ENYO Pharma SA
Lyon, France

Protocol Number: EYP001-201

IND Number: 142570

EudraCT number: 2019-001629-28

A PHASE 2a, RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF ORAL FXR MODULATOR EYP001a COMBINED WITH NUCLEOS(T)IDE ANALOGUES (NA) IN VIROLOGICALLY SUPPRESSED CHRONIC HEPATITIS B PATIENTS TO IMPROVE FUNCTIONAL CURE RATES

Investigational Product:	EYP001a
Study Phase:	Phase 2a
Study Director:	ENYO Pharma SA 60 avenue Rockefeller, Bâtiment Bioserra B. 69008 LYON FRANCE
Version / Date:	3.0 (Amendment 4) / 22 January 2020

The name, title, address and telephone number(s) of the sponsor's medical monitor is documented in the study contact list located in the site's study folder.

SPONSOR PROTOCOL SIGNATURE PAGE

Protocol Number: EYP001-201

Protocol Title: A Phase 2a, randomized, double-blind, placebo-controlled study of oral FXR modulator EYP001a combined with Nucleos(t)ide analogues (NA) in virologically suppressed chronic hepatitis B patients to improve functional cure rates

This study has been prepared and reviewed by the Sponsor for distribution to designated clinical sites, associated ethics committees/institutional review boards, designated contractors, regulatory agencies, and with permission by the Sponsor.

The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki and the guidelines on Good Clinical Practice.

Approved by the following:

Pietro Scalfaro		
Chief Medical Officer	Signature	Date
ENYO PHARMA		

INVESTIGATOR ACKNOWLEDGEMENT

Protocol Number: EYP001-201

Protocol Title: A Phase 2a, randomized, double-blind, placebo-controlled study of oral FXR modulator EYP001a combined with nucleos(t)ide analogues (NA) in virologically suppressed chronic hepatitis B patients to improve functional cure rates

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines, the Declaration of Helsinki and local regulations (as applicable).

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

I will provide all study personnel under my supervision with copies of this protocol and its related investigational product Investigator's Brochure, and access to all study-related information provided by the Sponsor and designated study monitor. I will discuss this study-related information with my staff to ensure that they are fully informed about the investigational product and the protocol.

I agree to provide all participants with a signed and dated copy of the informed consent document, as required by local regulations and ICH-GCP. I further agree to report to the Sponsor on any adverse events in accordance with the terms of this protocol, as per the applicable regulations where applicable.

Principal Investigator

_____ _____

Signature Date

PROTOCOL AMENDMENT SUMMARY

Document History

Document	**Date of Issue**
Protocol version 3.0 (Amendment 4)	22 January 2020
Protocol version 2.2 (Amendment 3)	09 August 2019
Protocol version 2.1 (Amendment 2)	17 July 2019
Protocol version 2.0 (Amendment 1)	03 July 2019
Original Protocol version 1.0	16 April 2019

Summary of Changes

LIST OF PROTOCOL CHANGES FROM PROTOCOL VERSION 2.2 (AMENDMENT 3) DATED 09 August 2019 TO PROTOCOL VERSION 3.0 (AMENDMENT 4) DATED 22 January 2020

<table>
<tr><th>Change ID#</th><th>Section Number</th><th>Protocol Version 2.2 (Amendment 3) dated 09 August 2019</th><th>Protocol Version 3.0 (Amendment 4) dated 22 January 2020</th></tr>
<tr><td rowspan="2">1</td><td rowspan="2">Title Page and Header throughout the document</td><td colspan="2">Change/rationale: Updated Title Page, and Header throughout the document to reflect the updated version no. and date.

Typo corrected in Enyo Pharma address in title page and address corrected in INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE p55:</td></tr>
<tr><td>Previously read:
ENYO Pharma SA
60 avenue Rockfeller,
Bâtiment Biosera B. 69008 LYON
FRANCE</td><td>Now reads:
ENYO Pharma SA
60 avenue Rockefeller,
Bâtiment Bioserra B. 69008 LYON
FRANCE</td></tr>
</table>

		Previously read: Version 2.2 (Amendment 3) / 09 August 2019	**Now reads:** Version ~~2.2~~**3.0** (Amendment ~~3~~**4**) / ~~09 August 2019~~**22 January 2020**
2	**Throughout the document.** **Sections 1.4.3.3, 1.5.1 and 5.4**	**Change/rationale:** The daily oral EYP001a dose to be administered during 16 weeks is reduced from 400 mg QD (two 200 mg tablets) to 200 mg QD (one 200 mg tablet). The rationale for dose selection has also been updated. The rationale for the change is as following: In an ongoing phase 2a trial (EYP001-202, 24 NASH subjects enrolled as of 18 December 2019) and in an ongoing phase 1 trial (EYP001-107, 9 NASH and 4 healthy subjects enrolled as of 18 December 2019), 100mg and 200mg EYP001a oral tablets were tested at the dose levels 100mg BID, 200mg QD and 400mg QD. These are the preliminary findings: **PK profile of EYP001 tablet:** ● The oral EYP001a tablet formulation appears to have higher bioavailability compared to the oral capsule formulation previously used in EYP001 phase 1 studies in healthy and subjects with CHB. ● The similar exposure seen in NASH subjects with the 200mg QD (1x200mg tablet) and the 400mg QD (2x200mg tablets) suggests a saturation phenomenon with exposure reaching a plateau over the 200mg dose level ● A similar EYP001 plasma concentrations were obtained in simulations performed for CHB subjects for the 200mg QD (1x200mg tablet) compared to concentrations after administration of the 400mg QD (2x200mg capsules). The later was previously tested and well tolerated in study EYP001-103 in CHB subjects. ● Finally the differences of the PK parameters after administration of 200mg, 400mg QD repeated oral EYP001a doses either as capsules or tablet show that the daily dose of 200mg given as tablet leads to an exposure similar to a daily dose of 400mg given as capsules (details in to IB memorandum dated 16 January 2020 [IB Memo, 2020]). **Safety & Tolerance:** ● **Pruritus:** In ongoing study EYP001-202, NASH subjects treated during 12 weeks with EYP001a 100mg BID or 200mg QD or 400mg QD or Placebo tablets, had an overall pruritus frequency of 15/24 (64%) subjects, all mild or moderate episodes, except for three Grade 3. Five pruritus episodes led to	

		early treatment termination. This is in contrast with previous experience in study EYP001-103, in which CHB subjects were treated during 4 weeks with EYP001a capsules, and had mostly mild or moderate pruritus episodes: 1 subject of 7 to 9 (11% to 14%) in each of the EYP001 arms (100 mg, 200 mg and 400 mg QD) but increased to 6 of 9 (67%) subjects treated with 200 mg BID. One subject terminated early because of pruritus. ● **ALT/AST:** In study EYP001-202, two grade 3 cases of isolated transient ALT/AST increases, with no signs of liver impairment, occurred around Day 56 of treatment. No Hy's law cases occurred (no confirmed DILI). The designation by the Primary Investigators (PIs) of the liver enzyme elevations did not consider these as clinically significant, with a variance over time with few outliers, overall not unexpected in the NASH patient population.. This compares and is in line with previous phase 1 trials results, where ALT and AST values were within the normal range following EYP001a administration in healthy subjects and in study EYP001-103 after 4 weeks of administration of EYP001a to CHB subjects, 5 subjects had Grade 3 (n=4) or 4 (n=1) ALT/AST increases without signs of liver impairment. The changes were interpreted as hepatic flares or typical of those seen in subjects with underlying chronic viral HBV liver disease. Taken together, these PK and safety/tolerance preliminary findings in the ongoing NASH and phase 1 trial obtained with the EYP001a tablet formulation do not support the use of the 400mg daily EYP001 dose as a tablet. The reduction to 200mg QD (1x200mg tablet) will generate an exposure similar to previously tested and well tolerated 400mg QD (2x200mg capsules). EYP001a 200mg tablet QD dose can be assessed safely in CHB subjects over the planned 16 week treatment period. For more details, please refer to IB memorandum dated 16 January 2020 (IB Memo, 2020)
		Previously read: - EYP001a 400 mg once daily - 2 x tablets of 200 mg - 400 mg QD was selected because it is the highest tested and well tolerated dose administered during 4 weeks to CHB patients with an effect on HBsAg reduction *1.4.3.3. Clinical Safety*
		Now reads: - EYP001a **200** ~~400~~ mg once daily - ~~2 x~~ **1** tablet~~s~~ of 200 mg - **An initial dose of** 400 mg QD **capsules** was selected because it ~~is~~ **was** the highest tested and well tolerated dose administered during 4 weeks to CHB patients with an effect on HBsAg reduction *1.4.3.3. Clinical Safety*

		Overall EYP001a is considered safe over the dose range of 100 mg to 400 mg QD and 200 mg BID. Aforementioned data support the selection of the 400 mg dose for study EYP001 201.	Overall EYP001a is considered safe over the dose range of 100 mg to 400 mg QD and 200 mg BID **given as capsules**. Aforementioned data **initially** support**ed** the selection of the 400 mg **tablet** dose for study EYP001 201. **Nevertheless, PK and safety/tolerance preliminary findings in ongoing EYP001-202 NASH phase 2a and in the EYP001-107 phase 1 NASH trials with the EYP001a tablet formulation, do not support the use of the 400mg daily single oral EYP001 dose with the tablet formulation. The reduction to 200mg QD (1x200mg tablet) will generate an exposure similar to 400mg QD (2x200mg capsules) dose that was previously tested and well tolerated. EYP001a 200mg tablet QD dose can be assessed safely in CHB subjects over the planned 16 week treatment period.**
		1.5.1. Rationale for Study Conduct Overall given the high need to improve functional HBV cure rates with a finite treatment and the observations of oral QD doses of EYP001a to be well tolerated, with a dose dependent signal on HBsAg reduction after only 4 weeks therapy, the exploration of an EYP001a prolonged treatment on top of NA seems justified. This study was designed to test the safety and the antiviral effect of 400 mg QD EYP001a when administered in combination with stable NA therapy over 16 weeks on HBsAg in CHB patients who are virologically suppressed on a stable NA therapy[1].	**1.5.1. Rationale for Study Conduct** Overall given the high need to improve functional HBV cure rates with a finite treatment and the observations of oral QD doses of EYP001a to be well tolerated, with a dose dependent signal on HBsAg reduction after only 4 weeks therapy, the exploration of an EYP001a prolonged treatment on top of NA seems justified. ~~This~~ **The** study **EYP001-201**was **initially** designed to test the safety and the antiviral effect of 400 mg QD EYP001a when administered in combination with stable NA therapy over 16 weeks on HBsAg in CHB patients who are virologically suppressed on a stable NA therapy[1]. **Nevertheless, in light of preliminary findings in ongoing EYP001-202 NASH phase 2a and in the EYP001-107 phase 1 NASH trials (Section 1.4.3.3)**

			the dosage has been modified to 200mg QD (1x200mg tablet) which generates a similar plasma exposure as 400mg QD (2x200mg) capsules, previously tested and well tolerated dose.
		5.4. Dose Rationale and Selection of Doses in the Study A dose of 400 mg QD EYP001a was selected because it is the so far highest tested over 4 weeks and was well tolerated by chronically infected-HBV patients. It also showed an apparent dose dependent signal on HBsAg reduction. Overall, EYP001a was safe and well tolerated over the dose range of 100 mg to 500 mg QD and 200 mg BID but was better tolerated with the QD regimen than with BID dosing. This is an early stage Phase 2a exploratory study to determine if adding EYP001a 16 week treatment on top of NA can induce a clinically meaningful and statistically significant reduction of HBsAg plasma levels after 16 weeks of combined treatment. A dose strength of 400 mg QD EYP001a was selected because it is the so far highest tested dose over 4 weeks and was well tolerated by CHB patients. It also showed an apparent dose dependent signal on HBsAg reduction. For practical reasons, no lower EYP001a doses are included in this study and an appropriate dose ranging study will be performed later, should results meet the study endpoints.	**5.4. Dose Rationale and Selection of Doses in the Study** ~~A dose of 400 mg QD EYP001a was selected because it is the so far highest tested over 4 weeks and was well tolerated by chronically infected-HBV patients. It also showed an apparent dose dependent signal on HBsAg reduction.~~ Overall, EYP001a was safe and well tolerated over the dose range of 100 mg to 500 mg QD and 200 mg BID but was better tolerated with the QD regimen than with BID dosing. This is an early stage Phase 2a exploratory study to determine if adding EYP001a 16 week treatment on top of NA can induce a clinically meaningful and statistically significant reduction of HBsAg plasma levels after 16 weeks of combined treatment. A**n initial** dose strength of 400 mg QD EYP001a **capsules** was selected because it is the so far highest tested dose over 4 weeks and was well tolerated by CHB patients. It also showed an apparent dose dependent signal on HBsAg reduction. ~~For practical reasons, no lower EYP001a doses are included in this study and an appropriate dose ranging study will be performed later, should results meet the study endpoints.~~ **However in an ongoing phase 2a trial (EYP001-202, 24 NASH subjects enrolled as of 18 December 2019) and in an ongoing phase 1 trial (EYP001-107, 9NASH and 4 healthy subjects enrolled as of**

			18 December 2019), 100mg and 200mg EYP001a oral tablets were tested at the dose levels 100mg BID, 200mg QD and 400mg QD. These are the preliminary findings: **PK profile of EYP001 tablet:** ● **The oral EYP001a tablet formulation appears to have higher bioavailability compared to the oral capsule formulation previously used in EYP001 phase 1 studies in healthy and subjects with NASH.** ● **The similar exposure seen in NASH subjects with the 200mg QD (1x200mg tablet) and the 400mg QD (2x200mg tablets) suggests a saturation phenomenon with exposure reaching a plateau over the 200mg dose level** ● **A similar EYP001 plasma concentrations were obtained in simulations performed for CHB subjects for the 200mg QD (1x200mg tablet) compared to concentrations after administration of the 400mg QD (2x200mg capsules). The later was previously tested and well tolerated in study EYP001-103 in CHB subjects.** ● **Finally the differences of the PK parameters after administration of 200mg, 400mg QD repeated oral EYP001a doses either as capsules or tablet** **Safety & Tolerance:** ● **Pruritus: In an ongoing study EYP001-202 , NASH subjects treated during 12 weeks (with EYP001a 100mg BID or 200mg QD or 400mg QD or Placebo tablets) had an**

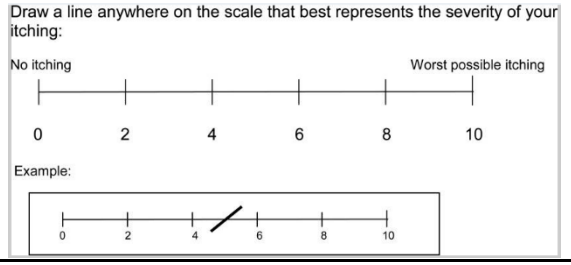
			overall pruritus frequency of 15/24 (64%) subjects, all mild or moderate episodes, except for three Grade 3. Five pruritus episodes led to early treatment termination. This is in contrast with previous experience in study EYP001-103, in which CHB subjects were treated during 4 weeks with EYP001a capsules, and had mostly mild or moderate pruritus episodes: 1 subject of 7 to 9 (11% to 14%) in each of the EYP001 arms (100 mg, 200 mg and 400 mg QD) but increased to 6 of 9 (67%) subjects treated with 200 mg BID. One subject terminated early because of pruritus. ● **ALT/AST: In study EYP001-202, two grade 3 cases of isolated transient ALT/AST increases, with no signs of liver impairment, occurred around Day 56 of treatment. No Hy's law cases occurred (no confirmed DILI). The designation by the Primary Investigators (PIs) of the liver enzyme elevations did not consider these as clinically significant, with a variance over time with few outliers, overall not unexpected in the NASH patient population. This compares and is in line with previous phase 1 trials results, where ALT and AST values were within the normal range following EYP001a administration in healthy subjects and in study EYP001-103 after 4 weeks of administration of EYP001a to CHBV subjects, 5 subjects had Grade 3 (n=4) or 4**

			(n=1) ALT/AST increases without signs of liver impairment. The changes were interpreted as hepatic flares or typical of those seen in subjects with underlying chronic viral HBV liver disease. **Taken together, these PK and safety/tolerance preliminary findings in the ongoing NASH and phase 1 trial obtained with the EYP001a tablet formulation do not support the use of the 400mg daily EYP001 dose as atablet. The reduction to 200mg QD (1x200mg tablet) will generate an exposure similar to previously tested and well tolerated 400mg QD (2x200mg capsules). EYP001a 200mg tablet QD dose can be assessed safely in CHB subjects over the planned 16 week treatment period.** **For more details, please refer to IB memorandum dated 16 January 2020 (IB Memo, 2020).**
3	**Throughout the document**	**Change/rationale:** Visit Day 0 has been updated to Day 1 to be consistent with EYP001 other clinical studies.	
		Previously read: Day 0	**Now reads:** ~~Day 0~~ **Day 1**
4	**Follow-up visits time window throughout the document**	**Change/rationale:** Extended time window for follow-up visit during maintenance period: helpful for the visit date arrangement for site	
		Previously read: FU visit 1 (Week 20 [Day 140 ± 3 days]) FU visit 2 (Week 28 [Day 196 ± 3 days]) FU visit 3 (Week 40 [Day 280 ± 3 days])	**Now reads:** FU visit 1 (Week 20 [Day 140 ± ~~3~~ **7** days]) FU visit 2 (Week 28 [Day 196 ± ~~3~~ **7** days]) FU visit 3 (Week 40 [Day 280 ± ~~3~~ **7** days])
5	**Section 6.2.2.9**	**Change/rationale:** error	

		Previously read: **6.2.2.9. Treatment Visit 9 (Week 16 [Day 112± 3 days])** • Dispense EYP001a or placebo and NA	**Now reads:** **6.2.2.9. Treatment Visit 9 (Week 16 [Day 112± 3 days])** • Dispense ~~EYP001a or placebo and~~ NA
6	**Section 6.2.3.2 and 6.2.3.3**	**Change/rationale:** discrepancy between section 6.2.3.2 and 6.2.3.3 and section 19.1 Appendix A - Schedule of Assessment*	
		Previously read: **6.2.3.2. Follow-up Visit 2 (Week 28 [Day 196± 3 days])** *(Page 97 of 139 in the Protocol)* • Perform liver imaging to screen patient for HCC. For patients with risk factors for HCC, i.e. any of these: family history with HCC, >40 years of age, male sex, born in Sub-Saharan Africa, Metabolic syndrome (obesity, diabetes), smoking, ALT>ULN, HBV DNA (>2,000 IU/mL), HBeAg-negative, Genotype C) during follow-up phase liver imaging is also performed at week 28. **6.2.3.3. Follow-up Visit 3/EoS Visit (Week 40 [Day 280± 3 days])** *(Page 97 of 139 in the Protocol)* ***none***	**Now reads:** **6.2.3.2. Follow-up Visit 2 (Week 28 [Day 196± ~~3~~7 days])** *(Page 97 of 139 in the Protocol)* ~~• Perform liver imaging to screen patient for HCC. For patients with risk factors for HCC, i.e. any of these: family history with HCC, >40 years of age, male sex, born in Sub-Saharan Africa, Metabolic syndrome (obesity, diabetes), smoking, ALT>ULN, HBV DNA (>2,000 IU/mL), HBeAg-negative, Genotype C) during follow-up phase liver imaging is also performed at week 28.~~ 6**.2.3.3. Follow-up Visit 3/EoS Visit (Week 40 [Day 280± ~~3~~7 days])** *(Page 97 of 139 in the Protocol)* • **Perform liver imaging to screen patient for HCC. For patients with risk factors for HCC, i.e. any of these: family history with HCC, >40 years of age, male sex, born in Sub-Saharan Africa, Metabolic syndrome (obesity, diabetes), smoking, ALT>ULN, HBV DNA (>2,000 IU/mL), HBeAg-negative, Genotype C) during follow-up phase liver imaging is also performed at week 40.**
7	**Section 19.2**	**Change/rationale:** Visual Analogue Scale (VAS) had been omitted and therefore was added in Appendix B along with 5-D pruritus scale previously appended to the study protocol.	

