SAFETY AND ANTIVIRAL EFFECT OF THE FARNESOID X RECEPTOR AGONIST EYP001 IN CHRONIC HEPATITIS B PATIENTS: A RANDOMISED PLACEBO CONTROLLED PHASE 1b STUDY

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INTRODUCTION

- Functional cure of chronic HBV (CHB) infection requires the loss of detectable HBV DNA and HBsAg from plasma, which is rarely achieved with available treatments.
- The nuclear farnesoid X receptor (FXR) is a host nuclear receptor supporting efficient HBV cccDNA transcription[1,2].
- FXR agonist inhibits *in vivo* HBV replication and cccDNA pool formation[3].

AIM

The FXR agonist EYP001 was evaluated for the safety and antiviral effect in CHB patients during a 4-week treatment course administered either as monotherapy or in combination with Pegylated interferon-α2a (PEG-IFNα2a).

METHOD

Non-cirrhotic subjects, HBsAg positive, with HBV DNA >1000 IU/mL, with no current antiviral treatment were randomised, in a multi-centre, placebo controlled, double blinded, Phase 1b trial: in Part A to blinded monotherapy with EYP001 (100mg QD, 200mg QD, 200mg BID or 400mg QD), placebo, or open-label entecavir (ETV 0.5 mg QD). In Part B placebo or EYP001 (150mg BID or 300mg QD) combined with PEG-IFNα2a were administered. Adverse events (AE), safety laboratory, EYP001 plasma concentrations, 7α-hydroxy4-cholesten-3-one (C4), FGF19, and HBV markers were assessed weekly. *Abbreviations: QD: quaque die/once daily, BID: bis in die/twice daily.*

RESULTS

Baseline: 73 CHB patients (39/34 male/female), 90% HBeAg neg, 70% treatment naïve, mean age: 39.8 years (range 19-63). Viral genotypes were: A(n=25), B(8), C(10), D(7), E(4) and unknown (19).

		Part A (n=48)						Part B (n=25)		
Parameter (units)	Statistic / stratum	EYP001 1x100mg (N=7)	EYP001 1x200 mg (N=8)	EYP001 1x400 mg (N=9)	EYP001 2x200 mg (N=9)	ETV 0.5 mg (N=7)	Placebo (N=8)	EYP001 1x300 mg +PEG-IFN 180µg (N=8)	EYP001 2x150 mg +PEG-IFN 180µg (N=9)	Placebo +PEG-IFN 180µg (N=8)
Race n (%)	Asian	2 (29%)	2 (25%)	4 (44%)	3 (33%)	2 (29%)	2 (25%)	2 (25%)	3 (33%)	2 (25%)
	Black	-	2 (25%)	1 (11%)	1 (11%)	2 (29%)	2 (25%)	2 (25%)	-	1 (13%)
	White	5 (71%)	4 (50%)	4 (44%)	5 (56%)	3 (43%)	4 (50%)	4 (50%)	6 (67%)	5 (63%)
HBV DNA Log10 IU/ml)	mean (SD)	6.1 (6.5)	3.5 (3.5)	4.4 (4.6)	7.4 (7.9)	4.3 (4.6)	6.4 (6.9)	7.5 (7.9)	7.5 (7.9)	7.5 (7.9)
HBsAg (IU/mL)	mean (SD)	4200 (3700)	4800 (4900)	11800 (12900)	8500 (11300)	3700 (5400)	6300 (5500)	14000 (18000)	14000 (25000)	40000 (89000)

Virology

- Part A: HBV DNA −3.6 log_{10}IU/mL (p<0.001) reduction with ETV only. HBsAg decrease of −0.1 log_{10}IU/mL (p<0.01) in the 400mg QD EYP001 group only.
- Part B: No additional effect of EYP001 with PEG-IFN on HBV DNA decline. Possible synergy of EYP001 with Peg-IFN on HBcrAg and HBV pgRNA.

	HBV DNA Log10 IU mL			HBVpgRNA Log10 Cps mL			HbsAg Log10 IU mL			qHBcrAg Log10 U mL		
Treatment Group	Estimate	95% CI	P-value	Estimate	95% CI	P-value	Estimate	95% CI	P-value	Estimate	95% CI	P-value
ETV 0.5 mg QD (n=7)	**-3.61**	(-4.19; -3.03)	**<0.01***	-0.34	(-1.52; 0.85)	0.57	-0.04	(-0.11; 0.03)	0.26	0.03	(-0.85; 0.91)	0.95
EYP001a 100 mg QD (n=7)	0.11	(-0.47; 0.69)	0.70	0.48	(-0.70; 1.66)	0.42	-0.02	(-0.09; 0.05)	0.51	-0.32	(-1.20; 0.56)	0.47
EYP001a 200 mg QD (n=8)	0.23	(-0.31; 0.78)	0.40	0.35	(-0.76; 1.45)	0.53	-0.03	(-0.10; 0.04)	0.39	0.24	(-0.58; 1.06)	0.57
EYP001a 400 mg QD (n=8)	0.08	(-0.44; 0.61)	0.75	0.26	(-0.82; 1.34)	0.64	-0.1	(-0.17;-0.04)	**<0.01***	0	(-0.78; 0.79)	0.99
EYP001a 200 mg BID (n=8)	0.17	(-0.37; 0.70)	0.53	0.02	(-1.10; 1.15)	0.97	-0.05	(-0.11; 0.02)	0.18	0.97	(0.15; 1.79)	**0.02***
Placebo (n=8)	-0.14	(-0.69; 0.40)	0.60	-0.7	(-1.81; 0.41)	0.21	-0.04	(-0.10; 0.03)	0.29	0.18	(-0.65; 1.00)	0.67
EYP001a 300 mg QD + PEG-INF (n=8)	-2.23	(-2.77;-1.68)	**<0.01***	-1.65	(-2.75;-0.54)	**<0.01***	0	(-0.07; 0.06)	0.91	-0.92	(-1.74;-0.10)	**0.03***
EYP001a 150 mg BID + PEG-INF (n=9)	-1.6	(-2.12;-1.08)	**<0.01***	-0.82	(-1.89; 0.26)	0.13	-0.05	(-0.12; 0.01)	0.10	-0.14	(-0.92; 0.65)	0.73
Placebo +PEG-INF (n=8)	-2.35	(-2.90;-1.81)	**<0.01***	-0.24	(-1.35; 0.86)	0.66	0.12	(0.05; 0.18)	**<0.01***	-0.36	(-1.18; 0.46)	0.39

