a single oral dose of EYP001, when administered either in the morning or in the evening, with or without food was assessed (Mean ± SD)

- Despite rapid elimination kinetics, EYP001 induced prolonged FXR engagement over at least 12 hours under all conditions, as shown by FGF19 increase and C4 decrease
- FGF19 and C4 PD profiles were similar across fasted and fed conditions. Difference between morning and evening dosing appeared on C4
- TBA levels were decreased in a fasted state, and rose after a meal, consistent with the bile acid physiology

DISCUSSION AND CONCLUSIONS

- In CHB patients EYP001, an oral non-bile salt synthetic FXR agonist
  - was safe and well tolerated and with similar PK profiles for fasted or fed, morning and evening dosing
  - engaged FXR evidenced by FGF19, C4 and TBA changes, with in particular a prolonged C4 decrease with evening dosing
- No significant effect on HBV markers was detected after single oral EYP001 doses. However an *in silico* model built in line with recent guidance to FDA [2], showed an inhibitory effect of EYP001 on HBV replication with prolonged treatment (Fig 4). A phase 1b study with 4 week EYP001 administration is ongoing

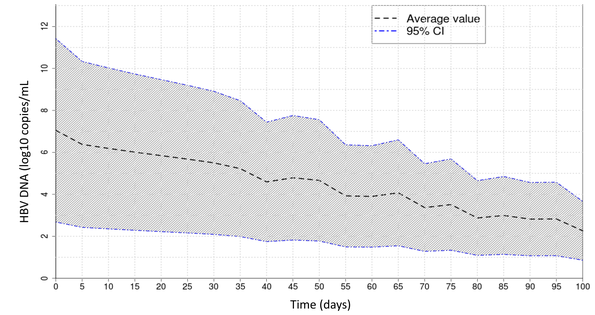

Figure 4. Prediction of HBV DNA inhibition following prolonged FXR agonism with EYP001

Evolution of the viral load was simulated in 100 CHB virtual responder patients treated during 100 days with EYP001 at a dosing regimen of 200 mg BID. Mean (black dashed line) and 95% confidence interval (blue dashed lines) of simulated antiviral responses are shown

ACKNOWLEDGEMENTS

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This Clinical Study is registered at ClinicalTrials.gov, Identifier NCT03320616

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