<table>
<tr><td></td><td></td><td>Previously read :

19.2. Appendix B: 5-D Pruritus Scale
No VAS</td><td>Now reads:

19.2. Appendix B: <s>5-D</s> Pruritus Scale
 
</td></tr>
<tr><td>8</td><td>Section 5.8</td><td colspan="2">Change/rationale:
The occurrence of pruritus is a known class effect of FXR agonist. It has been reported at varying frequency after the administration of EYP001a (12 to 66% depending on dose level and dosing regimen). Intensity is usually mild or moderate but can be severe interfering with subject daily activities. Recommendation of symptomatic treatment options are introduced in the protocol as well as criteria for a short drug holiday.</td></tr>
<tr><td></td><td></td><td>Previously read:
void</td><td>Now reads:

5.8.1. Pruritus management: guidance to investigators

Self-limited, mostly mild to moderate pruritus has been observed in clinical trials with EYP001 and in a higher proportion of patients who received twice daily dosing regimens. Pruritus has also been reported with other FXR agonists and in patients with NASH as part of the disease natural symptomatology and independent of any pharmacological treatment. Tolerance to pruritus may develop over continuous uninterrupted dosing of EYP001.</td></tr>
</table>

			The following three level therapeutic approach to pruritus can be applied: 1. Topical non-pharmacological or over the counter interventions to improve pruritus may be tried and can be advised to patients. These include application of moisturizers, cooling agents, antihistamines, taking cool showers/showering in the morning, using clear/gentle soaps and laundry detergents, application of cold packs or fabric strips soaked in cold water, avoidance of wool or other irritating fabrics, wearing loose-fitting clothing. 2. With likely no improvement of severe pruritus, a drug holiday of 2 to maximum 5 days may be considered and in such cases, we would encourage to contact the Medical Monitor 3. In situation where pruritus prevails and requires systemic oral pharmacological treatment, the following drugs may be considered at the investigator's judgment and taking into account individual clinical situation, pruritus severity and concomitant medications and comorbidities: antihistamines, hydroxyzine, opioid antagonists, gabapentin (note that the concomitant use of opioid agonists and gabapentin is not recommended).
9	**Synopsis and Section 3.1**	**Change/rationale:** Number of study sites has been updated from 10 sites to 14 sites	
		Previously read:	**Now reads:**

		Synopsis Number of Planned Participants: 49 patients are planned to be enrolled from approximately 10 sites. Study Design: A total of 49 eligible patients will be enrolled and randomized at approximately 10 study sites. **3.1. Description of Overall Study Design and Plan** In total 49 eligible patients will be enrolled and randomized at approximately 10 study sites.	**Synopsis** Number of Planned Participants: 49 patients are planned to be enrolled from approximately ~~10~~ **14** sites. Study Design: A total of 49 eligible patients will be enrolled and randomized at approximately ~~10~~ **14** study sites. **3.1. Description of Overall Study Design and Plan** In total 49 eligible patients will be enrolled and randomized at approximately ~~10~~ **14** study sites.
10	**Synopsis and Section 2.1.2**	**Change/rationale:** Secondary objective for HBV viral markers has been updated to include additional parameters for consistency with the assessments.	
		Previously read: • To determine HBV viral response, HBV pgRNA, HbcrAg and HbeAg at the end of the 16-week EYP001a treatment and Week 40 of follow-up.	**Now reads:** • To determine HBV viral response, HBV pgRNA, H~~b~~**B**crAg ~~and~~ H~~b~~**B**eAg**, anti-HBe and anti-HBs** at the end of the 16-week EYP001a treatment and **at** Week 40 of follow-up.
11	**Synopsis, Sections 2.2.2, 7.1 and 11.3.3.2**	**Change/rationale:** Timepoint Week 40 of maintenance period has been added to secondary endpoints HBV-pgRNA decline ($\Delta \log_{10}$) and HBcrAg decline ($\Delta \log_{10}$).	
		Previously read: • HBV pgRNA decline ($\Delta \log_{10}$) from Day 0 to Weeks 4, 8, 12 and 16 of treatment period • HBcrAg decline ($\Delta \log_{10}$) from Day 0 to Weeks 4, 8, 12 and 16 of treatment period	**Now reads:** • HBV-pgRNA decline ($\Delta \log_{10}$) from Day 1 to Weeks 4, 8, 12, 16 of treatment period **and Week 40 of maintenance period** • HBcrAg decline ($\Delta \log_{10}$) from Day 1 to Weeks 4, 8, 12, 16 of treatment period **and Week 40 of maintenance period**

12	**Section 8**	**Change/rationale:** Condition and procedure for additional chemistry has been included for clarity.	
		Previously read: **8. Safety Assessments** **Clinical laboratory** assessments will include: • **Additional chemistry:** Alpha 2 macroglobulin, autotaxin, cardiac troponin I, ferritin, phosphate and TSH	**Previously read:** **8. Safety Assessments** **Clinical laboratory** assessments will include: **Additional chemistry:** Alpha 2 macroglobulin, autotaxin, cardiac troponin I, ferritin, phosphate and TSH. **These markers will be assessed at the end of study on existing chemistry plasma aliquots collected on Day 1, Day 112 and Day 280, only if relevant improvements in liver inflammation or fibrosis are apparent.**

Additional minor changes have been made to improve clarity and consistency.

CLINICAL PROTOCOL SYNOPSIS

Title of Study:	A Phase 2a, randomized, double-blind, placebo-controlled study of oral FXR modulator EYP001a combined with nucleos(t)ide analogues (NA) in virologically suppressed chronic hepatitis B patients to improve functional cure rates
Protocol Number:	EYP001-201
EudraCT number	2019-001629-28
Investigational Product:	Name: EYP001a tablets Dose: 200 mg (1x tablet of 200 mg) Route of Administration: Oral
Reference/Comparator Product:	Name: Matching Placebo tablets Dose: 1 matching tablet Route of Administration: Oral
Combination Treatment:	NA: Entecavir (ETV) 0.5 mg daily (or per country specific label) or Tenofovir Disoproxil Fumarate (TDF) 300 mg daily which is equivalent to 245 mg of tenofovir disoproxil per country specific label, will be provided as the standard of care (SOC)
Indication:	Chronic hepatitis B (CHB)
Phase of Development:	Phase 2a
Study Centres:	Multi-centre study
Number of Planned Participants:	49 patients are planned to be enrolled from approximately 14 sites
Study Objectives:	**Primary Objective:** • To determine the effect of EYP001a on top of NA SOC therapy) on Hepatitis B surface antigen (HBsAg) plasma levels **Secondary Objectives:** • To establish the effect of EYP001a on top of NA on HBsAg responder rate at the end of the 16-week EYP001a treatment and at 24-week of follow-up (Week 40). • To establish the effect of EYP001a on top of NA on HBsAg loss rate at the end of the 16-week EYP001a treatment and at 24-week of follow-up (Week 40). • To establish the HBV virologic failure rate (breakthrough)[1] during the 24 weeks follow-up period after stopping EYP001a with ongoing NA (SOC therapy).

[1] Breakthrough is defined by quantifiable HBV DNA increase of ≥ 1 $\log_{10}$ HBV DNA copies/mL above LLOQ. Breakthrough samples will be further assessed for resistance assessments, including both for the nucleos(t)ide analogue as well as for EYP001a (e.g., sequence analysis of FXR response elements in HBV genome). Details will be described in the Laboratory manual.

	• To determine HBV viral response, HBV pgRNA, HBcrAg, HBeAg, anti-HBe and anti-HBs at the end of the 16-week EYP001a treatment and at Week 40 of follow-up. • To explore the safety profile of EYP001a treatment in combination with NA. • To determine the plasma concentration of EYP001a and PD markers (plasma C4 [7α-hydroxy-4-cholesten-3-one]), FGF19 (Fibroblast Growth Factor 19) and bile acid (BA).
Study Endpoints	<u>Primary Endpoint</u> • Efficacy assessed as HBsAg decline ($\Delta \log_{10}$) from Day 1 to Week 16 of treatment <u>Secondary Endpoints</u> • Efficacy assessed as: o HBsAg responder rate (decrease from baseline ≥ 1.0 on the $\log_{10}$ scale) at Week 16 of treatment and Weeks 20, 28 and 40 of follow-up. o HBsAg responder rate (decrease from baseline ≥ 0.5 on the log10 scale) at Weeks 12 and 16 of treatment and Weeks 20, 28 and 40 of follow up. o HBsAg loss rate (% patients with HBsAg < lower limit of quantification [LLOQ]) at Week 16 of treatment and Weeks 20, 28 and 40 of follow-up o HBsAg loss rate (Proportion of results that are Target Not Detected versus Target Detected) at Week 16 of treatment and Weeks 20, 28 and 40 of follow-up o Relapse rate HBsAg (% patients who became negative [HBsAg < LLOQ], then increased with HBsAg > LLOQ) at Week 16 of treatment period and Weeks 20, 28 and 40 during follow-up period o Virologic failure rate (breakthrough)[2]of HBV-DNA (% patients with a confirmed quantifiable HBV DNA increase of ≥ 1$\log_{10}$ HBV DNA copies/mL above LLOQ[3]) assessed at Week 16 of treatment period and Weeks 20, 28 and 40 during follow-up period

[2] Breakthrough samples will be further assessed for resistance assessments, including both for the nucleos(t)ide analogue as well as for EYP001a (e.g., sequence analysis of FXR response elements in HBV genome). Details will be described in the Laboratory manual. Also refer footnote no. 8 below.
[3] HBV DNA results <LLOQ will be reported as either <LLOQ/Detected (i.e. LLOQ/TD) or <LLOQ/Target Not Detected (i.e. LLOQ/TND), both are considered LLOQ.

	○ HBV-pgRNA decline ($\Delta \log_{10}$) from Day 1 to Weeks 4, 8, 12, 16 of treatment period and Week 40 of maintenance period ○ HBcrAg decline ($\Delta \log_{10}$) from Day 1 to Weeks 4, 8, 12, 16 of treatment period and Week 40 of maintenance period ○ HBeAg quantification for HBeAg pos patients and changes at Week 16 of treatment and Week 40 of follow-up ○ Fibroscan VCTE change from screening value to Weeks 16 and 40 or ET value • Safety and Tolerability assessed as: ○ Treatment-emergent adverse events (TEAEs) (including serious adverse events [SAEs]) ○ All-cause mortality ○ Clinical laboratory tests ○ Pruritus assessment ○ Vital signs (blood pressure, heart rate, respiratory rate, and temperature) ○ Concomitant medications ○ Physical examinations ○ 12-lead ECG • PK assessed as: ○ Plasma concentration of EYP001a or any relevant active metabolites (as identified in an ongoing phase 1 study). • PD markers: ○ Plasma C4 (7α-hydroxy-4-cholesten-3-one) ○ FGF19 ○ Plasma primary and secondary Bas
Study Design:	This is a prospective, multi-centre, randomized, double-blind, placebo-controlled, Phase 2a experimental study of oral FXR modulator EYP001a/placebo combined with NAs in virologically suppressed CHB patients to improve functional cure rates. A total of 49 eligible patients will be enrolled and randomized at approximately 14 study sites. Patients will be randomized prior to study drug (EYP001a or placebo and NA) administration on Day 1 in the ratio of 3:1 into 2 arms: • Experimental Arm: EYP001a 200 mg QD + NA daily (37 patients) • Control Arm: Placebo + NA daily (12 patients) Patients will also be stratified per HBeAg status, based on medical history or established during screening, to obtain a balanced randomization to both study arms.

	The maximum total engagement duration for eligible patients in this study is up to 370 days: 90 days screening, 112 days (16 weeks) treatment period and 168 days (24 weeks) follow-up.
	
	Patients enrolled in the study will be assessed as outpatients. Patient screening will occur no more than 90 days prior to the Day 1 visit. Eligible patients will undergo further assessments on Day 1 to qualify for study drug administration on Day 1.
	
	The visits during the study are planned as below:
	• Screening visit: 12 weeks (90 days)
	• 16 weeks treatment period:
	  • Treatment Visit 1 (Week 1 [Day 1])
	  • Treatment Visit 2 (Week 2 [Day 14 ±3 days])
	  • Treatment Visit 3 (Week 4 [Day 28 ±3 days])
	  • Treatment Visit 4 (Week 6 [Day 42 ±3 days])
	  • Treatment Visit 5 (Week 8 [Day 56 ±3 days])
	  • Treatment Visit 6 (Week 10 [Day 70 ± 3 days])
	  • Treatment Visit 7 (Week 12 [Day 84 ± 3 days])
	  • Treatment Visit 8 (Week 14 [Day 98 ± 3 days])
	  • Treatment Visit 9 (Week 16 [Day 112±3 days])
	• 24 weeks safety follow-up period:
	  • Follow-up Visit 1 (Week 20 [Day 140 ±7 days])
	  • Follow-up Visit 2 (Week 28 [Day 196 ±7 days])
	  • Follow-up Visit 3 (Week 40 [Day 280 ±7 days])
	Note: during follow-up patients are kept on NA until the end of the trial: Week 40 (consolidation Phase).
	
	Post study consolidation period: after Week 40, investigators can continue or stop NA therapy provided the following recommended plan is respected at the end of the study: after cessation of antiviral therapy, there is a transition of HBV care to a local provider for continued monitoring every 3 months for at least one year to monitor eventual HBV flares.
	
	Safety, tolerance, PK /PD and efficacy of EYP001a will be established in an outpatient setting.

Data Safety Monitoring Committee	An external, independent Data Safety Monitoring Committee (DSMC) will review all available unblinded preliminary safety study data when any stopping rules are met in two or more subjects. (Stopping rules details are described in the protocol Section 4.6.). DSMC will also review on two scheduled occasions for an interim analysis:

	1. First interim analysis on all available unblinded preliminary safety study data: Safety assessment when 50% (n=25) patients reach week 8 resulting in a decision on continuation of the study based on safety (Go/No go decision); enrolment would remain ongoing during this review 2. Second interim analysis on all available unblinded preliminary virology, safety, PK and PD study data: Safety and futility when 50% patients (n=25) reached week 12, resulting in a decision on continuation of the study (Go/No go decision) based on safety and evidence of a benefit of EYP001 (HBsAg, other secondary viral markers); enrolment is ongoing during this review The interim analyses will be performed on all available primary and secondary endpoints according to the SAP and DSMC charter, which describes the overall guidelines, composition, roles, and responsibilities of the independent DSMC for the EYP001-201 study, including the selection of DSMC members, timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings, data analysis recommendations, and DSMC relationships with other parties participating in the conduct of this study. Futility assessment will be performed by the DSMC according to defined rules (Section 11.5) to determine if EYP001 has no benefit at a point when 50% of subjects have reached 12 weeks of dosing. The study will not stop for efficacy at Week 12 interim analyses, even if efficacy boundary is crossed. The stopping of the study for futility will be considered by the DSMC by applying these rules. The criteria are not binding and DSMC can overrule if other interim results show beneficial results.
Study Stopping Rules	Stopping rules details will be further described in the Section 4.6. Dosing for a patient will be discontinued for any of the following events: 1. One occurrence of an SAE assessed to be definitely, probably or possibly related to dosing with the study drug. 2. One occurrence of a Grade 4 AE (i.e. life-threatening) assessed to be considered "possibly related" or "probably related" to the study drug 3. One occurrence a Grade 3 rash or higher or acute systemic allergic reaction. 4. Confirmation of any of the study drug discontinuation criteria as described in Section 8.3. 5. Occurrence of any condition that, in the opinion of the Investigator, significantly jeopardizes the wellbeing and

	safety of the patient and is assessed to be probably related to dosing with the study drug. 6. Clinically significant changes in vital signs or ECGs (such as arrhythmias) assessed to be considered "possibly related" or "probably related" to the study drug (i.e., no alternative explanation likely). 7. Clinically significant changes in the safety laboratory tests assessed to be considered "probably related" to the study drug (i.e., no alternative explanation likely). 8. A subject experiences a breakthrough (defined by quantifiable HBV DNA increase of $\geq$ 1 $\log_{10}$ HBV DNA copies/mL above LLOQ) the subject should return to the study site for a confirmatory measurement within two weeks, and if virologic breakthrough is confirmed, EYP001a or placebo dosing should be stopped and NA treatment should be continued or modified at the investigator's discretion. If two or more patients meet study drug stopping criteria #1, or #3 to #8, recruitment and dosing should be suspended or terminated for the remaining patients, pending the outcome of a DSMC review. The DSMC must review all safety data and provide clearance prior to dosing any additional patients. If one patient meets study drug stopping criteria #2, recruitment and dosing should be suspended or terminated for the remaining patients, pending the outcome of a DSMC review. If one patient experiences a Grade 5 common terminology criteria for adverse event (CTCAE) toxicity (based on CTCAE, version 5.0), or if more than 2 patients develop a Grade 3 CTCAE toxicity in the same category, the study will be paused, and safety reports will be submitted to the DSMC for review and clearance prior to dosing any additional patients. In other situations, re-initiation of study drug may be considered after consultation with the Medical Monitor.
Diagnosis and main criteria for Inclusion and Exclusion:	The study is open to chronic HBV carriers with no recent (3 months) history of any clinically significant conditions, which, in the opinion of the investigator, would jeopardize the safety of the patient or impact the validity of the study results. Diagnosed CHB is defined by the following values established during screening period: • HBV virally suppressed with HBV DNA < LLOQ[4] and on stable single NA treatment of at least 12 months

[4] The performance characteristics of the quantitative HBV DNA assay will be reported in the laboratory manual. The same assay will be used for all study visits. An FDA approved test will be used such as Abbott Realtime HBV Assay or COBAS HBV Test.

	duration (ETV or TDF)[5] • All genotypes, stratified A vs. non-A[6] • HBeAg negative or positive (expected ratio 7/3): stratification across study arms • HBsAg plasma levels >100 IU/mL[7]. **Inclusion Criteria:** Patients must satisfy all of the following criteria during screening to be enrolled in the study: 1. Has given voluntary written informed consent before performance of any study related procedure. 2. Must be 18 to 65 years of age, inclusive 3. Are on stable NA therapy for at least 12 months from the screening date (ETV or TDF)[8] 4. Has virally suppressed CHB: a. HBV DNA < LLOQ and serum HBsAg >100 IU/mL 5. Has liver imaging to screen for hepatocellular carcinoma or concomitant pancreaticobiliary disease either in the prior 6 months or at screening. 6. Has liver tests during the Screening Period defined as follows: a. The baseline values (i.e. two measurements at least 3 days apart: one can be from medical history if not older than 12 months and one during screening period) with both measurements of ALT or AST are ≤ 2 × ULN b. Normal or clinically not relevant levels of ALP (≤ 1.5 ULN) c. Has total bilirubin (TBL) ≤ 22.2 µmol/L, which corresponds to ≤ 1.3 mg/dL. d. Has conjugated (direct) bilirubin of ≤ 0.3 mg/dL (i.e. 5.1 µmol/L)

[5] Or equivalent effective NA: Lamivudine, adefovir dipivoxil, ETV, telbivudine and TDF have been approved in most Asia Pacific countries. Patients will be switched to ETV 0.5 mg or Tenofovir Disopropil 245 mg or Tenofovir Disoproxil Fumarate (TDF) 300 mg during screening period if they are not already taking this drug with the same dosage or equivalent.
[6] Genotype information will be collected from medical history, if not available best effort to assess in virologically appropriate plasma sample will be used.
[7] The performance characteristics of the HBsAg quantitative assay will be reported in the laboratory manual. The same assay will be used for all study visits. A validated test will be used (such as Quest Diagnostics quantitative HBsAg or DIASORIN LIAISON® XL HBsAg Quant ([REF] 310250). Rational: HBsAg level <100 IU/mL predictive for sustained response 2 years after EOT. The role of HBsAg levels in the current management of chronic HBV infection [Höner et al, 2014].
[8] Cross resistance has been described between lamivudine and ETV, as well as telbivudine. In case of previous therapy with lamivudine or telbivudine and current treatment with ETV, a possible cross resistance must be documented as to be unlikely by appropriate in vitro testing (mutational analysis M204V/I, rtT184, rtS202, or rtM250), else history of previous Lamivudine therapy leads to exclusion.

e. Has normal or clinically not relevant levels of GGT (≤ 2.0 ULN)
f. International normalized ratio ≤ 1.2 x ULN, unless on anticoagulant therapy
g. Platelet count ≥ 100 G/L
h. Has albumin ≥3.5 g/dL.

7. Is not of childbearing potential or, if of childbearing potential, is not pregnant as confirmed by a negative serum human chorionic gonadotropin test at screening and is not planning a pregnancy during the course of the study.
8. Women of childbearing potential (WOCBP) and male patients with WOCBP partners must agree to use a dual method of contraception as defined in the study protocol or practice complete abstinence from sexual intercourse if this is the patient's usual and preferred lifestyle throughout the duration of the study and for 90 days after stopping study drug. Patients who are using hormonal contraceptives should be instructed to use an additional contraceptive measure during the study. Note: A woman is considered of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile. A postmenopausal state is defined as no menses for >12 consecutive months without an alternative medical cause.
   A follicle-stimulating hormone level in the postmenopausal range will be used to confirm a postmenopausal state in women <55 years of age. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Exclusion Criteria:
A patient who meets any of the following exclusion criteria will be excluded from participation in the study:

1. Is an employee of a contract research organization (CRO), vendor, or Sponsor involved with this study.
2. Has known hepatocellular carcinoma or pancreaticobiliary disease.
3. Neutropenia (defined by two confirmed values within screening period of <1500/µL).
4. Has Gilbert syndrome.
5. Shows evidence of worsening liver function, defined as either a confirmed (two assessments at least 3 days apart) increase >2 ULN ALT or AST or an increase of >1.5 × first assessed value of TBL or associated with clinical signs or symptoms of liver impairment.
6. Has known or suspected non-CHB liver disease, including, but not limited to, Hepatitis D virus co-infection, alcoholic liver disease, non-alcoholic steatohepatitis diagnosed with liver biopsy, autoimmune disease, human immunodeficiency virus, active hepatitis

	C virus (HCV [9]), Wilson disease, hemochromatosis, hepatocellular carcinoma (normal AFP at screening required) or suspected or known other liver cancer, primary biliary cholangitis, primary sclerosing cholangitis, drug-induced liver injury (DILI), bile duct obstruction. 7. History of cirrhosis or liver decompensation, including ascites, hepatic encephalopathy, or presence of oesophageal varices. 8. Probable or possible F3 stage with a vibration controlled transient elastography (VCTE). Patients with normal baseline ALT and VCTE >8.8 kPa are excluded. Patients with baseline ALT >ULN (but <2ULN per EC5) and who have VCTE >10.5 kPa at baseline are excluded[10]. 9. Has known history of alcohol abuse or daily heavy alcohol consumption (females: >14 units of alcohol per week; males: >21 units of alcohol per week [1 unit of alcohol is equivalent to a half pint of beer {285 mL}, 1 measure of spirits {25 mL}, or 1 glass of wine {125 mL}]). Has an Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score of >3 points for men and women AND a full AUDIT score of >8 points at screening. Note: Only patients with AUDIT-C scores >3 points at screening will receive the full AUDIT and will be excluded if they score >8 points on the full AUDIT. Patients with AUDIT-C scores <3 points will not receive the full AUDIT. 10. Is pregnant or breastfeeding. 11. Has clinically relevant immunosuppression, including, but not limited to, immunodeficiency conditions such as common variable hypogammaglobulinemia. 12. Has a known pre-existing medical or psychiatric condition that could interfere with the patient's ability to provide informed consent or participate in study conduct, or that may confound study findings. 13. Has known dyslipidaemia with higher cardio-vascular risk from worsening lipid parameters (history of clinically significant cardiovascular or cerebrovascular disease during 12 months prior to study entry). 14. Has, in the opinion of the Investigator, clinically significant cardiovascular or cerebrovascular disease

[9] Note: HCV antibody (HCV Ab) positive individuals are not eligible, with the following 2 exceptions: (a) Patients previously treated with a registered drug for viral hepatitis C with at least a 1-year period since documented sustained virologic response may be eligible if HCV ribonucleic acid (RNA) is below the lower limit of quantification (LLOQ) and if all other eligibility criteria are met, and (b) patients with presence of HCV Ab if HCV RNA is below the LLOQ at screening without treatment (i.e., spontaneous clearance) may be eligible if all other eligibility criteria are met.