Table HBV Markers Log 10 changes from baseline to end of treatment Day 29. * p<0.05

Safety:

- No serious adverse events . No suspected unexpected adverse events.
- Dropouts: rash (n=2), pruritus (n=1), preexisting missed unrelated borderline QT prolongation.
- Most frequent AE: mild moderate gastrointestinal complaints. Transient pruritus seen in 4/32 (12.5%) patients with QD vs. 11/18 (61.1%) with BID regimens (p<0.05).
- 4 transient, isolated ALT/AST flares (Grade 3, n=3 and 4, n=1); some HBV DNA decrease; all patients continued EPY001 treatment per protocol.

TEAEs	Part A			Part B	
	EYP001 (n=33)	ETV(n=7)	Placebo (n=8)	EYP001(n=17)	Placebo (n=8)
≥ 1AE	45%	29%	38%	82%	75%
Gastrointestinal	39%	43%	13%	29%	38%
Headache	27%	0%	30%	35%	50%
Pyrexia	0%	0%	0%	47%	50%
Leukopenia	0%	0%	0%	24%	13%
Neutropenia	0%	0%	0%	53%	75%
Myalgia	11%	0%	25%	29%	50%
Skin disorder	33%	14%	0%	41%	13%

Pharmacodynamic Bile acid marker: a EYP001 dose-related

- C4 decrease from 14-31 ng/mL to 1-6 ng/mL vs. increased concentrations with ETV or placebo/PEG-IFN in the 35-46 ng/mL range.
- FGF-19 increase in a range of 399-2947 pg/mL vs. no change with ETV or placebo/peg-IFN (210-296 pg/mL)

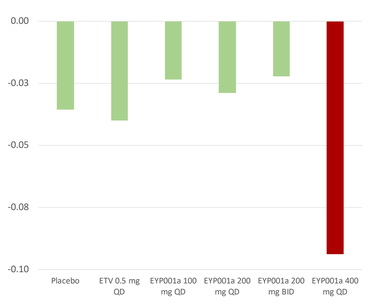

Figure 1: Part A groups HBsAg Day 29 mean change (Log10 IU/mL). *EYP001 400mg QD (red), p<0.01.*

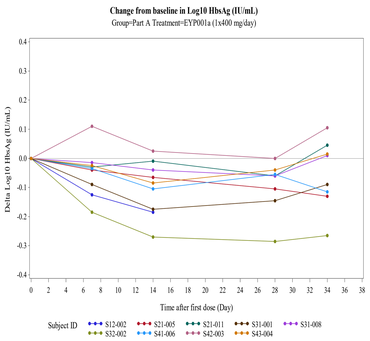

Figure 2 Individual HBsAg change (Log10 IU/mL) *over time in the EYP001 400mg QD group.*

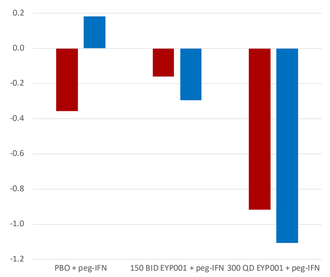

Figure 3 HBcrAg (Log10 IU/mL) mean changes from baseline*: in EYP001 or Placebo with PEG-IFN treated groups. Day 29 (red), EYP001 300mg + PEG-INF p=0.03. Follow up Day 35 (blue), EYP001 300mg + PEG-INF p=0.005. Note n=8 <LLOD, n=12 >LLOQ.*

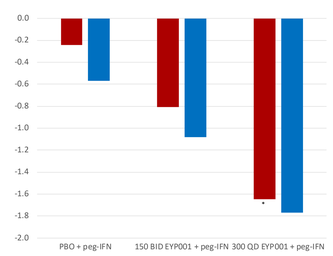

Figure 4 pgRNA (Log10 copies IU/mL) mean changes from baseline: *EYP001 or Placebo with PEG-IFN groups. Day 29 (red), EYP001 300mg + PEG-INF p<0.01. Follow up Day 35 (blue), EYP001 300mg + PEG-INF p<0.01. Note: n=9 <LLOD, n=6 >LLOQ.*

CONCLUSION

- EYP001 QD regimens were safe and well tolerated in CHB patients
- C4 and FGF19 response only in EYP001 group reflecting the engagement of patient FXR.
- With only 4 weeks treatment of EYP001 400mg QD a HBsAg reduction was observed.
- EYP001 may be synergistic with PEG-IFN. Further testing in Phase 2 trials is planned.

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