Vonafexor combined with peg-IFN in HBeAg-treatment naive CHB patients

P. SCALFARO[1], M. ODOUL[1], J. VONDERSCHER[1], R. DARTEIL[1], V. LE MEAUX[1], H. GIRMA[1], J. HEO[2], C.J. LIU[3], C.W. HSU[4], W.L. CHUANG[5], T.H. HU[6], W.K.W. SETO[7], A. KARAPET[8] and D. DURANTEL[9]

[1]ENYO Pharma SA, Lyon, France, [2]Pusan National University Hospital, Busan, South Korea, [3]National Taiwan University Hospital, Tapei, Taiwan, [4]Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan, [5]Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan, [6]Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [7]Queen Mary Hospital, Pokfulam, Hong Kong, [8]LyonaPharm Consulting, Lyon, France, [9]CIRI INSERM, Lyon, France

INTRODUCTION

Standard of care treatments for chronic hepatitis B infection (CHB) with nucleosid(t)e analogues (NA) or pegylated interferon alpha2a (peg-IFN) often fail to induce a functional cure, which is characterised by the sustained loss of hepatitis B surface antigen (HBsAg) with or without HBsAg antibody seroconversion leading to improved clinical outcomes [1]. There is a high need to improve CHB functional cure rates with a finite treatment duration. The nuclear farnesoid X receptor (FXR) is a key factor regulating bile acid homeostasis and a drug target for metabolic liver diseases. FXR is also involved in HBV replication. Vonafexor (code name EYP001) is a selective, synthetic, non-bile salt, carboxylic acid agonist of FXR and impacted HBsAg levels *in vitro* and in CHB patients. In a 4 week treatment phase 1b study it showed good tolerance and a 0.1 log HBsAg reduction and synergy with peg-IFN on transcriptional HBV markers [2].

This trial was designed to test the safety and anti-viral effect of Vonafexor targeting the host factor FXR and administered over 16 weeks in combination with peg-IFN to treatment naive CHB patients. We report preliminary week 16 results.

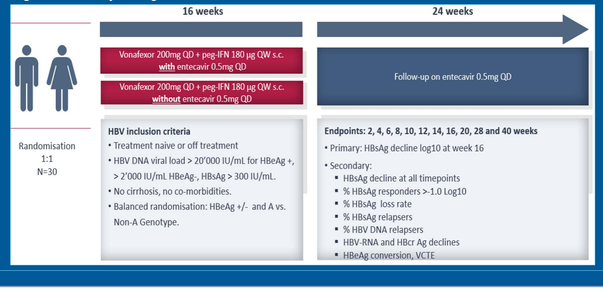
AIM

To evaluate the safety and antiviral effect of Vonafexor in combination with peg-IFN administered over 16 weeks to patients with CHB.

METHOD

In this ongoing multi-center, randomized, open-label Phase 2a trial, treatment naive CHB patients were randomized to a combination of oral Vonafexor 200mg QD with sub-cutaneous peg-IFN (180 mcg weekly QW) to which Entecavir (0.5 mg QD, ETV) was added (arm 1) or not (arm 2). Non-CHB or worsening liver disease were excluded. Experimental treatment during 16 weeks is followed by an ongoing 24 week maintenance with ETV (Figure A). Virology and safety assessments were collected every 2 weeks. Primary endpoints are the number of adverse events (AE) and the HBsAg decline from baseline to W16. Change from baseline to Week 28 in HBsAg was analyzed using a mixed effect model for repeated measures (MMRM). The model included treatment, HBsAg baseline, HBeAg baseline status (positive or negative), visit, and treatment-by-visit interaction as fixed effects and visit as a repeated measure.