[10] Tapper et al., 2015, Liang, 2017, Marcellin et al., 2009, Chon et al., 2012 and Chan et al., 2009.

	within 12 months prior to the first study drug administration, including, but not limited to, myocardial infarction, acute coronary syndrome, revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or ischemic stroke, or implanted defibrillator or pacemaker. 15. Has participated in any study with administration of an investigational drug in the past 30 days, or 5 half-lives, whichever is longer, prior to the first study drug administration in the current study. 16. Has had major visceral or orthopaedic surgery within 30 days prior to the first study drug administration in the current study. 17. Has a hypersensitivity to the study drug or to any of the excipients or placebo. 18. Has a history of relevant drug and/or food allergies. The term "relevant" applies if any of the following allergy conditions are met: a. Has had several episodes of drug-induced urticaria. b. Immediate allergic signs (e.g. rhinoconjunctivitis, respiratory) with 2 or more episodes (at whatever time in medical history) due to an identified drugs or food (seasonal rhinoconjunctivitis is not an exclusion). c. Has ongoing urticaria episodes (attributed to whatever allergen) or has other active (current) immediate type reaction allergies (e.g. allergic rhinoconjunctivitis, allergic asthma, or latex allergy). d. Has had a moderate or severe allergic reaction (Grade 2 per the World Allergy Organization reference table, i.e., isolated non-drug induced urticaria of Grade 1 is not relevant). e. Has any allergic condition that might require an emergency epinephrine injection (similar to the EpiPen® Auto-Injector). 19. Has used anti-HBV medications other than NAs within 90 days prior to screening. 20. Is using any of the following disallowed medications within 30 days or 5 half-lives prior to screening whichever is longer, or planned use later during study participation: vitamin K antagonists such as warfarin, anticancer (except anti-hormonal which are allowed) drug(s), immunomodulator(s), or immunosuppressant(s) or any drug with known liver toxicity for >2 weeks in the year prior to screening (e.g. amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, estrogens at doses greater than those used for hormone replacement, anabolic steroids, or valproic acid or other known hepatotoxins at the Investigator or Medical Monitor's

	discretion), ursodeoxycholic acid, or obeticholic acid within 90 days prior to screening. Agents (including over-the-counter weight loss preparations) or medications known to significantly impact body weight within 30 days prior to screening (e.g. sibutramine, phenetamine, and orlistat). 21. Is using lipid lowering drugs such as statins (other than rosuvastatin, atorvastatin, simvastatin, pravastatin, fluvastatin or lovastatin). 22. Has planned major visceral, orthopaedic or neuro surgery during the study period. 23. Has uncontrolled type 1 diabetes mellitus or type 2 diabetes mellitus (T2DM) (haemoglobin A1c >9.5%). 24. Has any of the following exclusionary laboratory results at screening: a. Estimated glomerular filtration rate <60 mL/min/1.73 m^2 (the Modification of Diet in Renal Disease formula). b. Thyroid-stimulating hormone >1.5× ULN or abnormal free triiodothyronine or free thyroxine. Note: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor if any of the above laboratory abnormalities are found. 25. Has a history of clinically significant gastrointestinal disease, especially peptic ulcerations, gastrointestinal bleeding, inflammatory bowel disease, bariatric surgery, renal, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, or cardiovascular disease or any other condition, which, in the opinion of the Investigator, would jeopardize the safety of the patient or impact the validity of the study results.
Duration of Treatment:	The maximum total engagement duration for eligible patients in this study is up to 370 days: 90 days screening, 112 days (16 weeks) treatment period and 168 days (24 weeks) follow-up
Criteria for Evaluation:	**Efficacy Variables** ● Primary o HBsAg decline ($\Delta \log_{10}$) from Day 1 to Week 16 of treatment ● Secondary o HBsAg responder rate (decrease from baseline ≥ 1.0 on the $\log_{10}$ scale) at Week 16 of treatment and Weeks 20, 28 and 40 of follow-up o HBsAg responder rate (decrease from baseline ≥ 0.5 on the log10 scale) at Weeks 12 and 16 of treatment and Weeks 20, 28 and 40 of follow up. o HBsAg loss rate (% patients with HBsAg < LLOQ) at Week 16 of treatment and Weeks 20, 28 and 40 of follow-up o HBsA loss rate (Proportion of results that are Target Not Detected versus Target Detected) at Week 16 of treatment and Weeks 20, 28 and 40 of follow-up

	○ Relapse rate HBsAg (% patients who became negative [HBsAg < LLOQ], then increased with HBsAg > LLOQ) at Week 16 of treatment period and Weeks 20, 28 and 40 during follow-up period ○ Virologic failure rate (breakthrough)[11] of HBV-DNA (% patients with a confirmed quantifiable HBV DNA increase of ≥ 1log$_{10}$ HBV DNA copies/mL above LLOQ[12]) assessed at Week 16 of treatment period and Weeks 20, 28 and 40 during follow-up period ○ HBV-pgRNA decline (Δ log$_{10}$) from Day 1 to Weeks 4, 8, 12 and 16 of treatment period and Week 40 of maintenance period. ○ HBcrAg decline (Δ log$_{10}$) from Day 1 to Weeks 4, 8, 12 and 16 of treatment period and Week 40 of maintenance period ○ HBeAg quantification for HBeAg pos patients and changes at Week 16 of treatment and Week 40 of follow-up ○ Fibroscan VCTE change from screening value to Weeks 16 and 40 or ET value **Pharmacokinetic Variables** Plasma concentration of EYP001a or any relevant active metabolites (as identified in an ongoing phase 1 study) will be assessed. Fasting plasma samples will be collected at all study visits pre-dose in the morning on Day 1 and at Weeks 2, 4, 6, 8, 10, 12, 14, and 16, and in the morning at the ET Visit. If by error patient has taken study medication on study visit days prior to coming to the clinic the accurate time of last dosing and blood draw will be recorded. Plasma will be stored at -80°C until analysis. Plasma samples will be analysed for EYP001a and any active metabolites using a validated liquid chromatography/mass spectrometry (LC-MS/MS) method. **Pharmacodynamic markers** EYP001a PD parameters to be determined include: ○ Plasma C4 (7α-hydroxy-4-cholesten-3-one) ○ FGF19 ○ Plasma primary and secondary Bas

[11] Breakthrough samples will be further assessed for resistance assessments, including both for the nucleos(t)ide analogue as well as for EYP001a (e.g., sequence analysis of FXR response elements in HBV genome). Details will be described in the Laboratory manual.
[12] HBV DNA results <LLOQ will be reported as either <LLOQ/Detected (i.e. LLOQ/TD) or <LLOQ/Target Not Detected (i.e. LLOQ/TND), both are considered LLOQ.

	Plasma C4, FGF19; Bas (total, primary, and secondary Bas [such as chenodeoxycholic acid {CDCA}, deoxycholic acid {DCA}, lithocholic acid {LCA}, and/or others as appropriate]) sampling will occur pre-dose paired with PK sampling at all visits during treatment period. A sample will also be collected at the Weeks 28 and 40 (EoS) or ET Visits. Samples for Bas will be collected and stored centrally frozen for subsequent assessment after the end of study pending ongoing BA profiling related to EYP001a pharmacology. **Safety and Tolerability** The safety and tolerability of EYP001a will be assessed throughout the study. Safety and tolerability will be determined by evaluating medical history (including evaluation of AEs and concomitant medication use) and assessments will include the monitoring of adverse events (AEs) and SAEs, and findings from physical examinations, vital signs, 12-lead ECGs, and clinical laboratory parameters.
Statistical Methods:	<u>Statistical Analysis Plan and General Statistical Methods</u> All data will be handled and processed according to the sponsor's representative (Novotech (Australia) Pty Ltd) SOPs, which are written based on the principles of GCP. A Statistical Analysis Plan (SAP) containing the detailed planned statistical methods will be finalized prior to locking of the study database for the interim and final analysis and will form the basis for the programming of the displays and analyses of the final study data. All statistical calculations will be performed using SAS® (SAS Institute Inc., Cary, NC, USA) or similar software. The statistical analyses will consist of both inferential and descriptive statistics. In general, the data will be presented by dose group. All collected and derived data will be included in the patient data listings. <u>Analysis Population:</u> The following analysis sets are defined for this study. *Intention-To-Treat (ITT) Set* defined as the set of all randomized patients, irrespective of whether a patient receives any study drug. This set will be based on randomized treatment and will be used for the baseline, demographic summaries and efficacy summaries. *Modified Intention-To-Treat (mITT) Set*, defined as the set of all randomized patients, who received any amount of study drug, have a measurable baseline HBsAg assessment and a 16-week post baseline efficacy assessment. This set will be based on

	randomized treatment and will be used for efficacy analyses. *Per Protocol (PP) Set* defined as the set of patients who meet the mITT set requirements and were not associated with a major protocol violation. This set will be identified before the start of the final analysis and will be used to support the analysis conducted for the primary efficacy endpoint. Patients will be analysed based on the actual treatment received. *Safety Analysis Set (SAS)* defined as all patients who receive at least one confirmed dose of the study drug and will be based on actual treatment received. The SAS will be used for all safety and tolerability analyses. *Pharmacokinetic (PK) Set* will consist of all patients who received any study drug administration and that have sufficient and interpretable EYP001a concentrations data. Patients with missing sample concentrations will be included in the PK set provided that the PK parameters can be adequately characterized based upon the remaining data. Protocol violations and individual patient profiles will be assessed on a case-by-case basis to determine if the patient, or specific concentration values, should be excluded from the PK set. *Pharmacodynamic (PD) Set* will consist of all patients included in the SAS with a measurable baseline PD assessment and at least one measurable post baseline PD assessment, will be included in the PD set. <u>Statistical Methods</u> Patient disposition will be summarized using counts and percentages. Demographic and baseline information including treatment history, HBV genotype, age, gender, body mass index, weight, and height will be summarised by treatment group using the ITT set. All Efficacy analyses will be based on the ITT set unless otherwise specified. All efficacy data will be summarised by study visit and treatment group. The PK analysis will be based on the PK set. Individual plasma concentrations and trough levels of EYP001a and any active metabolites will be listed for each patient and summarised by nominal sampling time point and treatment group with descriptive statistics. All concentrations below the limit of quantification will be labelled as such in the concentration data listings. Listings of individual patient plasma concentrations and actual blood sampling times and graphs of concentration versus time will be prepared. Plasma concentrations will be summarized using descriptive statistics. The actual PK sampling timepoints will be used for the PK analysis. Appropriate validated PK software (eg, Phoenix WinNonlin v6.3) will be used. A non-compartmental analysis

	will not be performed. The PD analysis will be based on the PD set. PD marker parameters will be summarized using descriptive statistics and will also be presented graphically per treatment group. Listings and summaries for all safety data will be presented using the Safety Set. Safety endpoints will be summarised by treatment group. No formal inferential statistics will be performed on safety assessments. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). All AE summaries will be restricted to TEAEs only and will be summarised by treatment group. All AEs will be listed and will include verbatim term, preferred term (PT), system organ class, treatment, severity, causality, seriousness, and action taken with regards to the study drug. Separate listings will be created for SAEs and events leading to treatment discontinuation. Clinical laboratory results will be summarised by treatment group and will include changes from baseline and counts of number of values out of normal range at each scheduled time point. Shift tables (categorical parameters) may also be used, as appropriate. Individual vital signs assessments will be listed for each patient. Summaries of vital signs by treatment group will include changes from baseline for each parameter at each scheduled time point. Individual ECG results will be listed for each patient. Summaries of ECGs by treatment group will include changes from baseline for each parameter at each scheduled time point. Physical examination findings will be listed for each patient and any changes described in the text of the final report. Exposure to study drug and concomitant medications will be listed by patient and coded using the most current WHO drug dictionary available at the Sponsor. The number and percentage of patients who used prior and/or concomitant medications will be summarised by Anatomic Therapeutic Chemical (ATC) classification levels and treatment group. <u>Determination of Sample Size:</u> Formal sample size calculations were performed. Using primary endpoint assessment assumptions, based on a t-test, 49 patients need to be enrolled. **<u>An unscheduled interim analysis</u>** of all available unblinded preliminary safety study data will be conducted when any stopping rules are met in two or more subjects. Two interim analysis are scheduled. 1. First interim analysis on all available unblinded preliminary safety study data:

Safety assessment when 50% (n=25) patients reach week 8 resulting in a decision on continuation of the study based on safety (Go/No go decision); enrolment would remain ongoing during this review

2. Second interim analysis on all available unblinded preliminary virology, safety, PK and PD study data: Safety and futility when 50% patients (n=25) reached week 12, resulting in a decision on continuation of the study (Go/No go decision) based on safety and evidence of a benefit of EYP001 (HBsAg, other secondary viral markers); enrolment is ongoing during this review

The interim analyses will be performed on all available primary and secondary endpoints according to the SAP and DSMC charter, which describes the overall guidelines, composition, roles, and responsibilities of the independent DSMC for the EYP001-201 study, including the selection of DSMC members, timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings, data analysis recommendations, and DSMC relationships with other parties participating in the conduct of this study.

The futility assessment will be performed to determine if EYP001 has no benefit at a point when 50% of subjects have reached 12 weeks of dosing. The futility assessment will be performed by the DSMC according to the following rules:

- A treatment effect of -1.0 on a log10 scale of HBsAg for the primary endpoint at 16 weeks, and a common standard deviation of 1.08 was assumed and the treatment effect would be -0.5 after 12 weeks of treatment, with common standard deviation of 0.7. Using a one-sided alpha of 0.05 and 80% power, a group sequential design, incorporating a futility and efficacy O'Brien-Fleming analysis when 50% of patients have reached 12 weeks of treatment, needs inclusion of 49 patients.
- Table 6 gives the probability of stopping early under the null and alternative hypothesis, at the time of the interim analysis. The probability of stopping correctly for futility is 40%. The probability of stopping wrongly for futility is only 3.5%.
- The efficacy boundary is crossed when the 12-week p-value is less than 0.001, or the difference is less than -0.971 on a log scale. The futility boundary is crossed when the 12-week p-value is higher than 0.603, or the difference is more than 0.085 on a log scale.

The stopping of the study for futility will be considered by the DSMC by applying these rules. The study will not stop for

	efficacy at Week 12 interim analyses, even if efficacy boundary is crossed. The criteria are not binding and DSMC can overrule if other interim results show beneficial results. Data will be summarized and presented by treatment group and time point in summary tables. Descriptive statistics including number of patients (N), means, standard deviations, medians, and minimum and maximum values will be presented for continuous variables. Counts and percentages will be presented for categorical variables. In addition, by-patient listing for all safety and efficacy data will be presented. Note that all interim analyses will be descriptive. The study design does not include any formal statistical guidelines for use at interim analysis. ENYO is developing a mathematical computational HBV disease model. The results from EYP001-201 will serve as clinical data for the calibration of in silico HBV patients simulating the effect of combinational treatments that will eventually support designing later trials. With its different sub-models (HBV replication and excretion, Bas metabolism, cholesterol metabolism, immune system, fibrosis, blood virus related changes, and EYP001a, ETV and PEG-IFNα2a drug models) the disease model of chronic HBV infection will be used to predict quantitative efficacy on relevant endpoints (DNA HBV in blood, HBsAg) in a representative virtual population. The computational model is a system of ordinary differential equations (ODEs) which integrates more than 300 biological variables and more than 1000 parameters. It will be used to explore the effect of combinations of different treatments regimens including EYP001a, ETV and PEG-IFNα2a. Iterations of the validated model will serve for the exploration of alternative arms in the EYP001-203 study (conducted in parallel EYP001-201, with treatment naive or virologically non-suppressed patients treated with EYP001a combined with NA and peg-IFN), by simulating different doses and treatment regimens. Disease model simulations will support future explorations of development strategies, with the upcoming EYP001a pivotal study designs.

LIST OF ABBREVIATIONS

AE(s)	Adverse Event(S)
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti-HBe	Antibody to Hepatitis B e antigen
Anti-HBs	Antibody to Hepatitis B surface antigen
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC_{last}	Area Under the Curve From 0 To The Last Measurable Point
AUDIT-C	Alcohol Use Disorders Identification Test-Concise
BA	Bile Acid
BID	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
BSEP	Bile Salt Export Pump
cccDNA	Covalently Closed Circular Deoxyribonucleic Acid
CDCA	Chenodeoxycholic Acid
CFR	Code of Federal Regulations
CHB	Chronic Hepatitis B infection
C_{max}	Maximum Plasma Concentration
CRF(s)	Case Report Form(S)
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DCA	Deoxycholic Acid
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic Acid
DSMC	Data Safety Monitoring Committee
EC_{50}	50% Of Maximal Effective Concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EoS	End of Study
ETV	Entecavir
FDA	Food and Drug Administration
FGF19	Fibroblast Growth Factor 19
FXR	Farnesoid X Receptor
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
HBsAg	Hepatitis B Surface Antigen
HBcrAg	Hepatitis B core-related Antigen
HBeAg	Hepatitis B e Antigen
HBV	Hepatitis B Virus
HBV DNA	Hepatitis B Virus Deoxyribonucleic Acid
HBV pgRNA	Hepatitis B Virus pregenomic RNA
HBx	Hepatitis B Virus X protein

HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation – Good Clinical Practice
IEC	Institutional Ethics Committee
IFN	Interferon
INR	international normalized ratio
IP	Investigational Product
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent to Treat
IWRS	Interactive Web Response System
LCA	Lithocholic Acid
LDH	Lactic Acid Dehydrogenase
LDL	Low Density Lipoprotein
LLOQ	Lower Limit of Quantification
MATE1	Multidrug and Toxin Extrusion 1
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
mRNA	Messenger Ribonucleic Acid
MRP2	Multidrug Resistance-Associated Protein 2
MS	Metabolic Syndrome
NA	Nucleos(T)ide Analogue
NTCP	Sodium Dependent Taurocholic Co Transporting Polypeptide
OATP	Organic Anion Transporter Polypeptide
ODE	Ordinary Differential Equation
PBC	Primary Biliary Cholangitis
PD	Pharmacodynamic
PE	Polyethylene
PK	Pharmacokinetic
PT	Preferred term
PVC	Polyvinyl Chloride
PVDC	Polyvinylidene Chloride
QD	Once Daily
RNA	Ribonucleic Acid
SAE(s)	Serious Adverse Event(S)
SAP	Statistical Analysis Plan
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDF	Tenofovir Disoproxil Fumarate
TEAE(s)	Treatment-Emergent Adverse Events
TFV	Tenofovir
T_{max}	Time for Maximal Concentration
TSH	Thyroid Stimulating Hormone
UDCA	Ursodeoxycholic Acid
ULN	Upper Limit of Normal
USA	United States of America

VCTE	Vibration Controlled Transient Elastography
VLDL	Very Low-Density Lipoprotein
WOCBP	Women of Childbearing Potential

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Investigators

The investigators are identified in separate documents in the Trial Master File.

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1. Introduction

1.1. Unmet Medical Need

ENYO Pharma is developing EYP001a, a selective, synthetic, non-bile salt, carboxylic acid agonist, or modulator, of the farnesoid X receptor (FXR), for the treatment of chronic hepatitis B (CHB) virus infections. Chronic liver diseases are major public health problems [Sanyal, 2011]. Current worldwide estimations show that 844 million people have chronic liver diseases, with a mortality rate of 2 million deaths per year. Patients with chronic hepatitis B virus (HBV) infection have increased rates of liver-related mortality due to the development of complications, including fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Therefore, there is an urgent need for improved treatment options for chronic liver diseases.

1.2. Background

Hepatitis B is a viral infection that causes both acute and chronic disease, with widespread geographic distribution. The primary route for transmission reported in Asia is vertical transmission from mother to new-born child, while it is contracted early in childhood in sub-Saharan Africa. In contrast, individuals in North America and Europe most commonly contract hepatitis B by sexual transmission, intravenous injection drug use, or tattoos. Among the adult population exposed to hepatitis B, fewer than 5% will develop chronic infection [Hyams, 1995]. Approximately 360 million people worldwide have evidence of CHB infection [WHO, 2014].

Although HBV infection can be efficiently prevented by vaccination, and managed with available treatments, to date there is no reliable cure for the 257 million individuals that are chronically infected worldwide with only 9% being aware of their condition [WHO, 2018]. In 2017, HBV was still the main cause for liver cirrhosis and liver cancer. Current treatments can achieve viral suppression, but long-term to lifelong therapies are needed for the majority of infected patients [Misra et al., 2009].
Available standard of care (SOC) treatments based on interferon (IFN) and nucleos(t)ide analogues (NAs) often fail to induce functional cure, defined by the off-treatment suppression of viral replication and the plasma hepatitis B surface antigen (HBsAg) loss and undetectable HBV deoxyribonucleic acid (DNA) levels [EASL, 2017]. Small molecules interfering with the viral life cycle are strongly needed for more effective and better tolerated therapies.

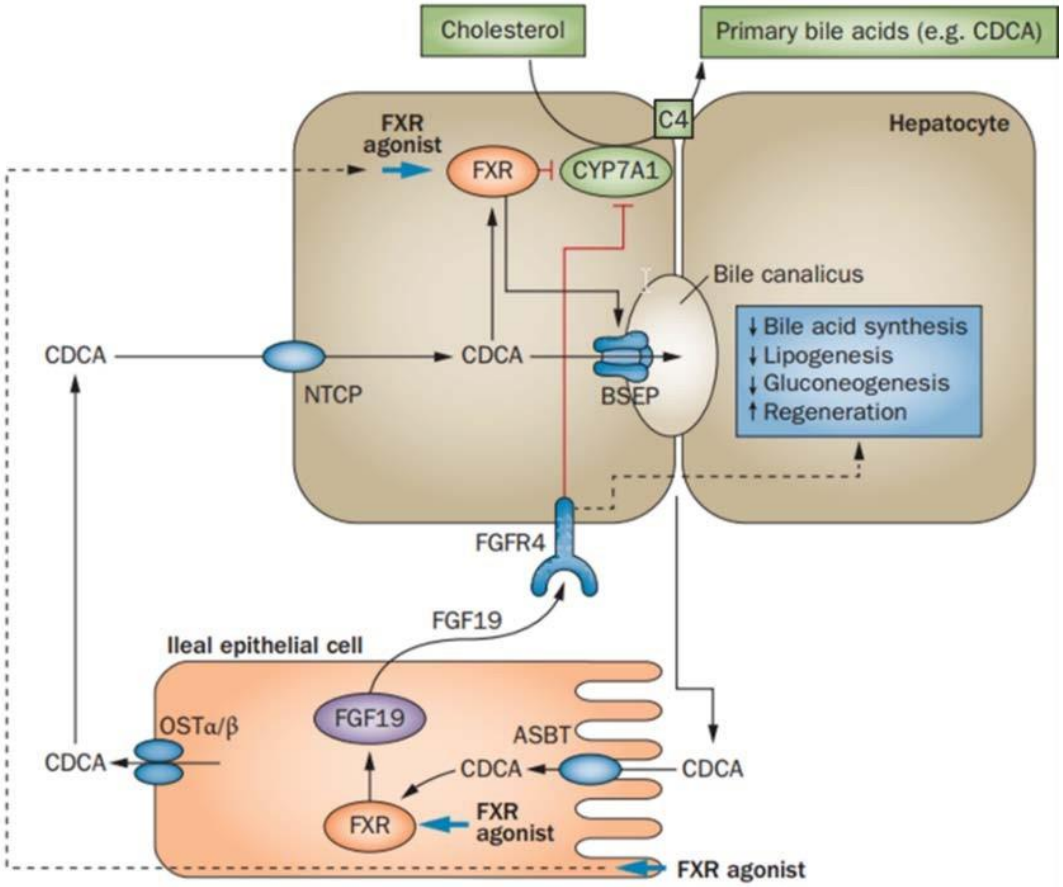
1.3. Role of FXR in HBV Infection

The FXR belongs to a family of receptors known as the nuclear hormone receptors which is highly expressed in the liver, intestine, kidney, and adrenal glands. One of the primary functions of FXR activation is to maintain bile acid (BA) homeostasis and to regulate BA biosynthesis from cholesterol, as shown in Figure 1.

Activation of FXR has favourable effect on liver growth and regeneration [Ali et al., 2015]. It has been shown to prevent and resolve liver fibrosis in rodents [Fiorucci et al., 2005] and to protect against HCC [Guo et al., 2015].

In addition, FXR has been found to be an important regulator of triglyceride and glucose homeostasis and a modulator of the intestinal microbiome. FXR agonists are therefore gaining attention as potential therapeutic agents in metabolic and hepatobiliary diseases.

Figure 1 FXR-induced BA Regulation

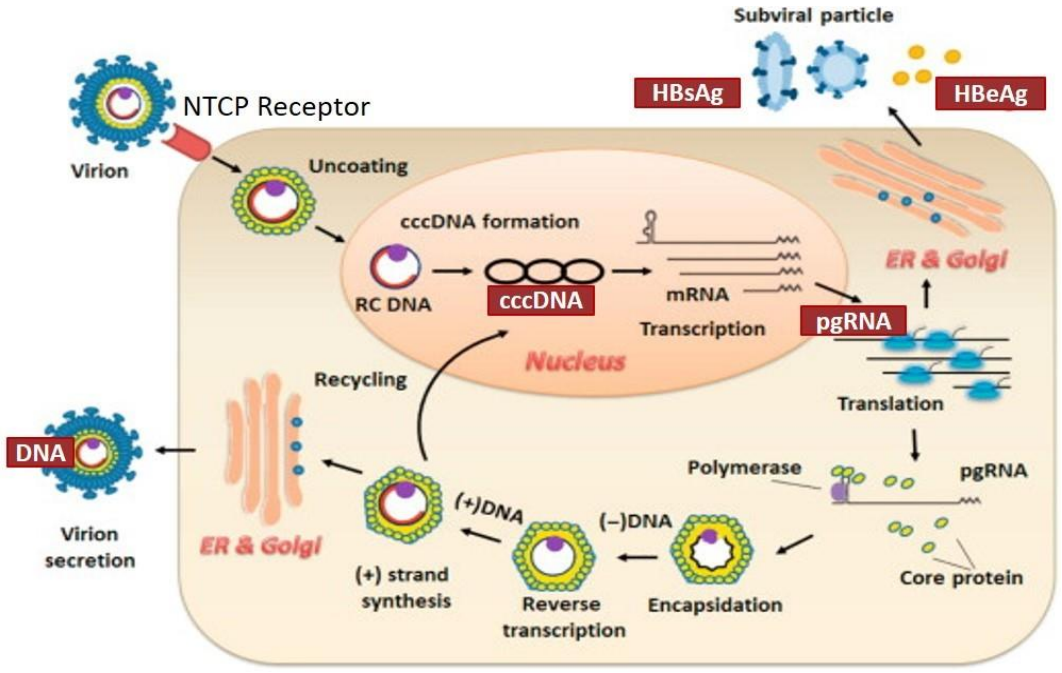


ASBT=apical sodium dependent bile acid transporter; BSEP=bile salt export pump; C4=7α-hydroxy-4-cholesten-3- one; CDCA=chenodeoxycholic acid; CYP7A1=cholesterol 7α-hydroxylase; FGF19=fibroblast growth factor 19; FGFR4=fibroblast growth factor receptor 4; FXR=farnesoid X receptor; NTCP=sodium dependent taurocholic co-transporting polypeptide; OSTαβ=organic solute transporter α and β

BAs are synthetized in the liver from cholesterol and secreted into the intestinal tract to facilitate digestion and absorption of nutrients. The BA precursor C4 has been shown to reflect BA biosynthesis. Most BAs are reabsorbed in the ileum, where they bind and activate FXR. This stimulates the synthesis of FGF19, which signals to the liver and downregulates BA biosynthesis (adapted from Schaap et al., 2013).

HBV and bile salts metabolism appear tightly interdependent [Lamontagne et al., 2016]. Virions enter hepatocytes by binding to heparan sulphate proteoglycans and to the sodium dependent taurocholic co-transporting polypeptide (NTCP), a hepatocyte bile salt transporter, as shown in Figure 2. The HBV genome enhancer II/core promoter region has 2 response elements for FXR. FXR agonists have a strong inhibitory effect on HBV pregenomic RNA (pgRNA), DNA, and protein synthesis and reverse partly virus induced modifications of FXR-dependent gene expressions [Yan et al., 2012].

Figure 2 HBV Entry and Replication Pathway



In May 2016, the Food and Drug Administration (FDA) granted an accelerated approval to the synthetic bile salt and FXR agonist OCALIVA™ (obeticholic acid) for the treatment of primary biliary cholangitis (PBC) and liver cirrhosis in adults with an inadequate response to ursodeoxycholic acid (UDCA) [OCALIVA ® Summary Basis of Approval (SBA); OCALIVA US Package Insert (USPI), 2016]. No other FXR agonist has been approved so far.

1.4. Overview of Investigational Product

1.4.1. Mechanism of Action

The FXR is a nuclear receptor that acts as a master regulator of BA metabolism and signalling, as well as glucose and lipid metabolism. Activation of FXR inhibits BA biosynthesis and increases BA conjugation, transport, and excretion, thereby protecting the liver from the harmful effects of bile accumulation. FXR led to considerable interest as a therapeutic target for the treatment of metabolic and hepatobiliary diseases.

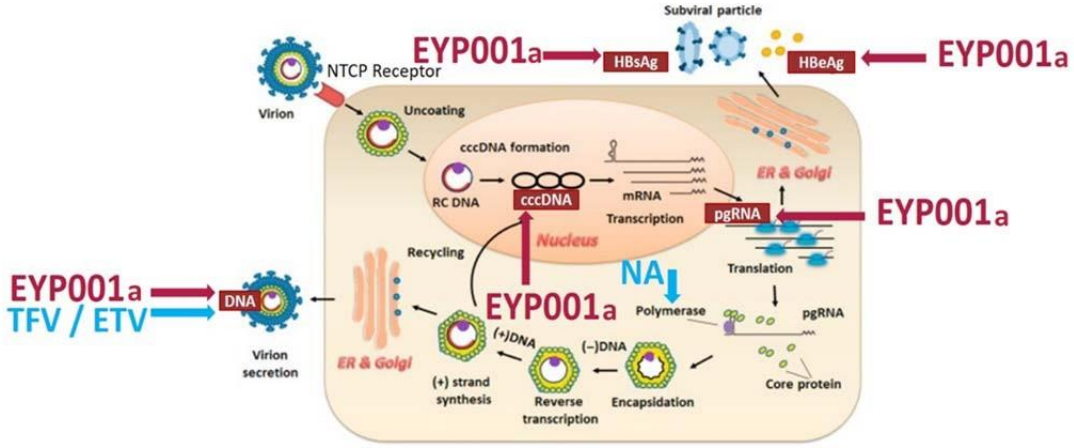
In EYP001a Phase 1 trials the physiological FXR engagement has been confirmed, both in healthy subjects and CHB patients via the analysis of 2 pharmacodynamic (PD) markers reflecting FXR activation: fibroblast growth factor 19 (FGF19) and the BA biosynthesis precursor C4 (7α- hydroxy-4-cholesten-3-one). In addition, FXR is a target for the inhibition of HBV replication as seen in non-clinical models (please refer to the IB, 2019).

EYP001a is a synthetic, orally active, non-bile salt, non-steroidal, carboxylic acid FXR agonist. EYP001a is an agonist and modulator of the nuclear FXR, a key regulator of bile, lipid, and glucose metabolism.

FXR is an important part of the machinery required for the expression of an episomal HBV genome known as the covalently closed circular DNA (cccDNA), characterizing chronic infection in the nuclei of infected hepatocytes. cccDNA expression is necessary to produce all HBV encoded proteins and infectious viral particles. It encodes 2 FXR response elements to which the FXR receptor binds forming a large multimeric, transactivation protein complex on the cccDNA. Each of the proteins in the transactivation complex contributes to the efficiency of cccDNA expression. The hepatitis B virus X protein (HBx) participates in the transactivation complex, the activity of which is regulated by FXR modulators in such a manner that the allosteric effects of FXR/agonist binding cause the transactivation complex to fall apart, therefore impairing expression of the HBV cccDNA. Consequently, FXR agonists inhibit HBV cccDNA gene expression and the expression of the HBV encoded proteins and infectious viral particles. Overall FXR led to considerable interest as a therapeutic target for the treatment of metabolic and hepatobiliary diseases.

The mechanism of action of EYP001a and the NAs tenofovir (TFV) and entecavir (ETV) is shown in Figure 3.

Figure 3 Representation of the HBV Life Cycle and Suggested Mechanism of Action of EYP001a and NAs on HBV Markers



DNA: deoxyribonucleic acid; ETV: entecavir; HBeAg: hepatitis B e-antigen; HBsAg: hepatitis B surface antigen; mRNA: messenger ribonucleic acid; NA: nucleos(t)ide analogue; NTCP: sodium dependent taurocholic co-transporting polypeptide; pgRNA: pg/precure ribonucleic acid; TFV: tenofovir.

1.4.1.1. Scientific Rationale

The key HBV receptor at the hepatocyte plasma membrane is NTCP, which is the main bile salts receptor allowing internalization of the virus [Yan et al., 2012]. Competition of HBsAg and bile salts for NTCP modifies the flux of bile salts and their intracellular concentrations which in turn alter the function of the nuclear bile salt receptor FXR. HBV infection thus set up a low activation FXR equilibrium characterized by increased FXR expression and down or up-regulation of gene activated or repressed, respectively, by FXR [Oehler et al., 2014; Slijepcevic et al., 2015].

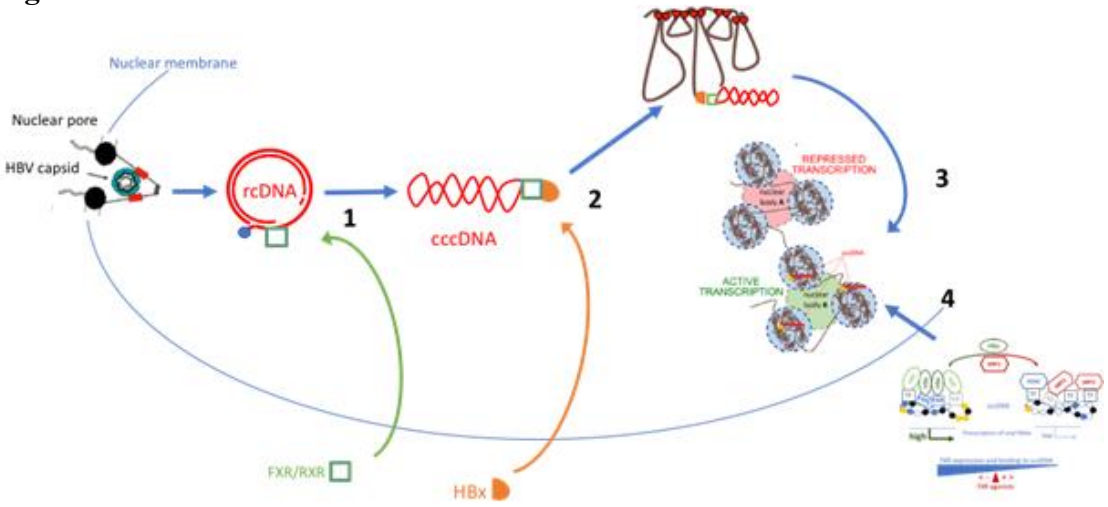
FXR is a proviral nuclear factor for both cccDNA maintenance and/or completion, and transcription rate of viral mRNAs in differentiated HepaRG cells [Radreau et al., 2016;

Mouzannar et al., 2018]. FXR expression down-regulation reduces HBV replication. The 2 proviral activities of FXR are repressed by treatment with FXR ligand GW4064. Down-regulation of FXR expression and treatment with FXR ligand have additive effect on cccDNA while, on transcription, the effect of ligand seems to prevail on the effect of reduction of FXR expression.

FXR is recruited at 2 FXR response elements, 2 short double-stranded DNA sequences, and the regulatory regions of the HBV genome [Ramière et al., 2008]. Binding of FXR is released by FXR ligand, an effect at odds of that is observed on the promoter of several genes dependent on FXR for their expression (manuscript in preparation).

The effect of FXR ligand GW4064 on transcription is dependent on the presence of the viral protein HBx [Mouzannar et al., 2018]. Effect on cccDNA does not depend on HBx. FXR and HBx interact (FXRAF1/HBx 3d αhelix) [Niu et al., 2017] and FXR can recruit HBx on viral sequences. HBx is mandatory for efficient transcription and is actively recruited to the cccDNA [Belloni et al., 2009]. The mechanisms of the proviral activity of HBx are still under investigation in the HBV community. HBx might trigger cccDNA localization at perichromatin site forming transcriptionally active domains [Hensel et al., 2018], but debated [Moreau et al., 2018], induce the degradation of the SMC5/6 complex [Decorsière et al., 2016], or regulate the balanced recruitment of Sirtuin 1 (SIRT1) and HBx on cccDNA [Belloni et al., 2009]. The current model of HBV/FXR interactions is depicted in Figure 4.

Figure 4 Current Model of FXR/HBV Interactions



1. FXR is recruited to the viral genome at 2 FXRE. FXR recruitment to rcDNA may favour the recruitment of nuclear factors for cccDNA completion and maintenance
2. FXR recruits HBx on the cccDNA, which is a critical viral pro-transcriptional factor
3. HBx likely allows the tethering of cccDNA at fibre loops at perichromatin sites forming TAD; cccDNA is maintained in transcription active supranucleosomal structures
4. FXR agonists may further regulate cccDNA transcriptional activity through regulation of the balance on cccDNA of FXR 2 interactants SIRT1 and HBx

Bile salt/FXR pathway may define inner hepatocyte environments, defined by FXR expression and activation level and associated with various risks of chronic infection. Tuning of FXR pathway varies with age and may contribute to HBV infection evolution as suggested by the AAV-HBV model of infection in mice.

In the adeno-associated virus-HBV model of infection in mice, treatment with FXR ligand represses HBV replication (HBV DNA and HBsAg) in adult mice but not in young mice (<8 weeks). Bile salts pathway mature with intestine microbiome and age suggesting that indeed FXR-bile salts metabolism may contribute to age-dependent chronic versus acute HBV infections proportion [Mouzannar et al., 2018].

1.4.2. Summary of Nonclinical Experience

In vitro, EYP001a activates FXR with a 50% of maximal effective concentration (EC_{50}) of 4 nM as measured by Fluorescence Resonance Energy Transfer and 3 µM as measured by FXR transactivation assay.

A primary PD study in a model of diabetic mice (db/db mice) showed that treatment with EYP001a resulted in a dose-dependent reduction in total cholesterol and triglycerides.

Safety pharmacology studies showed no effect of EYP001a up to 120 mg/kg on the central nervous system or cardiovascular system. No relevant findings were identified in the respiratory system.

1.4.2.1. Pharmacokinetics

Pharmacokinetic (PK) and toxicokinetic profiles of EYP001a were analysed in rats and dogs. In both species, reduced exposure was observed with repeat dosing, probably related to a decreased absorption resulting from a potential induced decrease of BA production. Exposure was consistently lower in males.

EYP001a is mainly cleared via metabolism.

In in vitro studies, EYP001a showed a slight induction of cytochrome P450 (CYP) 3A4 mRNA expression in human hepatocytes and no induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. EYP001a exhibited no inhibitory effect on human CYP1A2, CYP2C19, and CYP2D6, minor inhibition of CYP2B6, CYP3A4/5, and moderate to strong inhibition of CYP2C9 and CYP2C8. EYP001a showed in vitro inhibition of organic anion transporter polypeptide 1B1 and 1B3 (organic anion transporter polypeptide [OATP]1B1 and OATP1B3).

EYP001a has a moderate inhibitory potency on bile salt export pump (BSEP) and a slight inhibitory potency on multidrug resistance-associated protein 2 (MRP2); EYP001a showed moderate inhibitory potency on multidrug and toxin extrusion 1 (MATE1) and multidrug and toxin extrusion 2K protein (MATE2K) uptake transporters.

1.4.2.2. Pharmacodynamics

Considering both urine and faeces in rats and dogs, the major metabolites were M24 (resulting from cleavage of EYP001a) and M14 (a diol). Few metabolites were detected in plasma samples while most of them were excreted in faeces and, to a limited extent, in urine.

1.4.2.3. Toxicology

The potential toxicological effects of EYP001a have been evaluated in a standard battery of in vitro genotoxicity studies and in single- and repeat-dose studies in rats and dogs. These 2 species were selected based on metabolic studies which indicated that they represent best the metabolic fate of EYP001a. No lethal effect was noted up to 120 mg/kg,

the highest dose tested, in any of the repeated dose toxicity studies performed in the 2-animal species.

EYP001a was not mutagenic in the bacterial reverse mutation test.

Reproductive toxicity studies evaluating the fertility and early embryonic development were performed in rats and rabbits. There was no overt teratogenic potential of EYP001a.

For more details on preclinical experience, please refer to Section 4 of the IB [IB, 2019].

1.4.3. Summary of Clinical Experience

The PK, PD, and safety of EYP001a have been investigated in 180 subjects (96 healthy volunteers and 84 patients with CHB) across 4 EYP001a Phase 1 studies (for details, please refer to the IB [IB, 2019]). The subjects received treatment as follows: 137 have been treated with EYP001a (76 healthy volunteers and 61 chronic HBV patients). These 4 studies include 3 completed clinical studies and in 1 study that is clinically complete but with the clinical study report (CSR) pending (data presented as of 27 August 2018).

EYP001a was safe and well tolerated over the dose range of 60 mg to 500 mg once daily (QD) and 200 mg twice daily (BID). QD regimens were better tolerated compared to BID 150 mg and 200 mg, with less treatment-related emergent AE i.e., pruritus. In a Phase 1b study (), 73 CHB patients were assessed during a 4-week EYP001a treatment: A total of 48 subjects in Part A with EYP001a monotherapy and 25 subjects in Part B with EYP001a combined with pegylated interferon (peg-IFN,) comprised the study. Genotypes were: A: n=25, B: n=8, C: n=10, D: n=7 and E: n=4. 90% of patients were HBeAg negative and treatment naive. The most common treatment-emergent adverse events (TEAEs), typically transient and of mild to moderate intensity, were gastrointestinal (GI) disorders, headache, fatigue or flu-like (pyrexia, myalgia) symptoms mostly in Part B peg-IFN treated subjects. Pruritus was reported mainly by subjects receiving BID dosing regimen (200 mg BID [67%] and 150 mg BID [56%] vs. 11% to 14% in QD). No off-target findings, clinically significant changes in vital signs or electrocardiograms, serious adverse event (SAE) or suspected unexpected serious adverse reaction (SUSAR) were reported. After 4 weeks of EYP001a administration to chronically infected HBV subjects, alanine amino transferase (ALT) and aspartate amino transferase (AST) values were within the normal range. Three subjects had Grade 3 and 1 had a Grade 4 hepatic flare (ALT/AST increase without signs of liver dysfunction in other liver tests) which were normal (total bilirubin, gamma glutamyl transferase [GGT], alkaline phosphatase [ALP], international normalized ratio [INR] and albumin). These changes were interpreted as typical of those seen in subjects with underlying chronic liver disease with clinically not significant slight ALT changes.

This Phase 1b study also explored the effect on HBV replication markers after 4-week treatment with EYP001a monotherapy or in combination with peg-IFN. A significant reduction of HBV DNA was seen with standard-of-care (SOC) drugs. More importantly, EYP001a reduced HBsAg (up to -0.3 $\log_{10}$ in some patients [AUC of HBsAg $\log_{10}$ changes]), HBV pgRNA up to -1.7 $\log_{10}$ and a trend for HBcrAg up to -0.9 $\log_{10}$ when combined with peg-IFN were found (Table 1,Figure 5 and Figure 6).