Figure A: Study design



RESULTS

Reported data are preliminary. Enrolled patients (n=20) had a mean age of 46.9 years, 50% were female and 100% Asian (Figure B). Frequent Treatment Emergent Adverse Events (TEAE) were as expected and similarly causaly related to Vonafexor (VONA) and/or peg-IFN (Figure C) except for flue-like symptoms. TEAE were mostly mild (40%) or moderate (39%). Ten patients had isolated Alanine Aminotransferase/Aspartate Aminotransferase (ALT/AST) flares (grading per multiples of Upper Limit of Normal (ULN)) resolving with dosing interruptions. They were considered therapeutic flares (isolated transient ALT/AST increases) likely peg-IFN mediated (Figure D, evaluation of Drug-Induced Serious Hepatotoxicity, eDISH) with no DILI defining events. One patient was monitored in hospital during 3 days with also favourable outcome. Of note some patients showed viral response without Grade ≥2 flares (Figure E). Surprisingly all (n=12) HBeAg- patients, who reached W16, had a pronounced and significant HBV DNA and HBsAg decline, whereas HBeAg+ (n=6) showed less response both for HBV-DNA and HBsAg: -3.8(0.4) log10 IU/mL (mean, SE, p<0.001) vs. -0.7 (0.5, p=0.21) and -0.8 (0.1, p<0.001) vs. -0.0 (0.1, p=0.96) respectively (Figure F). On W20 HBeAg- patients reached HBsAg decline of -1.0 log10 (0.09, p<0.0001), compared to HBeAg+ with 0.0 log 10 (0.13, p=0.86). In addition, HBeAg- patients had a more pronounced HBsAg decline with dual (arm 2) over triple treatment (arm 1): HBsAg change -1.1 (0.1) log10 IU/mL (mean, SE, p<0.001) vs. -0.6 (0.1, p<0.001). Finally on W20 all available HBeAg- patients (10/10, p<0.001) had HBV DNA <limit of quantification (LOQ: 1.3 log10 = 20 IU/mL). A to short treatment duration, or dosing interruptions, explain the HBsAg flares seen during follow-up in some patients (Figure E).

Figure B: Baseline characteristics. **ALT <ULN except n=3 with ALT>ULN and <2xULN. # p<0.05*

Female, n (%)	10 (50)
Male, n (%)	10 (50)
Age, years (SD)	46.9 (9.1)
Asian n (%)	20 (100)
HBeAg status, n (%): Negative	13 (65)
HBV genotype, n (%): B	6 (30)
HBV genotype, n (%): determination ongoing	14 (70)
ALT* U/L (mean, SD)	33 (14.2)
HBV-DNA $\log_{10}$ IU/ML (mean, SD): HBeAg positive	7.8 (1.0)
HBV-DNA $\log_{10}$ IU/ML (mean, SD): HBeAg negative	4.6 (1.2)#
qHBsAg $\log_{10}$ IU/ML (mean, SD): HBeAg positive	4.2 (0.6)
qHBsAg $\log_{10}$ IU/ML (mean, SD): HBeAg negative	3.0 (0.4)#

Figure C: TEAE related to Vonafexor or peg-IFN (N, % patients)

TEAE (high level term)	N VONA	% VONA	N peg	% peg
Liver function analyses	11	55	10	50
Pruritus	11	55	7	35
Hepatocellular damage and hepatitis	2	10	1	5
Asthenic conditions	1	5	3	15
Diarrhoea (excl infective)	1	5	0	0
Febrile disorders	1	5	4	20
Menstruation and uterine bleeding	1	5	1	5
Nasal congestion and inflammations	1	5	0	0
Purpura and related conditions	1	5	1	5
Skeletal and cardiac muscle analyses	1	5	1	5
White blood cell analyses	0	0	3	15
Headaches NEC	0	0	2	10
Muscle pains	0	0	2	10
Platelet analyses	0	0	2	10

Figure D: eDish plot: total bilirubin (TB) vs. ALT

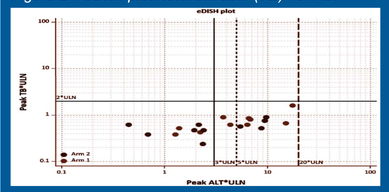


Figure E: Two characteristic patient time-course. *Liver tests expressed as x ULN. Viral markers (HBV DNA, HBsAg) as log10 IU/mL, grey dotted line HBV DNA limit of quantification (1.3 log10). Left fig: 65 yr Asian male, right fig: 50 yr Asian male.*