Table 1 HBV replication marker changes from baseline to end of treatment (Day 29) and at follow up (Day 35)

			HBV DNA (Log_{10} IU/mL)		HBV pgRNA (Log_{10} Cps/mL)		HBsAg (Log_{10} IU/mL)		HBcrAg (Log_{10} U/mL)	
Treatment	**Day**	**n**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
EYP001a (1x100 mg/day)	Day 29	7	0.11	0.5	0.48	1.2	-0.02	0.1	-0.32	1.1
	Day 35	7	-0.40	1.2	-0.06	1.2	0.01	0.1	0.02	0.5
EYP001a (1x200 mg/day)	Day 29	8	0.23	0.4	0.35	1.7	-0.03	0.1	0.24	1.1
	Day 35	8	0.16	0.5	0.90	1.9	-0.03	0.1	0.22	0.6
EYP001a (1x400 mg/day)	Day 29	8	0.06	0.3	0.23	1.4	**-0.09***	0.1	0.02	0.1
	Day 35	8	-0.04	0.4	0.51	1.2	-0.05	0.1	0.01	0.2
EYP001a (2x200 mg/day)	Day 29	7	0.12	0.3	-0.08	1.9	-0.02	0.1	1.21	2.2
	Day 35	8	-0.10	0.4	**-1.20**	1.6	-0.03	0.1	0.78	1.2
EYP001a (1x300 mg/day) +Peg-INF	Day 29	8	**-2.23***	1.4	**-1.65***	1.9	0	0.1	**-0.92**	1.6
	Day 35	8	**-2.45***	1.5	**-1.77***	1.8	0.04	0.1	**-1.11**	1.4
EYP001a (2x150 mg/day) +Peg-INF	Day 29	8	**-1.80***	1.0	**-0.92**	1.8	-0.05	0.2	-0.18	0.2
	Day 35	9	**-1.78***	1.3	**-1.08**	1.7	-0.02	0.1	-0.29	1.0
ETV (open-label 0.5 mg/day)	Day 29	7	**-3.61***	0.7	-0.34	2.0	-0.04	0.1	0.03	0.6
	Day 35	7	**-3.79***	0.6	**-1.14**	2.3	-0.05	0.1	0.56	1.4
Placebo	Day 29	8	-0.14	0.2	-0.70	1.0	-0.04	0.1	0.18	1.3
	Day 35	8	-0.15	0.2	0.16	2.4	-0.01	0.0	0.31	1.4
Placebo +Peg-INF	Day 29	8	**-2.35***	0.9	-0.24	1.0	**0.12***	0.1	-0.36	0.9
	Day 35	8	**-1.93***	0.8	-0.57	0.6	**0.10***	0.1	0.18	1.4

Legend: bold are numerical trends ($p<0.10$) not statistically significant
* statistically significant ($p<0.05$)

Figure 5 Individual changes HBsAg levels (log_{10} IU/mL) from Day 1 to Day 35, in cohort EYP001a 400mg QD group of study EYP001-103

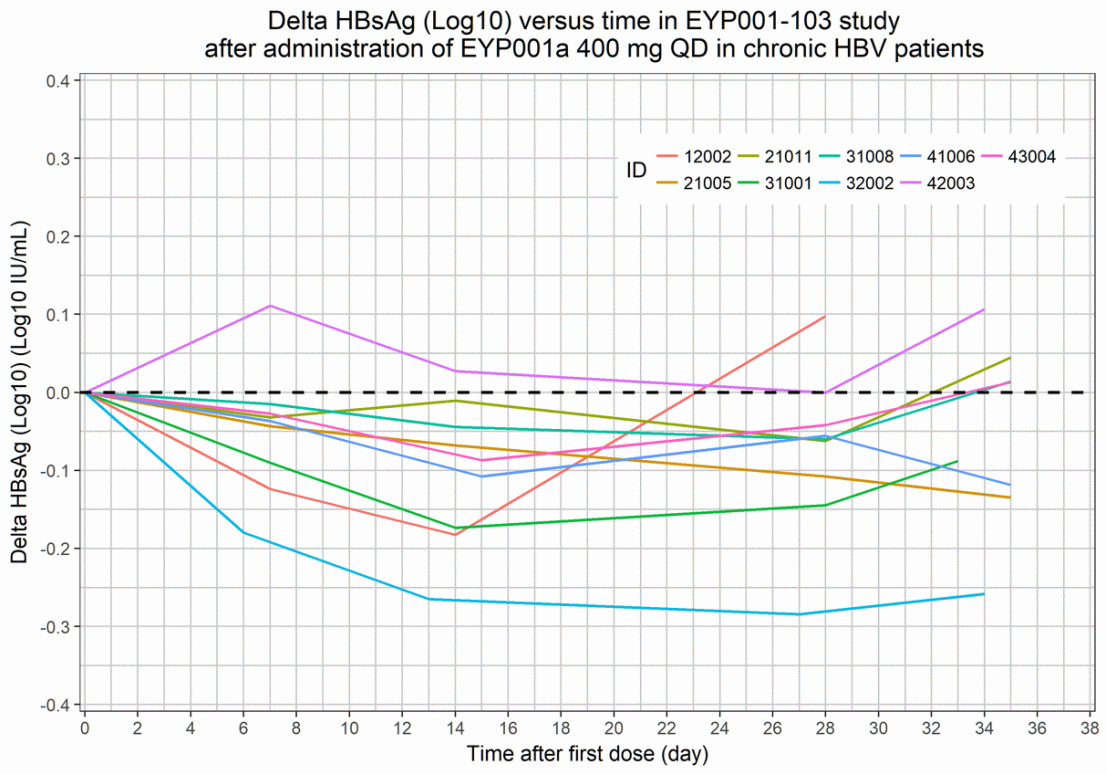
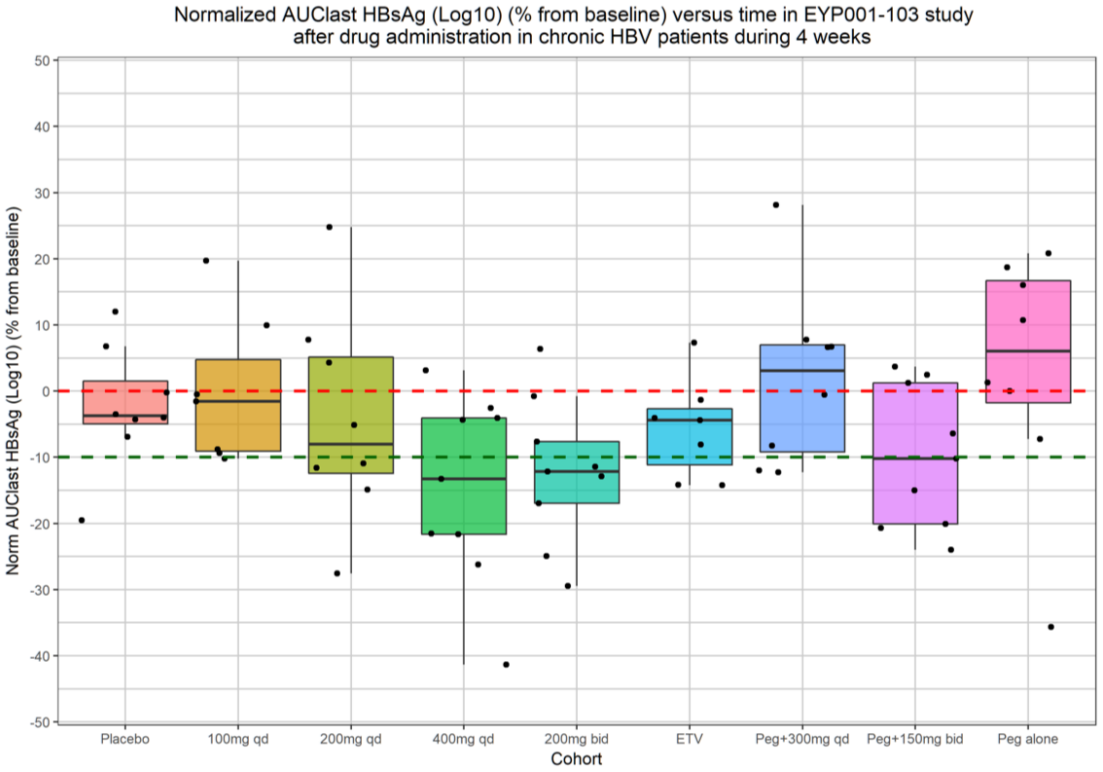


Figure 6 Changes of HBsAg levels (log_{10} IU/mL) expressed as AUC from baseline Day 1 to Day 29 in study EYP001-103



Legend: The coloured box represents the interquartile interval of the AUC; the thick black line corresponds to the median. The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Black dots represent individual AUCs.

Analysis of PD markers of FXR activation, confirmed physiological FXR engagement through EYP001a.

For details pertaining to clinical experience, please refer to Section 1.5 of the IB [IB, 2019].

1.4.3.1. Clinical Pharmacokinetics

The PK analysis from the phase I study revealed that EYP001a was rapidly absorbed in fasting conditions with a lag time of 15 to 30 minutes with plasma concentrations reaching C_{max} between 2.3 and 4 hours.

Results of food-effect phase I study EYP001-102 suggest that oral doses of EYP001a were well tolerated and did not produce any relevant drug-related TEAEs, other than mild GI symptoms, and one subject with mild self-limited pruritus. EYP001a reached similar C_{max} with all 4 dosing conditions, whereas T_{max} tended to increase with food. Overall, EYP001a PK in chronically infected HBV subjects seemed to be slightly influenced by food, with a delay of few hours in the absorption process, leading to a lower C_{max}. EYP001a exposure (AUC) appeared to be slightly higher under food conditions and the variability on EYP001a PK and the small number of subjects (n=11) did not allow to demonstrate the bioequivalence on C_{max}, AUC_{last} and AUC. Despite rapid EYP001a elimination kinetics, FGF19 and C4 showed a prolonged FXR target engagement over at least 24 hours.

1.4.3.2. Clinical Pharmacodynamics

Analysis of FGF19 and the BA biosynthesis precursor C4, which are two established PD markers of FXR activation, confirmed physiological FXR engagement through EYP001a.

1.4.3.3. Clinical Safety

Overall, EYP001a was safe and well tolerated over the dose range of 100 mg to 500 mg QD and 200 mg BID but was better tolerated with the QD regimen than with BID dosing. The most common treatment-emergent adverse events (TEAEs) were gastrointestinal (GI) disorders. These TEAEs were transient and were of mild to moderate intensity. Pruritus was reported, mainly in subjects in the 200 mg BID and 150 mg BID groups. No off-target effect was evidenced. There were no clinically significant changes in vital signs or 12-lead electrocardiograms (ECGs). No SAE or SUSAR was reported.

In most cases, ALT and AST values were within the normal range following EYP001a administration in healthy subjects and after single administration in chronically infected HBV subjects. After 4 weeks of administration of EYP001a to chronically infected HBV subjects, 5 subjects had Grade 3 (n=4) or Grade 4 (n=1) ALT/AST increases without signs of liver dysfunction for all other liver tests (total bilirubin, gamma glutamyl transferase [GGT], ALP, international normalized ratio [INR], and albumin). These changes were interpreted as hepatic flares typical of those seen in patients with underlying chronic viral HBV liver disease with clinically not significant slight ALT changes.

Overall EYP001a is considered safe over the dose range of 100 mg to 400 mg QD and 200 mg BID given as capsules. Aforementioned data initially supported the selection of the 400 mg tablet dose for study EYP001-201. Nevertheless, PK and safety/tolerance preliminary findings in ongoing EYP001-202 NASH phase 2a and in the EYP001-107 phase 1 NASH trials with the EYP001a tablet formulation, do not support the use of the 400mg daily single oral EYP001 dose with the tablet formulation. The reduction to 200mg QD (1x200mg tablet) will generate an exposure similar to 400mg QD (2x200mg capsules) dose that was previously tested and well tolerated. EYP001a 200mg tablet QD dose can be assessed safely in CHB subjects over the planned 16 week treatment period.

For more details on effects in humans, please refer to Section 5 of the IB [IB, 2019].

1.5. Research Hypothesis

1.5.1. Rationale for Study Conduct

Based on the available nonclinical and clinical Phase 1 data, EYP001a shows engagement of FXR with pharmacological effects expected to be related to the hepatobiliary system and lipid metabolism. From the available data no off-target effect has been evidenced. In healthy human and chronically infected HBV patients, no clinically significant or relevant changes in safety laboratory tests were observed with the administration over 15 days of repeated oral doses of EYP001a from 60 to 500 mg QD.

EYP001a showed no potential for QT prolongation in QT-EYP001a concentration analysis. Overall, clinical data showed that EYP001a was safe and well tolerated over the dose range of 60 mg to 500 mg QD and 200 mg BID. QD regimens were better tolerated compared to BID 150 mg and 200 mg, with less treatment-related emergent AE i.e., pruritus.

The phase I study explored the effect on HBV replication markers after 4-week treatment with EYP001a monotherapy or in combination with peg-IFN. A significant reduction of HBV DNA was seen with SOC drugs. EYP001a was also found to reduce HBsAg, HBV pgRNA and HBcrAg when combined with peg-IFN (Table 1, Figure 5 and Figure 6).

Standard of care (SOC) HBV treatments based on interferon (IFN) and nucleos(t)ide analogues (NAs) often fail to induce a functional cure, which is defined by the off-treatment suppression of viral replication (i.e. undetectable HBV DNA levels) and the plasma HBsAg loss. NA are usually prescribed indefinitely to CHB patients and lead to HBV DNA particles suppression in the plasma. However, a functional cure, is not frequent, at best in the 1% to 3% range for NA and up to 10% with peg-IFN after 48 weeks of treatment. This is due to the persistence of HBV cccDNA in the hepatocytes. Current guidelines recommend indefinite NA because an expected high relapse rates after NA discontinuation. Pegylated interferon alfa (pegIFNa) treatment is therefore, often considered in mild to moderate CHB patients, however combination therapies with NA are not generally recommended, since no additional benefit is proven [Zhang et al., 2016]. In a recent randomised controlled trial, the 72-week HBsAg loss rates were superior in the pegIFNa and Tenofovir Disoproxil Fumarate (TDF) treated patients compared to those observed in patients receiving pegIFNa alone or TDF alone (9% vs. 3% vs. 0%) [Marcellin et al., 2016]. The clear dichotomy between the immune response present in acute, resolved versus chronic persistently HBV-infected patients leads to therapeutic strategies designed to boost HBV-specific immunity in CHB patients. Because antigen persistence in the liver seems to be a major factor driving the HBV-specific CD4 and CD8 T-cell defects, the suppression of HBV antigen production can lead to a functional reconstitution of antiviral T-cell responses [Tan et al., 2015]. From an epidemiology perspective it is important to note that the prevalence of HBeAg negative CHB has been increasing over the last few decades and has become the commonest type of HBV infection in many countries of the world [Alexopoulou and Karayiannis, 2014].

Finite Peg-IFN therapy for 48 weeks leads to more frequent HBsAg seroconversion, however it remains unclear if in combination with NA there is an additive effect. HBsAg loss is also more frequent with certain HBV genotypes (A>B>C>D), low HBV DNA loads, high ALT and low HBsAg levels.

Finally although previous studies reported that after NA discontinuation a sustained viral response can be obtained in up to 50% of CHB patients virally suppressed with a stable yearlong NA therapy, recently two studies reported the unfavourable preliminary results for NA discontinuation: the Australian HBV-STOP interim showed in HBeAg negative patients that at week 48 after stopping NA 100% had reactivation of HBV DNA, 55% were in the immune control phase and 14% had restarted NA therapy. A HBsAg reduction >1 $\log_{10}$ was observed in 57% at 48 weeks. Only 1/44 patients had an HBsAg loss and 32% had ALT flares (defined >5x ULN). The Toronto study in a similar HBV population of n=67, mostly Asian, HBeAg positive or negative, virologically suppressed patients and who were randomized to stop (67%) or maintain NA (33%), showed at 48 weeks of follow-up after stopping that 74% had relapsed and only 2/67 patients had HBsAg loss, 21% had ALT >10x ULN and another 10% ALT >5x ULN.

Overall given the high need to improve functional HBV cure rates with a finite treatment and the observations of oral QD doses of EYP001a to be well tolerated, with a dose-dependent signal on HBsAg reduction after only 4 weeks therapy, the exploration of an EYP001a prolonged treatment on top of NA seems justified. The study EYP001-201was initially designed to test the safety and the antiviral effect of 400 mg QD EYP001a when administered in combination with stable NA therapy over 16 weeks on HBsAg in CHB patients who are virologically suppressed on a stable NA therapy[1].

Nevertheless, in light of preliminary findings in ongoing EYP001-202 NASH phase 2a and in the EYP001-107 phase 1 NASH trials (Section 1.4.3.3) the dosage has been modified to 200mg QD (1x200mg tablet) which generates a similar plasma exposure as 400mg QD (2x200mg) capsules, previously tested and well tolerated dose.

1.5.2. Benefit-Risk Assessment

EYP001a is a synthetic, small, non-bile salt agonist of the nuclear FXR, which plays a pivotal role in BA metabolism. EYP001a is in early stage development and has no proven clinical efficacy.

Overall at the current stage of development, EYP001a is considered safe and well tolerated for oral doses of 500 mg QD over 15 days (study EYP001 C01), 400 mg QD and 200 mg BID over 29 days (study EYP001 103).

Refer to Sections 1.4.2 and 1.4.3 for summary of nonclinical and clinical experience with EYP001a, respectively.

In line and within the range of reported changes for other investigational FXR agonists, as well as the FDA- and European Medicines Agency-approved FXR agonist OCALIVA® (synthetic bile salt), EYP001a may modify lipid blood profiles in the long term. This appears to be a class effect with an unknown risk in the long term and requires monitoring in patients considered for chronic treatment with FXR agonist. The potential risks of long-term high density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol profile modifications need to be weighed against the possible therapy benefits – additional information from ongoing and future studies will be sought for a complete and accurate determination of this potential risk. In addition, patients should be monitored for liver-related adverse reactions and pruritus.

Overall, based on available nonclinical and clinical data, and prior knowledge with FXR agonist showing favourable effect on liver growth and regeneration and prevention or resolution of liver fibrosis, and the possible favourable effect on HBsAg reduction, the risk-benefit profile of EYP001a is judged as acceptable for the further exploration in chronically infected HBV patients.

[1] Note: an independent 2nd phase 2a study named EYP001-203 will be conducted in parallel for treatment naïve virally not suppressed patients (i.e. HBV DNA >20'000 IU/mL) assessing EYP001a effect combined with NA and peg-IFN.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

- To determine the effect of EYP001a on top of NA (SOC therapy) on HBsAg plasma levels

2.1.2. Secondary Objectives

- To establish the effect of EYP001a on top of NA on HBsAg responder rate at the end of the 16-week EYP001a treatment and at 24-week of follow-up (Week 40).
- To establish the effect of EYP001a on top of NA on HBsAg loss rate at the end of the 16-week EYP001a treatment and at 24-week of follow-up (Week 40).
- To establish the HBV virologic failure rate (breakthrough)[2] during the 24-weeks follow-up period after stopping EYP001a with ongoing NA.
- To determine HBV viral response, HBV pgRNA, HBcrAg, HBeAg, anti-HBe and anti-HBs at the end of the 16-week EYP001a treatment and Week 40 of follow-up.
- To explore the safety profile of EYP001a treatment in combination with NA.
- To determine the plasma concentration of EYP001a and PD markers (plasma C4 [7α-hydroxy-4-cholesten-3-one]), FgF19 and BAs.

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Efficacy assessed as HBsAg decline ($\Delta \log_{10}$) from Day 1 to Week 16 of treatment

2.2.2. Secondary Endpoints

- Efficacy assessed as:
  - HBsAg responder rate (decrease from baseline ≥ 1.0 on the $\log_{10}$ scale) at Week 16 of treatment and Weeks 20, 28 and 40 of follow up.
  - HBsAg responder rate (decrease from baseline ≥ 0.5 on the $\log_{10}$ scale) at Weeks 12 and 16 of treatment and Weeks 20, 28 and 40 of follow up.
  - HBsAg loss rate (% patients with HBsAg < LLOQ) at Week 16 of treatment and Weeks 20, 28 and 40 of follow-up.
  - HBsAg loss rate (Proportion of results that are Target Not Detected versus Target Detected) at Week 16 of treatment and Weeks 20, 28 and 40 of follow-up
  - Relapse rate HBsAg (% patients who became negative [HBsAg < LLOQ], then increased with HBsAg > LLOQ) at Week 16 of treatment period and Weeks 20, 28 and 40 during follow-up period

[2] Breakthrough is defined by quantifiable HBV DNA increase of ≥ 1 $\log_{10}$ HBV DNA copies/mL above LLOQ. Breakthrough samples will be further assessed for resistance assessments, including both for the nucleos(t)ide analogue as well as for EYP001a (e.g., sequence analysis of FXR response elements in HBV genome). Details will be described in the Laboratory manual. Also refer footnote no. 9 below.

- Virologic failure rate (breakthrough)[3] of HBV-DNA (% patients with a confirmed quantifiable HBV DNA increase of ≥ 1$\log_{10}$ HBV DNA copies/mL above LLOQ[4]) assessed at Week 16 of treatment period and Weeks 20, 28 and 40 during follow-up period
- HBV-pgRNA decline (Δ $\log_{10}$) from Day 1 to Weeks 4, 8, 12, 16 of treatment period and Week 40 of maintenance period
- HBcrAg decline (Δ $\log_{10}$) from Day 1 to Weeks 4, 8, 12, 16 of treatment period and Week 40 of maintenance period
- HBeAg quantification for HBeAg pos patients and changes at Week 16 of treatment and Week 40 of follow-up
- Fibroscan VCTE change from screening value to Weeks 16 and 40 or ET value

- Safety and Tolerability assessed as:
  - Treatment-emergent adverse events (TEAEs) (including SAEs)
  - All-cause mortality
  - Clinical laboratory tests
  - Pruritus assessment
  - Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
  - Concomitant medications
  - Physical examinations
  - 12-lead ECG

- PK assessed as:
  - Plasma concentration of EYP001a or any relevant active metabolites (as identified in an ongoing phase 1 study)

- PD biomarkers:
  - Plasma C4 (7α-hydroxy-4-cholesten-3-one)
  - FGF19
  - Plasma primary and secondary BAs

3. Study Plan

3.1. Description of Overall Study Design and Plan

This is a prospective, multi-centre, randomized, double-blind, placebo controlled, Phase 2a experimental study of oral FXR modulator EYP001a/placebo combined with NA in virologically suppressed CHB patients to improve functional cure rates.

[3] Breakthrough samples will be further assessed for resistance assessments, including both for the nucleos(t)ide analogue as well as for EYP001a (e.g., sequence analysis of FXR response elements in HBV genome). Details will be described in the Laboratory manual.
[4] HBV DNA results <LLOQ will be reported as either <LLOQ/Detected (i.e. LLOQ/TD) or <LLOQ/Target Not Detected (i.e. LLOQ/TND), both are considered LLOQ.

In total 49 eligible patients will be enrolled and randomized at approximately 14 study sites. Patients will be randomized prior to study drug (EYP001a or placebo and NA) administration on Day 1 in the ratio of 3:1 into 2 arms:

- **Experimental Arm**: EYP001a 200 mg QD + NA daily (37 patients)
- **Control Arm**: Placebo + NA daily (12 patients)

Patients will also be stratified per HBeAg status, based on medical history HBeAg value or established during screening, to obtain a balanced randomization to both study arms.

The maximum total engagement duration for eligible patients in this study is up to 370 days: 90 days screening, 112 days (16 weeks) treatment period and 168 days (24 weeks) follow-up.

Patients enrolled in the study will be assessed as outpatients. Patient screening will occur no more than 90 days prior to the Day 1 visit. Eligible patients will undergo further assessments on Day 1 to qualify for study drug administration on Day 1.

A diagrammatic representation of the study design is presented in Figure 7:

Figure 7 Study Design

The visits during the study are planned as below:

- Screening visit: 12 weeks (90 days)
- 16 weeks treatment period:
  - Treatment Visit 1 (Week 1 [Day 1])
  - Treatment Visit 2 (Week 2 [Day 14 ±3 days])
  - Treatment Visit 3 (Week 4 [Day 28 ±3 days])
  - Treatment Visit 4 (Week 6 [Day 42 ±3 days])
  - Treatment Visit 5 (Week 8 [Day 56 ±3 days])
  - Treatment Visit 6 (Week 10 [Day 70 ± 3 days])
  - Treatment Visit 7 (Week 12 [Day 84 ± 3 days])
  - Treatment Visit 8 (Week 14 [Day 98 ± 3 days])
  - Treatment Visit 9 (Week 16 [Day 112±3 days])
- 24 weeks safety follow-up period:
  - Follow-up Visit 1 (Week 20 [Day 140 ±7 days])
  - Follow-up Visit 2 (Week 28 [Day 196 ±7 days])
  - Follow-up Visit 3 (Week 40 [Day 280 ±7 days])

  Note: during follow-up patients are kept on NA until the end of the trial: Week 40

(consolidation Phase).

- Post study consolidation period: after Week 40, the investigator can continue or stop NA therapy provided the following recommended plan is respected at the end of the study: after cessation of antiviral therapy, there is a transition of HBV care to a local provider for continued monitoring every 3 months with clinical and ALT/AST assessments for at least one year to monitor eventual HBV flares.

Please refer to Section 6 for planned assessments/activities at each study visit.

Safety, tolerance, PK /PD and efficacy of EYP001a will be established in an outpatient setting. An external, independent Data Safety Monitoring Committee (DSMC) will review all available unblinded preliminary virology, safety, PK and PD results when any stopping rules (Section 4.6) are met in two or more subjects and on two occasions for a scheduled interim analysis. Please refer to Section 3.3 for details.

3.2. Rationale for Study Design

This study is designed to test the effect of 200 mg QD EYP001a over 16 weeks on HBsAg in CHB patients who are virally suppressed while on stable NA therapy. The study will employ a randomized, double blind, placebo-controlled design.

In EYP001a Phase 1 trials the physiological FXR engagement has been confirmed, both in healthy subjects and CHB patients via the analysis of two PD markers reflecting FXR activation: FGF19 and the BA biosynthesis precursor C4. Overall FXR led to considerable interest as a therapeutic target for the treatment of metabolic and hepatobiliary diseases, such as CHB.

Randomized, double-blind placebo-controlled designs are generally acknowledged as standard for minimizing the risk of biased estimates of subjective endpoints such as safety, tolerability and efficacy. For rationale of dose selection, please refer Section 5.4.

Both male and female participants are included because CHB, a potential clinical indication for EYP001a, affects both genders.

In order to minimize the risk to study patients and maximize the information gained from the study for further development, an independent DSMC will review all available unblinded preliminary virology, safety, PK, and PD results when any stopping rules are met in two or more subjects and on two occasions for a scheduled interim analysis.

3.3. Data Safety Monitoring Committee (DSMC)

An external, independent DSMC will review all available unblinded preliminary virology, safety, PK, and PD results when any stopping rules are met in two or more subjects (Stopping rules details are described in the protocol Section 4.6.). DSMC will also review on two scheduled occasions for an interim analysis:

1. First interim analysis on all available unblinded preliminary safety study data:

   Safety assessment when 50% (n=25) patients reach week 8 resulting in a decision on continuation of the study based on safety (Go/No go decision); enrolment would remain ongoing during this review

2. Second interim analysis on all available unblinded preliminary virology, safety, PK

and PD study data:

Safety & futility when 50% (n=25) patients reached week 12, resulting in a decision on continuation of the study (Go/No go decision) based on safety & evidence of a benefit of EYP001 (HBsAg, other secondary viral markers); enrolment is ongoing during this review

The interim analyses will be performed on all available primary and secondary endpoints according to the SAP and DSMC charter, which describes the overall guidelines, composition, roles, and responsibilities of the independent DSMC for the EYP001-201 study, including the selection of DSMC members, timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings, data analysis recommendations, and DSMC relationships with other parties participating in the conduct of this study.

The futility assessment will be performed by the DSMC according to the futility rules detailed in Section 11.5, to determine if EYP001 has no benefit at a point when 50% of subjects have reached 12 weeks of dosing. The study will not stop for efficacy at Week 12 interim analyses, even if efficacy boundary is crossed. The stopping of the study for futility will be considered by the DSMC by applying these rules. The criteria are not binding and DSMC can overrule if other interim results show beneficial results.

3.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all study visits, including the last Visit or the last scheduled procedure required for statistical analysis or safety follow-up.

The end of this study is defined as the date when the last Visit of the last participant occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later.

Follow-up Visit 3 planned in Week 40 on Day 280 ±7 days is considered as EoS visit. An early termination (ET) Visit is planned for patients who discontinue early from the study for any reason. This visit is planned for a follow-up approximately one week after administration of their last dose of any study medication, regardless of how many days the patient was in the study.

4. Study Population

4.1. Number of Participants

The study is open to chronic HBV carriers with no recent (3 months) history of any clinically significant conditions, which, in the opinion of the investigator, would jeopardize the safety of the patient or impact the validity of the study results.

Diagnosed CHB is defined by the following values established during screening period:

- HBV virally suppressed with HBV DNA <LLOQ [5] and on stable single NA treatment of at least 12 months duration (ETV or TDF)[6]
- All genotypes, stratified A vs. non-A[7]
- HBeAg negative or positive (expected ratio 7/3): stratification across study arms
- HBsAg plasma levels >100 IU/mL[8].

4.2. Inclusion Criteria

Patients must satisfy all of the following criteria during screening to be enrolled in the study:

1. Has given voluntary written informed consent before performance of any study related procedure.
2. Must be 18 to 65 years of age, inclusive
3. Are on stable NA therapy at least 12 months from the screening date (ETV or TDF)[9]
4. Has virally suppressed CHB:
    a. HBV DNA <LLOQ and serum HBsAg >100 IU/mL
5. Has liver imaging to screen for hepatocellular carcinoma or concomitant pancreaticobiliary disease either in the prior 6 months or at screening.
6. Has liver tests during the Screening Period defined as follows:
    a. The baseline values (i.e. two measurements at least 3 days apart: one can be

[5] The performance characteristics of the quantitative HBV DNA assay will be reported in the laboratory manual. The same assay will be used for all study visits. An FDA approved test will be used such as Abbott Realtime HBV Assay or COBAS HBV Test.
[6] Or equivalent effective NA: Lamivudine, adefovir dipivoxil, ETV, telbivudine and TDF have been approved in most Asia Pacific countries. Patients will be switched to ETV 0.5 mg or Tenofovir Disopropil 245 mg or Tenofovir Disoproxil Fumarate (TDF) 300 mg during screening period if they are not already taking this drug with the same dosage or equivalent.
[7] Genotype information will be collected from medical history, if not available best effort to assess in virologically appropriate plasma sample will be used.
[8] The performance characteristics of the HBsAg quantitative assay will be reported in the laboratory manual. The same assay will be used for all study visits. A validated test will be used (such as Quest Diagnostics quantitative HBsAg or DIASORIN LIAISON® XL HBsAg Quant ([REF] 310250).
Rational: HBsAg level <100 IU/mL predictive for sustained response 2 years after EOT. The role of HBsAg levels in the current management of chronic HBV infection [Höner et al, 2014].
[9] Cross resistance has been described between lamivudine and ETV, as well as telbivudine. In case of previous therapy with lamivudine or telbivudine and current treatment with ETV, a possible cross resistance must be documented as to be unlikely by appropriate in vitro testing (mutational analysis M204V/I, rtT184, rtS202, or rtM250), else history of previous Lamivudine therapy leads to exclusion.

from medical history if not older than 12 months and one during screening period) with both measurements of ALT or AST are ≤ 2 × ULN

b. Normal or clinically not relevant levels of ALP (≤ 1.5 ULN)

c. Has total bilirubin (TBL) ≤ 22.2 μmol/L, which corresponds to ≤ 1.3 mg/dL

d. Has conjugated (direct) bilirubin of ≤ 0.3 mg/dL (i.e. 5.1 μmol/L)

e. Has normal or clinically not relevant levels of GGT (≤ 2.0 ULN)

f. International normalized ratio ≤ 1.2 x ULN, unless on anticoagulant therapy

g. Platelet count ≥ 100 G/L

h. Has albumin ≥3.5 g/dL.

7. Is not of childbearing potential or, if of childbearing potential, is not pregnant as confirmed by a negative serum human chorionic gonadotropin test at screening and is not planning a pregnancy during the course of the study.

8. Women of childbearing potential (WOCBP) and male patients with WOCBP partners must agree to use a dual method of contraception as defined in the study protocol or practice complete abstinence from sexual intercourse if this is the patient's usual and preferred lifestyle throughout the duration of the study and for 90 days after stopping study drug. Patients who are using hormonal contraceptives should be instructed to use an additional contraceptive measure during the study.
Note: A woman is considered of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile. A postmenopausal state is defined as no menses for >12 consecutive months without an alternative medical cause.
A follicle-stimulating hormone level in the postmenopausal range will be used to confirm a postmenopausal state in women <55 years of age. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

4.3. Exclusion Criteria

A patient who meets any of the following exclusion criteria will be excluded from participation in the study:

1. Is an employee of a contract research organization (CRO), vendor, or Sponsor involved with this study.

2. Has known hepatocellular carcinoma or pancreaticobiliary disease.

3. Neutropenia (defined by two confirmed values within screening period of <1500/μL).

4. Has Gilbert syndrome.

5. Shows evidence of worsening liver function, defined as either a confirmed (two assessments at least 3 days apart) increase >2 ULN ALT or AST or an increase of >1.5 × first assessed value of TBL or associated with clinical signs or symptoms of liver impairment.

6. Has known or suspected non-CHB liver disease, including, but not limited to, Hepatitis D virus co-infection, alcoholic liver disease, non-alcoholic steatohepatitis diagnosed with liver biopsy, autoimmune disease, human immunodeficiency virus, active hepatitis C virus (HCV[10]), Wilson disease, hemochromatosis, hepatocellular carcinoma (normal AFP at screening required) or suspected or known other liver cancer, primary biliary cholangitis, primary sclerosing cholangitis, drug-induced liver injury (DILI), bile duct obstruction.

7. History of cirrhosis or liver decompensation, including ascites, hepatic encephalopathy, or presence of oesophageal varices.

8. Probable or possible F3 stage with a vibration controlled transient elastography (VCTE). Patients with normal baseline ALT and VCTE >8.8 kPa are excluded. Patients with baseline ALT >ULN (but <2ULN per EC5) and who have VCTE >10.5 kPa at baseline are excluded [11].

9. Has known history of alcohol abuse or daily heavy alcohol consumption (females: >14 units of alcohol per week; males: >21 units of alcohol per week [1 unit of alcohol is equivalent to a half pint of beer {285 mL}, 1 measure of spirits {25 mL}, or 1 glass of wine {125 mL}]). Has an Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score of >3 points for men and women AND a full Alcohol Use Disorders Identification Test (AUDIT) score of >8 points at screening. Note: Only patients with AUDIT-C scores >3 points at screening will receive the full AUDIT and will be excluded if they score >8 points on the full AUDIT. Patients with AUDIT-C scores <3 points will not receive the full AUDIT.

10. Is pregnant or breastfeeding.

11. Has clinically relevant immunosuppression, including, but not limited to, immunodeficiency conditions such as common variable hypogammaglobulinemia.

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[10] Note: HCV antibody (HCV Ab) positive individuals are not eligible, with the following 2 exceptions: (a) Patients previously treated with a registered drug for viral hepatitis C with at least a 1-year period since documented sustained virologic response may be eligible if HCV ribonucleic acid (RNA) is below the lower limit of quantification (LLOQ) and if all other eligibility criteria are met, and (b) patients with presence of HCV Ab if HCV RNA is below the LLOQ at screening without treatment (i.e., spontaneous clearance) may be eligible if all other eligibility criteria are met.

[11] Tapper et al., 2015, Liang, 2017, Marcellin et al., 2009, Chon et al., 2012 and Chan et al., 2009

12. Has a known pre-existing medical or psychiatric condition that could interfere with the patient's ability to provide informed consent or participate in study conduct, or that may confound study findings.

13. Has known dyslipidaemia with higher cardio-vascular risk from worsening lipid parameters (history of clinically significant cardiovascular or cerebrovascular disease during 12 months prior to study entry).
14. Has, in the opinion of the Investigator, clinically significant cardiovascular or cerebrovascular disease within 12 months prior to the first study drug administration, including, but not limited to, myocardial infarction, acute coronary syndrome, revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or ischemic stroke, or implanted defibrillator or pacemaker.

15. Has participated in any study with administration of an investigational drug in the past 30 days, or 5 half-lives, whichever is longer, prior to the first study drug administration in the current study.

16. Has had major visceral or orthopaedic surgery within 30 days prior to the first study drug administration in the current study.

17. Has a hypersensitivity to the study drug or to any of the excipients or placebo.

18. Has a history of relevant drug and/or food allergies. The term "relevant" applies if any of the following allergy conditions are met:

    a. Has had several episodes of drug-induced urticaria.

    b. Immediate allergic signs (e.g. rhinoconjunctivitis, respiratory) with 2 or more episodes (at whatever time in medical history) due to an identified drugs or food (seasonal rhinoconjunctivitis is not an exclusion).

    c. Has ongoing urticaria episodes (attributed to whatever allergen) or has other active (current) immediate type reaction allergies (e.g. allergic rhinoconjunctivitis, allergic asthma, or latex allergy).

    d. Has had a moderate or severe allergic reaction (Grade 2 per the World Allergy Organization reference table, i.e., isolated non-drug induced urticaria of Grade 1 is not relevant).

    e. Has any allergic condition that might require an emergency epinephrine injection (similar to the EpiPen® Auto-Injector).

19. Has used anti-HBV medications other than NAs within 90 days prior to screening.

20. Is using any of the following disallowed medications within 30 days or 5 half-lives prior to screening whichever is longer, or planned use later during study participation: vitamin K antagonists such as warfarin, anticancer (except anti-hormonal which are allowed) drug(s), immunomodulator(s), or

immunosuppressant(s) or any drug with known liver toxicity for >2 weeks in the year prior to screening (e.g. amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, estrogens at doses greater than those used for hormone replacement, anabolic steroids, or valproic acid or other known hepatotoxins at the Investigator or Medical Monitor's discretion), ursodeoxycholic acid, or obeticholic acid within 90 days prior to screening. Agents (including over-the-counter weight loss preparations) or medications known to significantly impact body weight within 30 days prior to screening (e.g. sibutramine, phenetamine, and orlistat).

21. Is using lipid lowering drugs such as statins (other than rosuvastatin, atorvastatin, simvastatin, pravastatin, fluvastatin or lovastatin).

22. Has planned major visceral, orthopaedic or neuro surgery during the study period.

23. Has uncontrolled type 1 diabetes mellitus or type 2 diabetes mellitus (T2DM) (haemoglobin A1c >9.5%).

24. Has any of the following exclusionary laboratory results at screening:

    a. Estimated glomerular filtration rate <60 mL/min/1.73 m^2 (the Modification of Diet in Renal Disease formula).

    b. Thyroid-stimulating hormone >1.5× ULN or abnormal free triiodothyronine or free thyroxine.

    Note: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor if any of the above laboratory abnormalities are found.

25. Has a history of clinically significant gastrointestinal disease, especially peptic ulcerations, gastrointestinal bleeding, inflammatory bowel disease, bariatric surgery, renal, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, or cardiovascular disease or any other condition, which, in the opinion of the Investigator, would jeopardize the safety of the patient or impact the validity of the study results.

4.4. Prohibitions and Restrictions in the study

Potential patients must be willing to adhere to the following prohibitions and restrictions during the course of the study:

1. Must restrict consumption of caffeinated drinks to 2 per day during the study and refrain from any consumption for at least 12 hours prior to study visits
2. Must refrain from undertaking any strenuous exercise 48 hrs before all Visits
3. Must refrain from alcohol and/or drug substance abuse during the course of the study

4.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study

but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Re-screening will be allowed within the screening period of 90 days. Screen failures related to laboratory results will only be considered for re-screening. Rescreened participants should be assigned the same participant number as for the initial screening.

4.6. Stopping Rules

Dosing for a patient will be discontinued for any of the following events:

1. One occurrence of an SAE assessed to be definitely, probably or possibly related to dosing with the study drug.
2. One occurrence of a Grade 4 AE (i.e. life-threatening) assessed to be considered "possibly related" or "probably related" to the study drug
3. One occurrence a Grade 3 rash or higher or acute systemic allergic reaction.
4. Confirmation of any of the study drug discontinuation criteria as described in Section 8.3.
5. Occurrence of any condition that, in the opinion of the Investigator, significantly jeopardizes the wellbeing and safety of the patient and is assessed to be probably related to dosing with the study drug.
6. Clinically significant changes in vital signs or ECGs (such as arrhythmias) assessed to be considered "possibly related" or "probably related" to the study drug (i.e., no alternative explanation likely).
7. Clinically significant changes in the safety laboratory tests assessed to be considered "probably related" to the study drug (i.e., no alternative explanation likely).
8. A subject experiences a breakthrough (defined by quantifiable HBV DNA increase of $\geq$ 1 $\log_{10}$ HBV DNA copies/mL above LLOQ) the subject should return to the study site for a confirmatory measurement within two weeks, and if virologic breakthrough is confirmed, EYP001a or placebo dosing should be stopped and NA treatment should be continued or modified at the investigator's discretion.

If two or more patients meet study drug stopping criteria #1, or #3 to #8, recruitment and dosing should be suspended or terminated for the remaining patients, pending the outcome of a DSMC review. The DSMC must review all safety data and provide clearance prior to dosing any additional patients.

If one patient meets study drug stopping criteria #2, recruitment and dosing should be suspended or terminated for the remaining patients, pending the outcome of a DSMC review.

If one patient experiences a Grade 5 common terminology criteria for adverse event (CTCAE) toxicity (based on CTCAE, version 5.0), or if more than 2 patients develop a Grade 3 CTCAE toxicity in the same category, the study will be paused, and safety reports

will be submitted to the DSMC for review and clearance prior to dosing any additional patients.

In other situations, re-initiation of study drug may be considered after consultation with the Medical Monitor.

4.7. Participant withdrawal criteria

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason, including the occurrence of an AE or noncompliance with the protocol.

Participants who withdraw from the study for any reason will not be replaced unless it is mutually agreed upon, in writing, by the Investigator, the medical monitor, and Sponsor.

If a participant withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study and primary reason will be recorded. An ET Visit is planned for a follow-up approximately one week after administration of their final last dose of study medication, regardless of how many days the patient was in the study.

If a participant is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside the reference range, the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or AE is achieved.

4.8. Study Termination

ENYO Pharma may terminate this study prematurely, for reasonable cause, provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study for reasonable cause, after providing written notice to ENYO Pharma in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If ENYO Pharma terminates the study for safety reasons, ENYO Pharma will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

5. Treatments

5.1. Identity of Investigational Product

EYP001a is a white to off-white immediate-release (IR) tablet containing 200 mg of drug substance.

Placebo tablets will be of identical appearance as the active EYP001a. The number of placebo tablets to be administered will be adjusted as may be necessary to match the number of EYP001a tablets administered.

NA treatment: ETV 0.5 mg daily or Tenofovir Disoproxil Fumarate (TDF) 300 mg daily which is equivalent to 245 mg of tenofovir disoproxil per country specific label will be provided as the SOC.

5.1.1. Packaging and Labelling

EYP001a tablets (200 mg) or placebo will be packaged as 7 tablets in an aluminium polyvinyl chloride (PVC)/polyethylene (PE)/polyvinylidene chloride (PVDC) blister pack.

The study doses to be administered to a patient will be labelled according to the PIC/S Guide to Good Manufacturing Practice for Medicinal Products. The detail on the labels will include, but not be limited to:

- The notation- 'For Clinical Trial Use Only';
- Protocol number;
- Investigator/site identification;
- Trial participant number;
- Name of sponsor;
- Route of administration;
- Batch number;
- Retest date/expiry date.

Detailed instructions for the labelling, supply and dispensing instructions of EYP001a are described in the study pharmacy manual.