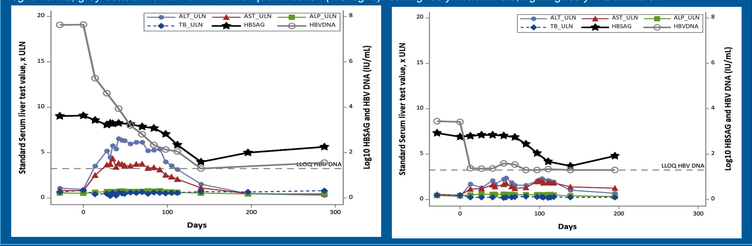
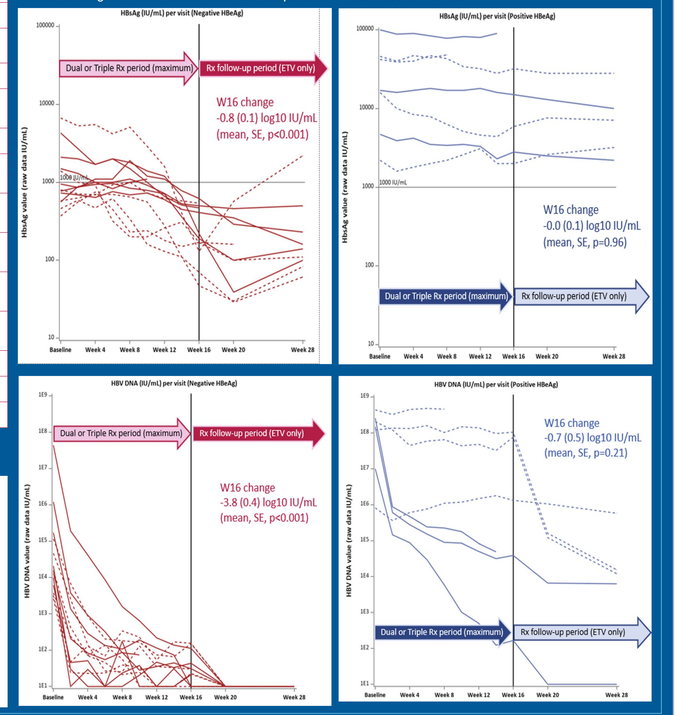


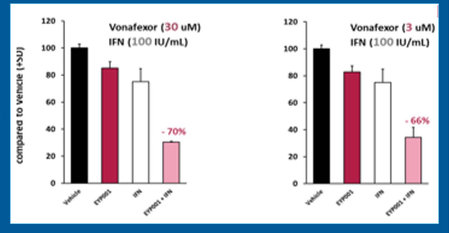
Figure F: Ongoing HBsAg and HBV-DNA data collection of individual patient timeseries per HBeAg status: red left fig HBeAg-, blue right fig HBeAg+. *The period from baseline to W16 (Day 112) is the experimental treatment period with administration of either triple therapy (=solid lines, Vonafexor 200mg QD on top of peg-IFN (180 mcg QW) and Entecavir (0.5 mg QD) or dual therapy (= dashed lines, Vonafexor 200mg QD on top of peg-IFN (180 mcg QW). The follow-up period is from W17 (Day 113) to W40 (Day 280) with administration of Entecavir 0.5 mg QD only. Note: patients with ALT/AST Grade 2 or higher had dose reductions/interruptions until decrease of ALT/AST.*



CONCLUSIONS

Vonafexor administered on top of peg-IFN induced a marked early HBsAg decline in HBeAg- treatment naive CHB patients. An early HBsAg decline with similar effect size is usually not obtained with peg-IFN based treatments [3]. Longer durations are expected to avoid HBsAg rebounds seen during follow-up. No clear relationship between transaminase flares and viral response was found. The synergistic response and involved cellular signalling pathways are further investigated. An FXR related synergy with peg-IFN effects may involve FXR controlled cellular pathways with links to the innate immunity. Tests in primary human hepatocytes (PHH) treated with Vonafexor and peg-IFN showed a strong potentiation (Figure G).

Figure G: Fresh PHH infected with HBV (high levels of infection). % HBsAG secretion compared to vehicle (SD)



Distinguishing an immune inactive CHB HBeAg- patient (i.e. in phase 3 with low HBV DNA ≤2,000 IU/mL with persistently normal ALT) from an immune active CHB (i.e. in phase 4 with both elevated HBV DNA and ALT levels) also called HBeAg- chronic hepatitis, is not always straightforward. HBeAg- patients in this trial had all increased HBV DNA but normal or nearly normal ALT categorising them in between these phases. Combining FXR agonist Vonafexor with an immunomodulator could be an attractive host-target based strategy with improved functional cure rates. HBeAg- CHB patients, who have low rates of spontaneous disease remission with persistent hepatocellular inflammation, fibrosis and cirrhosis [4]. They will be selected in future trials with optimized regimens and HBV drugs combinations.

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The trial is registered at Clinicaltrials.gov: NCT04365933

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CONTACT INFORMATION

ENYO Pharma SA, BIOSERRA 1 Bâtiment B, 60 avenue Rockefeller, 69008 Lyon, France. contact@enyopharma.com - www.enyopharma.com