5.1.2. Storage

EYP001a tablets are stable when packaged in blisters composed of PVC/PE/PVDC with aluminium foil backing at 15-25ºC.

EYP001a will be supplied dispensed ready for patient dosing by a designated drug depot distributor for the sponsor. Study drug supplies will be stored securely under the appropriate conditions at the study site according to the applicable regulatory requirements. Based on available stability data, EYP001a tablets should be stored at room temperature (15-25ºC). Refer to the Directions for Use for additional storage requirements in the study pharmacy manual. The clinical site must ensure that the products are stored in a secure area under recommended storage conditions. It is the responsibility of the investigator to ensure that the integrity of packaged investigational products not be jeopardized prior to dispensing.

All materials supplied are for use only in this clinical study and should not be used for any other purpose.

All investigational products will be administered in accordance with the investigator's prescription and it is the investigator's responsibility to ensure that an accurate record of "investigational product issued and returned" is maintained.

Only participants enrolled in the study may receive the investigational products, in accordance with all applicable regulatory requirements. Only authorized and trained site staff may supply or administer the investigational products.

5.1.3. Description

Table 2 provides a comprehensive summary of the study drug to be administered in this study.

Table 2 Comprehensive Details of EYP001a / placebo

	Investigational Product	
Product Name:	EYP001a	Matching placebo
Dosage Form:	Tablet	Tablet
Unit Dose	200 mg	1
Route of Administration	Oral	Oral
Physical Description	White to off-white tablet	White to off-white tablet
Manufacturer of Drug Substance	PCAS (France)	NA
Formulation/Manufacturing of Drug Product	Catalent (Germany)	Catalent (Germany)

For a complete list of excipients, please refer to the study pharmacy manual.

NA treatment (ETV or TDF) will be provided in combination with EYP001a and placebo as a SOC per the dosing guidelines presented in the country-specific label(s). Entecavir (ETV) 0.5 mg daily (or per country specific label) or Tenofovir Disoproxil Fumarate (TDF) 300 mg daily which is equivalent to 245 mg of tenofovir disoproxil will be given per country specific label). Patients will continue to receive NA treatment during the follow-up phase as well.

5.2. Treatments Administered

A single daily dose of 200 mg of EYP001a, using one 200 mg tablet, will be orally administered in the morning fed or fasted with plain water.

The investigator is responsible for the education of study staff in the correct dispensing of the study drug. The investigator/designee is responsible for the education of study patients in the correct administration of the study drug when dosing at home.

Note: On each treatment visit the study drug should be administered after PK/PD blood sampling.

5.3. Method of Assigning Participants to Treatment Groups

Sequential screening numbers will be assigned to participants at the time of informed consent signing. As they are enrolled into the study, participants will be assigned to a unique randomization number which are randomly assigned to treatment according to the specified randomization scheme.

The randomization schedule will be computer-generated before the start of the study.

An Interactive Web Response System (IWRS) will be employed to manage patient randomization and treatment assignments.

5.4. Dose Rationale and Selection of Doses in the Study

EYP001a Phase 1 data in healthy subjects showed that EYP001a was well tolerated after single and multiple oral administration from 30 to 800 mg (single ascending doses) and from 60 to 500 mg (multiple ascending doses). For all dosing conditions despite similar rapid EYP001a elimination, FGF19 and C4 showed a prolonged FXR target engagement up to at least 24 hours, which was not influenced by fasting or fed condition or by morning or evening administration (Study EYP001-102). EYP001a was safe in chronically infected-HBV patients treated over 4 weeks with doses of 100 mg QD, 150 mg BID, 200 mg QD, 200 mg BID, 300 mg QD, and 400 mg QD, EYP001a. The most frequent TEAEs were headache, pruritus, abdominal pain, and diarrhea. Pruritus was mostly seen with BID administration and was of mild or moderate intensity and lasting from 5 to 36 days. In addition, the QD doses showed better tolerance with few pruritus TEAEs.
Overall, EYP001a was safe and well tolerated over the dose range of 100 mg to 500 mg QD and 200 mg BID but was better tolerated with the QD regimen than with BID dosing.

This is an early stage Phase 2a exploratory study to determine if adding EYP001a 16-week treatment on top of NA can induce a clinically meaningful and statistically significant reduction of HBsAg plasma levels after 16 weeks of combined treatment. An initial dose strength of 400 mg QD EYP001a capsules was selected because it was the so far highest tested dose over 4 weeks and was well tolerated by CHB patients. It also showed an apparent dose-dependent signal on HBsAg reduction.

However in an ongoing phase 2a trial (EYP001-202, 24 NASH subjects enrolled as of 18 December 2019) and in an ongoing phase 1 trial (EYP001-107, 9NASH and 4 healthy subjects enrolled as of 18 December 2019), 100mg and 200mg EYP001a oral tablets were tested at the dose levels 100mg BID, 200mg QD and 400mg QD. These are the preliminary findings:

PK profile of EYP001 tablet:

- The oral EYP001a tablet formulation appears to have higher bioavailability compared to the oral capsule formulation previously used in EYP001 phase 1 studies in healthy and subjects with NASH.
- The similar exposure seen in NASH subjects with the 200mg QD (1x200mg tablet) and the 400mg QD (2x200mg tablets) suggests a saturation phenomenon with exposure reaching a plateau over the 200mg dose level
- A similar EYP001 plasma concentrations were obtained in simulations performed for CHB subjects for the 200mg QD (1x200mg tablet) compared to concentrations after administration of the 400mg QD (2x200mg capsules). The later was previously tested and well tolerated in study EYP001-103 in CHB subjects.

- Finally the differences of the PK parameters after administration of 200mg, 400mg QD repeated oral EYP001a doses either as capsules or tablet

Safety & Tolerance:

- **Pruritus:** In an ongoing study EYP001-202 , NASH subjects treated during 12 weeks (with EYP001a 100mg BID or 200mg QD or 400mg QD or Placebo tablets) had an overall pruritus frequency of 15/24 (64%) subjects, all mild or moderate episodes, except for three Grade 3. Five pruritus episodes led to early treatment termination. This is in contrast with previous experience in study EYP001-103, in which CHB subjects were treated during 4 weeks with EYP001a capsules, and had mostly mild or moderate pruritus episodes: 1 subject of 7 to 9 (11% to 14%) in each of the EYP001 arms (100 mg, 200 mg and 400 mg QD) but increased to 6 of 9 (67%) subjects treated with 200 mg BID. One subject terminated early because of pruritus.
- **ALT/AST:** In study EYP001-202, two grade 3 cases of isolated transient ALT/AST increases, with no signs of liver impairment, occurred around Day 56 of treatment. No Hy's law cases occurred (no confirmed DILI). The designation by the Primary Investigators (PIs) of the liver enzyme elevations did not consider these as clinically significant, with a variance over time with few outliers, overall not unexpected in the NASH patient population. This compares and is in line with previous phase 1 trials results, where ALT and AST values were within the normal range following EYP001a administration in healthy subjects and in study EYP001-103 after 4 weeks of administration of EYP001a to CHB subjects, 5 subjects had Grade 3 (n=4) or 4 (n=1) ALT/AST increases without signs of liver impairment. The changes were interpreted as hepatic flares or typical of those seen in subjects with underlying chronic viral HBV liver disease.

Taken together, these PK and safety/tolerance preliminary findings in the ongoing NASH and phase 1 trial obtained with the EYP001a tablet formulation do not support the use of the 400mg daily EYP001 dose as a tablet. The reduction to 200mg QD (1x200mg tablet) will generate an exposure similar to previously tested and well tolerated 400mg QD (2x200mg capsules). EYP001a 200mg tablet QD dose can be assessed safely in CHB subjects over the planned 16 week treatment period.

For more details, please refer to IB memorandum dated 16 January 2020 (IB Memo, 2020)**.**

5.5. Selection and Timing of Dose for each Participant

The study drug will be administered to patients randomized in the study based on the assigned treatment arm:

- **Experimental Arm**: EYP001a 200 mg QD + NA daily (37 patients)
- **Control Arm**: Placebo + NA daily (12 patients)

5.6. Contraindications

Although there is no indication from dose-ranging studies that EYP001a has an effect on embryo-foetal development in rats and rabbits, and there are no data in humans, pregnancy should be avoided in women receiving this compound. Women of childbearing potential (WOCBP) should undergo pregnancy testing prior to initiation of EYP001a and periodically during treatment. In addition, adequate contraceptive methods should be consistently used by males and females during and for 90 days after stopping treatment

with EYP001a. Patients should be counselled on the use of contraception before beginning treatment with EYP001a.

EYP001a is also contraindicated in nursing mothers, as it is not known if EYP001a or any of its metabolites are excreted in breast milk.

EYP001a should also be contraindicated in patients with clinically significant hypersensitivity to any components of its formulation.

5.7. Potential Risks and Adverse Reactions

EYP001a may lead to mild or moderate GI symptoms observed in trial subjects (including dyspepsia, nausea, hypersalivation, diarrhea, vomiting and abdominal pain). These are transient, short-lasting and self-limited, no specific treatment or measure is required. Other observed possible drug-related TEAEs were mild pruritus, headache, dizziness, muscular symptoms, increased hepatic enzymes, and skin reactions.

EYP001a may lead to HDL decrease and/or LDL increase. Although this is in line and within the range of reported changes for other FXR agonists under development or the approved synthetic bile salt OCALIVA®, and it appears as a likely class effect with an unknown risk in the long term. It requires monitoring in patients considered for chronic treatment with FXR agonist. The potential risks of a long-term cholesterol profile modifications need to be weighed against the possible therapy benefits.

For more details, please refer to Section 6 of the IB [IB, 2019].

5.8. Dose Interruptions and Reductions

Dosages for study drug should be maintained constant during the study. However, safety criteria for stopping doses (temporarily or permanently) for individual patients is described in Section 4.6.

5.8.1. Pruritus management: guidance to investigators

Self-limited pruritus mostly mild to moderate has been observed in clinical trials with EYP001 and in higher a proportion of patients who received twice daily dosing regimens. Pruritus has also been reported with other FXR agonists and in patients with NASH as part of the disease natural symptomatology and independent of any pharmacological treatment. Tolerance to pruritus may develop over continuous uninterrupted dosing of EYP001.

The following three level therapeutic approach to pruritus can be applied:

1. Topical non-pharmacological or over the counter interventions to improve pruritus may be tried and can be advised to patients. These include application of moisturizers, cooling agents, antihistamines, taking cool showers/showering in the morning, using clear/gentle soaps and laundry detergents, application of cold packs or fabric strips soaked in cold water, avoidance of wool or other irritating fabrics, wearing loose-fitting clothing.
2. With likely no improvement of severe pruritus, a drug holiday of 2 to maximum 5 days may be considered and in such cases, we would encourage to contact the

Medical Monitor

3. In situation where pruritus prevails and requires systemic oral pharmacological treatment, the following drugs may be considered at the investigator's judgment and taking into account individual clinical situation, pruritus severity and concomitant medications and comorbidities: antihistamines, hydroxyzine, opioid antagonists, gabapentin (note that the concomitant use of opioid agonists and gabapentin is not recommended).

5.9. Blinding

Study site personnel, including the Investigator and study team, as well as the study patients, will remain blinded to the treatment assignment throughout the course of the study.

Blinding of study treatment will be managed by the packaging and labelling vendor and should be maintained by the clinical investigative site's pharmacy in accordance with the Pharmacy Manual. In the event of a medical emergency where breaking the blind is required to provide medical care to the patient, the investigator may obtain treatment assignment for that patient.

IWRS should be used as the primary method of breaking the blind. If IWRS cannot be accessed, the investigator should contact the Sponsor medical monitor to break the blind. Treatment assignment should remain blinded unless that knowledge is necessary to guide patient emergency medical care. The investigator is requested to notify the Medical Monitor and Sponsor including the medically compelling justification to unblind a patient's treatment assignment.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a patient's treatment assignment is disclosed to the investigator, the patient will have study treatment discontinued. All patients will be followed until study completion unless consent to do so is specifically withdrawn by the patient.

The Sponsor or designee may independently unblind cases for expedited reporting of SUSARs as required by regulators.

5.10. Prior and Concomitant Therapy

Prior medication will be defined as any medication taken within 30 days prior to screening and stopped prior to the first dose of study drug.

Concomitant medication will be defined as any medication taken during the study between the date of the first dose of study drug and the date of the EoS/ET Visit. Any medications started after the EoS/ET will not be considered concomitant medications.

Alcohol and drug substance abuse and any other IPs/devices are prohibited during the course of the study.

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented on the electronic case reported form (eCRF). Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be

avoided. Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions, but any taken by the patient should be documented appropriately on the eCRF.

Drugs transported by OATP1B1 have potential for drug-drug interaction with EYP001a. Therefore, use of lipid lowering drugs such as statins (other than rosuvastatin, atorvastatin, simvastatin, pravastatin, fluvastatin or lovastatin) need Sponsor's approval.

Any change in regimen for any concomitant medication, including restricted concomitant medications, must be reported to the Sponsor in a timely manner.

Details of concomitant medications from Screening through (EoS) participation should be recorded in the patient's source documents and in the eCRF. In addition, medications taken within the past 30 days prior to Screening should also be recorded.

5.11. Treatment Compliance

The study drug (EYP001a/Placebo and NA) will be dispensed to the patients by the Investigator or study site personnel dedicated to the study on the treatment visits 1, 3, 5, 7 and 9 (for EYP001a/Placebo dispensation is only at visits 1 and 5, as each boxe is for 8 weeks of treatment). Please note 16 weeks of treatment (EYP001a/Placebo and NA) with 8 weeks treatment units will be dispensed. Should the patient "loose" treatment units the check on sufficient treatment can be made at each fortnightly visit. Patient diary will be provided on the treatment visits 1, 2, 3, 4, 5, 6, 7, 8 and 9. NA will also be dispensed along with patient diary, on the follow up visits 1 and 2. Patients will administer the study drug (EYP001a/placebo and NA) outside the study sites (at home) during the treatment period (Week 1 to Week 16) and follow-up period (Week 17 to Week 40) as instructed by Investigator or study-site personnel and will record the dosing details in the patient diary to document compliance.

Data pertaining to tablet count for the study drug will be collected on the treatment visits 2, 3, 4, 5, 6, 7, 8 and 9; on all follow-up visits and on ET visit. If a patient's drug administration and site-related procedures are not conducted as defined in the protocol, the Investigator will make note of ensuring compliance to the protocol for future activities.

The date and time of each study drug administration and accompanying activity recorded in the patient diary will be transcribed in the eCRF. Detailed instructions for the dispensing instructions of EYP001a are described in the study pharmacy manual.

5.12. Drug Accountability

The PI or appropriately trained designee will maintain an accurate record of the receipt of the study drug shipment, including the date and quantity received. Refer to the Pharmacy Manual for further information.

In addition, an accurate drug dispensing record will be kept that specifies the amount dispensed to each patient and the date of dispensing.

A drug accountability inventory record to account for all dispending and return of any used and unused study drug must be maintained and available by the site staff for inspection at any time. At the end of the study, the study drug will be reconciled, and copies of the complete record of study drug accountability will be provided to the Sponsor.

5.13. Investigational Product Handling and Disposal

The study drug will be sent to the study site under appropriate storage conditions. Upon receipt of study drug, study staff are to open the shipment and verify that the amount and identity of the contents match that stated in the enclosed shipping form. The Sponsor (or designee) is to be notified immediately about any irregularities, discrepancies, or damage.

The Investigator must not supply the study drug to any person except those named as Sub-Investigators or designated staff. They must not dispense any study drug from the designated study to non-study patients or individuals. Site personnel must not re-label or give study drug to individuals not enrolled in the study.

The Investigator must ensure that all study drug received at the study site is inventoried and accounted for and that dispensed study drug is recorded in the eCRF and in the Study Medication Log. The Site Monitor will verify study drug accountability during monitoring visits. The study staff will maintain a full record of study drug accountability as described in Section 5.12.

Upon completion of the study, used and unused study drug are to be returned to the Sponsor (or designee) or, if prior Sponsor approval is obtained, disposed of in accordance with applicable site procedures. ENYO Pharma (Sponsor) or its designee will provide instructions for the return or destruction of study drug.

Study staff must maintain documentation of any missing or unreturned study drug. The final disposition of all study drug received at the site is to be documented.

Detailed instructions for the handling and disposal instructions of EYP001a are described in the study pharmacy manual.

6. Study Assessments and Procedures

6.1. Informed Consent

Written informed consent to use or disclose protected health information, must be obtained from a prospective participant before any study-specific procedures are performed for that individual. SOC assessments performed before informed consent is obtained may be utilized to screen for study eligibility. Participants will read the informed consent form (ICF), after being explained about the study. Before signing the ICF, participants will have an opportunity to discuss the contents of the ICF with study centre staff. Participants will be made aware that they may withdraw from the study at any time. Participants who agree to participate in the study will sign the most recently approved ICF and will be provided with a copy of the fully executed documents. The original, executed ICF will be maintained in the respective participant's clinical study file.

Refer to Section 13: Ethical Considerations. The schedule of events for the study is described below and in Section 19: Appendices for more details.

6.2. Schedule of assessments

Schedule of assessments are presented in Section 19.1 and discussed below.

6.2.1. Screening Evaluations

Patients will be assigned screening numbers (Format: three-digit site number '-'three-digit participant number e.g. 001-001, 001-002, etc.) consecutively by the Investigator or designee at the time the patient signs the ICF. For all patients screened, the Investigator or designee will record the eligibility criteria assessment in the medical record. A screening and enrolment log will capture the screening number for each patient, the date of screening and a screen fail reason(s) for patients that are not eligible to participate.

Enrolment for this study is defined as any patient that has received at least one dose of the investigational product. The enrolment number of the patient will remain the same as the screening number.

Patient who is first designated as a screen failure prior to being randomized may be rescreened upon Sponsor or designee approval. Patients will be randomized into the study once all eligibility criteria are confirmed.

All screening tests must be performed within study Weeks -12 to -1, unless otherwise indicated. Procedures to be performed at Screening Visit includes the following:

- Obtain signed written informed consent prior to screening
- Check patient's eligibility
- Review and record patient's demographic details
- Review and record patient's medical history
- Review and record patient's prior and concomitant medications
- Perform drugs of abuse screen[12]
- Record patient's height and body weight
- Calculate body mass index (BMI)
- Perform complete physical examination
- Perform vital signs (systolic/diastolic blood pressure [BP], heart rate, temperature, respiratory rate) evaluation
- Perform AUDIT-C
- Perform clinical laboratory analysis including haematology, serum chemistry panel, coagulation tests, lipid and metabolic profile and TSH.
- Perform serum pregnancy test (for WOCBP only)
- Perform Dipstick urinalysis for all male and female patients
- Perform 12-Lead ECG
- Sampling for analysis of HBV response markers
- Perform Fibroscan VCTE
- Perform Liver imaging (unless done within 6 months prior screening)

All screening Viral serology tests must be performed within study Weeks -12 to -8, unless

[12] For drugs such as amphetamines, methamphetamine, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tricyclic antidepressants and THC (cannabis).

otherwise indicated and test to be performed at Screening Visit includes the following:

- Perform Viral serology: anti-HIV, anti-HCV[13], anti-HDV, quantitative HBV-DNA, quantitative HBsAg, anti-HBs, anti-HBe.

Note: all the PD and PK samplings during the study must be performed before study drug administration.

6.2.2. Treatment Period (Week 1 to Week 16)

The treatment period begins with the administration of study drug and the study procedures are allocated on Treatment Visits 1 (Week 1 [Day 1]), 2 (Week 2 [Day 14 ± 3 days]), 3 (Week 4 [Day 28 ± 3 days]), 4 (Week 6 [Day 42 ± 3 days]), 5 (Week 8 [Day 56 ± 3 days]), 6 (Week 10 [Day 70 ± 3 days]), 7 (Week 12 [Day 84 ± 3 days]), 8 (Week 14 [Day 98 ± 3 days]) and 9 (Week 16 [Day 112±3 days]). The patients will be outpatient during the treatment period. Please refer Section 19.1 for overall activities planned for the treatment period.

6.2.2.1. Treatment Visit 1 (Week 1 [Day 1])

The treatment Visit 1 is planned on Day 1. Following activities are planned for the visit:

- Confirm patient's eligibility prior to randomization
- Review and record patient's prior and concomitant medications
- Perform drugs of abuse screen pre-dose
- Record patient's body weight
- Calculate BMI
- Perform symptom-directed physical examination
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose
- Perform AUDIT-C
- Randomization
- Pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis including haematology, serum chemistry panel (including liver safety testing: ALT, AST, Alkaline Phosphatase, Gamma Glutamyl Transferase (GGT), Total Bilirubin and Albumin), coagulation tests and lipid and metabolic profile
- Perform urine pregnancy test (for WOCBP only)
- Perform Dipstick urinalysis for all male and female patients
- Perform 12-Lead ECG
- Sampling for analysis of HBV response markers[14]

[13] For positive HCV antibody-test results only, a PCR-based quantitative HCV viral load assessment will also be performed.
[14] All subjects must have the blood samples collected at pre-dose for quantitative HBV tests: HBsAg, HBV-DNA, HBV-pgRNA, HBcrAg and HBeAg (the later only for anti-HBe positives subjects).

- PD biomarker sampling
- Liver fibrosis and inflammation assessment
- PK Sampling
- Dispense patient diary and explain use
- Dispense EYP001a or placebo and NA (choice between ETV or TFV is at the Investigator discretion)

6.2.2.2. Treatment Visit 2 (Week 2 [Day 14 ± 3 days])

The treatment Visit 2 is planned on Day 14 ± 3 days in Week 2. Following activities are planned for the visit:

- Review and record patient's prior and concomitant medications
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose
- Pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis only liver safety testing: ALT, AST, ALP, GGT, total bilirubin, thrombocytes and albumin
- Sampling for analysis of HBV response markers
- PD biomarker sampling
- PK Sampling
- Review returned patient diary and dispense new diary
- Collect used/unused study drug and assess compliance

6.2.2.3. Treatment Visit 3 (Week 4 [Day 28 ± 3 days])

The treatment Visit 3 is planned on Day 28 ± 3 days in Week 4. Following activities are planned for the visit:

- Review and record patient's prior and concomitant medications
- Record patient's body weight
- Calculate BMI
- Perform symptom-directed physical examination
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose
- Pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis including haematology, serum chemistry panel, coagulation tests, lipid and metabolic profile and TSH.
- Perform urine pregnancy test (for WOCBP only)
- Perform Dipstick urinalysis for all male and female patients
- Perform 12-Lead ECG
- Sampling for analysis of HBV response markers
- PD biomarker sampling
- Liver fibrosis and inflammation assessment
- PK Sampling
- Review returned patient diary and dispense new diary
- Dispense NA
- Collect used/unused study drug and assess compliance

6.2.2.4. Treatment Visit 4 (Week 6 [Day 42 ± 3 days])

The treatment Visit 4 is planned on Day 42 ± 3 days in Week 6. Following activities are planned for the visit:

- Review and record patient's prior and concomitant medications
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose
- Pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis only liver safety testing: ALT, AST, ALP, GGT, total bilirubin, thrombocytes and albumin
- Sampling for analysis of HBV response markers
- PD biomarker sampling
- PK Sampling
- Review returned patient diary and dispense new diary
- Collect used/unused study drug and assess compliance

6.2.2.5. Treatment Visit 5 (Week 8 [Day 56 ±3 days])

The treatment Visit 5 is planned on Day 56 ± 3 days in Week 8. Following activities are planned for the visit:

- Review and record patient's prior and concomitant medications
- Record patient's body weight
- Calculate BMI
- Perform symptom-directed physical examination
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose
- Pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis including haematology, serum chemistry panel, coagulation tests, lipid and metabolic profile and TSH.
- Perform urine pregnancy test (for WOCBP only)
- Perform Dipstick urinalysis for all male and female patients
- Perform 12-Lead ECG
- Sampling for analysis of HBV response markers
- PD biomarker sampling
- Liver fibrosis and inflammation assessment
- PK Sampling
- Review returned patient diary and dispense new diary
- Dispense EYP001a or placebo and NA
- Collect used/unused study drug and assess compliance

6.2.2.6. Treatment Visit 6 (Week 10 [Day 70 ± 3 days])

The treatment Visit 6 is planned on Day 70 ± 3 days in Week 10. Following activities are planned for the visit:

- Review and record patient's prior and concomitant medications
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose

- Pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis only liver safety testing: ALT, AST, ALP, GGT, total bilirubin, thrombocytes and albumin
- Sampling for analysis of HBV response markers
- PD biomarker sampling
- PK Sampling
- Review returned patient diary and dispense new diary
- Collect used/unused study drug and assess compliance

6.2.2.7. Treatment Visit 7 (Week 12 [Day 84 ± 3 days])

The treatment Visit 7 is planned on Day 84 ± 3 days in Week 12. Following activities are planned for the visit:

- Review and record patient's prior and concomitant medications
- Record patient's body weight
- Calculate BMI
- Perform symptom-directed physical examination
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose
- Pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis including haematology, serum chemistry panel, coagulation tests, lipid and metabolic profile and TSH
- Perform urine pregnancy test (for WOCBP only)
- Perform Dipstick urinalysis for all male and female patients
- Perform 12-Lead ECG
- Sampling for analysis of HBV response markers
- PD biomarker sampling
- Liver fibrosis and inflammation assessment
- PK Sampling
- Review returned patient diary and dispense new diary
- Dispense NA
- Collect used/unused study drug and assess compliance

6.2.2.8. Treatment Visit 8 (Week 14 [Day 98 ± 3 days])

The treatment Visit 8 is planned on Day 98 ± 3 days in Week 14. Following activities are planned for the visit:

- Review and record patient's prior and concomitant medications
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose
- Pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis only liver safety testing: ALT, AST, ALP, GGT, total bilirubin, thrombocytes and albumin
- Sampling for analysis of HBV response markers
- PD biomarker sampling

- PK Sampling
- Review returned patient diary and dispense new diary
- Collect used/unused study drug and assess compliance

6.2.2.9. Treatment Visit 9 (Week 16 [Day 112 ±3 days])

The treatment Visit 9 is planned on Day 112 ± 3 days in Week 16. Following activities are planned for the visit:

- Review and record patient's prior and concomitant medications
- Record patient's body weight
- Calculate BMI
- Perform symptom-directed physical examination
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose
- Pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis including haematology, serum chemistry panel, coagulation tests, lipid and metabolic profile and TSH.
- Perform urine pregnancy test (for WOCBP only)
- Perform Dipstick urinalysis for all male and female patients
- Perform 12-Lead ECG
- Sampling for analysis of HBV response markers
- PD biomarker sampling
- Liver fibrosis and inflammation assessment
- Perform Fibroscan VCTE
- PK Sampling
- Review returned patient diary and dispense new diary
- Dispense NA
- Collect used/unused study drug and assess compliance

6.2.3. Follow-up Period (Week 17 to Week 40)

The study procedures during the follow-up period are allocated on Follow-up Visits 1 (Week 20 [Day 140 ± 7 days]), 2 (Week 28 [Day 196 ± 7 days]) and 3 (Week 40 [Day 280 ± 7 days]). The patients will be outpatient during the follow-up period. Please refer Section 19.1 for overall activities planned for the follow-up period.

6.2.3.1. Follow-up Visit 1 (Week 20 [Day 140 ± 7 days])

The follow-up Visit 1 is planned on Day 140 ± 3 days in Week 20. Following activities are planned for the visit:

- Review and record patient's prior and concomitant medications
- Record patient's body weight
- Calculate BMI
- Perform symptom-directed physical examination
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose
- Pruritus assessment
- AE monitoring

- Perform clinical laboratory analysis including haematology, serum chemistry panel, coagulation tests and lipid and metabolic profile
- Sampling for analysis of HBV response markers
- PD biomarker sampling
- Liver fibrosis and inflammation assessment
- Review returned patient diary and dispense new diary
- Dispense NA
- Collect used/unused study drug and assess compliance

6.2.3.2. Follow-up Visit 2 (Week 28 [Day 196 ± 7 days])

The follow-up Visit 2 is planned on Day 196 ± 3 days in Week 28. Following activities are planned for the visit:

- Review and record patient's prior and concomitant medications
- Record patient's body weight
- Calculate BMI
- Perform symptom-directed physical examination
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose
- Perform pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis including haematology, serum chemistry panel, coagulation tests and lipid and metabolic profile
- Sampling for analysis of HBV response markers
- PD biomarkers sampling
- Liver fibrosis and inflammation assessment
- Review returned patient diary and dispense new diary
- Dispense NA
- Collect used/unused study drug and assess compliance

6.2.3.3. Follow-up Visit 3/EoS Visit (Week 40 [Day 280 ± 7 days])

The follow-up Visit 3/EoS Visit is planned on Day 280 ± 3 days in Week 40. Following activities are planned for the visit:

- Review and record patient's prior and concomitant medications
- Record patient's body weight
- Calculate BMI
- Perform symptom-directed physical examination
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate) evaluation pre-dose
- Perform pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis including haematology, serum chemistry panel, coagulation tests and lipid and metabolic profile
- Sampling for analysis of HBV response markers
- PD biomarkers sampling
- Liver fibrosis and inflammation assessment

- Perform Fibroscan VCTE
- Review returned patient diary
- Collect used/unused study drug and assess compliance
- Perform liver imaging to screen patient for HCC. For patients with risk factors for HCC, i.e. any of these: family history with HCC, >40 years of age, male sex, born in Sub-Saharan Africa, Metabolic syndrome (obesity, diabetes), smoking, ALT>ULN, HBV DNA (>2,000 IU/mL), HBeAg-negative, Genotype C) during follow-up phase liver imaging is also performed at week 40.

6.2.4. Early Termination (ET) Visit

The ET Visit is planned for patients who discontinue early from the study for any reason, for a follow-up approximately one week after administration of their final last dose of any study medication, regardless of how many days the patient was in the study. Please refer Section 19.1 for the collection of data based on the following activities planned for the visit:

- Review and record patient's prior and concomitant medications
- Record patient's body weight
- Calculate BMI
- Perform symptom-directed physical examination
- Perform vital signs (systolic/diastolic BP, heart rate, temperature, respiratory rate)
- Pruritus assessment
- AE monitoring
- Perform clinical laboratory analysis including haematology, serum chemistry panel, coagulation tests and lipid and metabolic profile
- Perform serum pregnancy test (for WOCBP only)
- Perform Dipstick urinalysis for all male and female patients
- Perform 12-Lead ECG
- Sampling for analysis of HBV response markers
- PD biomarker sampling
- Liver fibrosis and inflammation assessment
- Perform Fibroscan VCTE
- PK sampling
- Review returned patient diary
- Collect used/unused study drug and assess compliance

6.3. Appropriateness of Measurements

Standard efficacy, PK, PD, statistical, clinical and laboratory procedures will be utilized in this study.

7. Efficacy Variables

The efficacy of EYP001a will be assessed via the following efficacy variables:

7.1. Definitions

Primary efficacy variables
The primary efficacy variables are:

- HBsAg decline ($\Delta \log_{10}$) from Day 1 to Week 16 of treatment period

Secondary efficacy variables
The secondary efficacy variables are as follows:

- HBsAg responder rate (decrease from baseline $\geq$ 1.0 on the $\log_{10}$ scale) at Week 16 of treatment and Weeks 20, 28 and 40 of follow up.
- HBsAg responder rate (decrease from baseline $\geq$ 0.5 on the log10 scale) at Weeks 12 and 16 of treatment and Weeks 20, 28 and 40 of follow up.
- HBsAg loss rate (% patients with HBsAg < LLOQ) at Weeks 16 of treatment period and Weeks 20, 28 and 40 of follow-up.
- HBsAg loss rate (proportion of results that are Target Not Detected versus Target Detected) at Weeks 16 of treatment period and Weeks 20, 28 and 40 of follow-up.
- relapse rate HBsAg (% patients who became negative [HBsAg < LLOQ], then increased with HBsAg > LLOQ) at Week 16 of treatment period and Weeks 20, 28 and 40 during follow-up period.
- Virologic failure rate (breakthrough)[15] of HBV DNA (% patients with a confirmed quantifiable HBV DNA increase of $\geq$ 1$\log_{10}$ HBV DNA copies/mL above LLOQ[16]) assessed at Week 16 of treatment period and Weeks 20, 28 and 40 during follow-up period
- HBV pgRNA decline ($\Delta \log_{10}$) from Day 1 to Weeks 4, 8, 12 and 16 of treatment period and Week 40 of maintenance period
- HBcrAg decline ($\Delta \log_{10}$) from Day 1 to Weeks 4, 8, 12 and 16 of treatment period and Week 40 of maintenance period
- HBeAg quantification for HBeAg pos patients and changes at Week 16 of treatment and Week 40 of follow-up
- Fibroscan VCTE change from screening to Weeks 16 and 40 or ET

Analysis of HBV response markers:

- Samples for analysis of quantitative HBsAg and quantitative HBV-DNA will be collected at pre-dose on all study visits during treatment period and Weeks 20, 28 and 40 of follow-up or at the ET visit.
- Samples for analysis of quantitative HBV pgRNA and HBcrAg will be collected at pre-dose on all study visits during treatment period and Week 40 of maintenance during follow-up period or at the ET visit.

[15] Breakthrough samples will be further assessed for resistance assessments, including both for the nucleos(t)ide analogue as well as for EYP001a (e.g., sequence analysis of FXR response elements in HBV genome). Details will be described in the Laboratory manual.
[16] HBV DNA results <LLOQ will be reported as either <LLOQ/Detected (i.e. LLOQ/TD) or <LLOQ/Target Not Detected (i.e. LLOQ/TND), both are considered LLOQ.

- Sample for analysis of HBeAg, anti-HBe and anti-HBs will be collected at screening or Day 1, then pre-dose at Week 16, Week 40 (EoS visit) or ET Visit.

7.2. Drug Concentration Measurements

The analysis of IP (EYP001a) in serum samples, as well as the analysis of biomarkers, will be performed at a Bioanalytical Laboratory using validated or qualified methods. The bioanalytical reports for the determinations will be included in the clinical study report (CSR).

8. Safety Assessments

The safety and tolerability of EYP001a will be assessed throughout the study.

Safety and tolerability will be determined by evaluating medical history (including evaluation of AEs and concomitant medication use) and assessments will include the monitoring of adverse events (AEs) and Serious Adverse Events (SAEs), and findings from physical examinations, vital signs, 12-lead ECGs, and clinical laboratory parameters.

Clinical laboratory assessments will include:

- **Haematology**: red blood cell count, white blood cell count and differential; quantitatively - leukocytes, erythrocytes, haemoglobin, haematocrit; partial automated differentiation - thrombocytes, lymphocytes, monocytes, eosinophils, basophils, neutrophils, and platelets.
  Coagulation: quantitatively - prothrombin time (reported in seconds and as INR), activated partial thromboplastin time, and fibrinogen
- **Serum chemistry**: ALT, albumin, ALP, amylase, AST, blood urea nitrogen, calcium, creatine kinase, creatinine phosphokinase (CPK), creatinine, Estimation of glomerular filtration rate, GGT, glucose, lactate dihydrogenase, potassium, sodium, total bilirubin (if >ULN, add conjugated bilirubin), total protein, uric acid.
- **Additional chemistry**: Alpha 2 macroglobulin, autotaxin, cardiac troponin I, ferritin, phosphate and TSH. These markers will be assessed at the end of study on existing chemistry plasma aliquots collected on Day 1, Day 112 and Day 280, only if relevant improvements in liver inflammation or fibrosis are apparent.
- **Lipid and metabolic profiles**: branched-chain amino acid concentrations as liver function test, haemoglobin A1c, homeostatic model assessment for insulin resistance (morning fasting glucose and insulin), lipoprotein insulin resistance index by nuclear magnetic resonance based on serum cholesterol, HDL-C, LDL-C, triglycerides, apolipoprotein B, small dense LDL, and lipoprotein(a).
  Lipoprotein particle size; small LDL particle number, small very low-density lipoprotein (VLDL) particle number, VLDL size
- **Urinalysis (dipstick qualitatively)**: bilirubin, nitrite, blood, pH, glucose, protein, haemoglobin, specific gravity, ketones, urobilinogen, and leukocytes);
- **Pregnancy** testing.

Laboratory parameters combined with AE, ECG and clinical assessments will be established at each study visit. They are considered appropriate measures for the following reasons:

- EYP001a Phase 1 studies showed pharmacological effects related to target FXR engagement as expected in the digestive system and lipid metabolism. From the available data no off-target effect has been evidenced. No dose-related or clinically significant changes in haematology or clinical chemistry laboratory values were evidenced so far.
- The study population will be adequately monitored through ECG, the safety lab, in particular liver enzymes, CPK, and cardiac troponin I, which aids in the risk stratification of patients with potentially unstable angina or non-ST segment elevation acute coronary syndromes with increased probability of ischemic events requiring urgent revascularization procedures.
- Patients with cirrhotic liver disease are excluded from this study.

8.1. Adverse Events and Adverse Event Reactions

Adverse Event (AE): Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction (ADR): In the pre-approval, clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered ADRs.

The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected ADR: An adverse reaction, the nature and severity of which is not consistent with the applicable product information (e.g. IB for an unapproved medicinal product).

8.1.1. Recording of Adverse Events

All AEs during the course of the trial will be reported in the appropriate section in the eCRF. The investigator will give his or her opinion as to the relationship of the adverse event to the investigational product. The Investigator should attempt to establish a diagnosis of the AE based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE verbatim term rather than individual signs/symptoms.

All AEs regardless of relationship to the study drug during the period starting from the time the participant signed the ICF through 7 days after the last study drug dose will be recorded in the eCRF.

8.1.2. Follow-up of Adverse Events

All events will be followed to resolution or stabilization or until 30 days after the patient completes the study. A final assessment of outcome will be made at that time.

8.1.3. Relationship to the Study Drug

The relationship of each AE to study drug is to be assessed by the Investigator according to categories in in Table 3.

Table 3 Criteria for Determination of AE Relationship to Study Drug

Unrelated	The event is definitely not associated with the study drug. Other conditions including concurrent illness, progression or expression of the disease state, or reaction to a concurrent medication explain the reported AE.
Unlikely	The temporal association, subject history and/or circumstances are such that the study drug is not likely to have had an association with the observed event. Other conditions including concurrent illness, progression or expression of the disease state, or reaction to a concurrent medication, appear to explain the reported AE.
Possibly Related	The event follows a reasonable temporal sequence from study drug but could have been produced by the subject's clinical state or other therapies administered to the subject.
Probably Related	The event follows a reasonable temporal sequence from the study drug abates upon discontinuation of the study drug and cannot be reasonably explained by known characteristics of the subject's clinical state
Definitely Related	The event follows a reasonable temporal sequence from the study drug abates upon discontinuation or cannot be explained by known characteristics of the subject's clinical state.

8.1.4. Intensity Assessment

The intensity of each AE is to be assessed by the Investigator according to the CTCAE, version 5.0; please refer Table 4.

Table 4 CTCAE Severity grade description

Grade 1	**Mild**	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	**Moderate**	Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living*
Grade 3	**Severe**	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living**. Note: An experience may be severe but may not be serious, (e.g. severe headache).

Grade 4	**Life-Threatening**	Life-threatening consequences; urgent intervention indicated.
Grade 5	**Fatal**	Death related to AE.
***Note**: A semi-colon indicates 'or' within the description of the grade.* **Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.* ***Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.*		

8.1.5. Abnormal Laboratory Values

All laboratory results must be filed in the participant's medical record and monitored. The Investigator or designee must review laboratory results in a timely manner demonstrated by signature/date and assignment of clinical significance assessment. Non-clinically-significant laboratory abnormalities, i.e., minor deviations from the normal range, are expected and it is likely that no medical intervention will be required. Abnormal laboratory results should not be considered AEs unless they are associated with a diagnosis.

Any grade laboratory abnormality that is considered to be clinically significant by the Investigator will be recorded on the AE eCRF. An abnormal test result will be considered as an AE if it is not associated with an already reported AE, diagnosis, or pre-existing condition; if there is a change in concomitant medication or intervention is needed, in direct response to a Grade 3 or 4 laboratory result and if investigator considers the laboratory result to be clinically significant

All such laboratory abnormalities should be repeated and reassessed for 'seriousness' by the Investigator or designee as soon as possible. If a result meets the regulatory definition of 'serious', it should be reported as an SAE following regulatory and protocol requirements. Repeat laboratory tests should be performed regularly to monitor patient status.

8.1.6. Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the trial. Such conditions should be recorded on the Medical History eCRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the trial. When recording such events on an SAE Report Form and/or AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

8.2. Serious Adverse Events

8.2.1. Definition

An SAE (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires in-patient hospitalization or prolongation of existing hospitalization

  NOTE: inpatient hospital admission refers to an overnight stay in a health care facility
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event described as an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization: Treatment within or admission to the following facilities will not meet the hospitalization criteria (however, if any other seriousness criteria as specified above are met, the event will be considered an SAE and reported immediately):

- Hospital visit of <24 hours duration (e.g. patient presented to emergency room, but not admitted to ward)
- Hospitalization of subjects to receive study treatment
- Subjects admitted to a hospice or nursing home for elective non-specific, general care or social reasons
- Hospitalization for prescheduled or elective procedures (such as for pain management, disease staging/restaging procedures or protocol specific procedures).

Suspected unexpected serious adverse reaction (SUSAR), is defined as any AE for which there is a reasonable possibility that the study drug caused the AE of which the specificity or severity is not consistent with those noted in the current protocol and/or IB and meets one of the above criteria for serious. This refers to any AE that has not been previously observed, (e.g. included in the IB), rather than from the perspective of such an event not being anticipated from the pharmacological properties of the product.

Unexpected Adverse Event is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unapproved IP).

8.2.2. Reporting of Serious Adverse Events

All SAEs regardless of relationship to the study drug during the period starting from the time the patient signed the ICF through 7 days after the last study drug dose, will be

recorded in the eCRF. Once the Investigator becomes aware of an SAE, he/she must report the SAE to the Sponsor safety representative within 24 hours of knowledge of the event.

Safety Contact Information:

Pharmalex:

Telephone: +34 976 204 400

Fax: +34 976 204 402

Email: EnyoSafety@pharmalex.com

A written SAE report must include a full description of the event including the below parameters (include any protocol specific requirements):

- Diagnosis or description of event
- Onset date
- Severity assessment
- Causal relationship to the investigational product
- Assessment of seriousness of the event
- Corrective treatment administered for the SAE
- Action taken related to study drug include the following: dose interruption, dose delay, dose reduction, or study drug discontinuation
- Outcome of event and end date

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to Sponsor Safety representative within 24 hours of receipt of follow-up information.

The Investigator must update the SAE form and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to the ENYO safety designee via fax or email.

The Investigator is responsible for reporting all SAEs to the appropriate Institutional Review Board/Institutional Ethics Committee (IRB/IEC) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB/IEC has been properly notified.

8.2.3. Follow-up of Serious Adverse Events

All events will be followed to resolution or stabilization or until 30 days after the patient completes the study. A final assessment of outcome will be made at that time.

8.3. Drug-Induced Liver Injury

8.3.1. Normal values at baseline

Drug-induced liver injury (DILI) monitoring in patients with **normal liver transaminases and bilirubin at baseline** should be performed throughout the study according to the procedures summarized below:

- If patients with normal baseline liver indices develop elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 upper limit of normal (ULN) or total bilirubin (TBL) >1.5 ULN values during the study, repeat testing should be performed within 48 hours.

- If there are persistent elevations (ALT or AST >2 ULN or TBL >1.5 ULN) upon repeat testing, close observation (testing and physical examination 2 to 3 times per week) should be implemented. An important purpose of the close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as 1 of the following: acute viral hepatitis, alcoholic and autoimmune hepatitis, hepatobiliary disorders, cardiovascular causes, or concomitant treatments. Discontinuation of study drug should be considered.

Study drug should be discontinued, and the patient should be followed until resolution of signs or symptoms, in the following situations:

- ALT or AST >8 ULN.

- ALT or AST >5 ULN for more than 2 weeks.

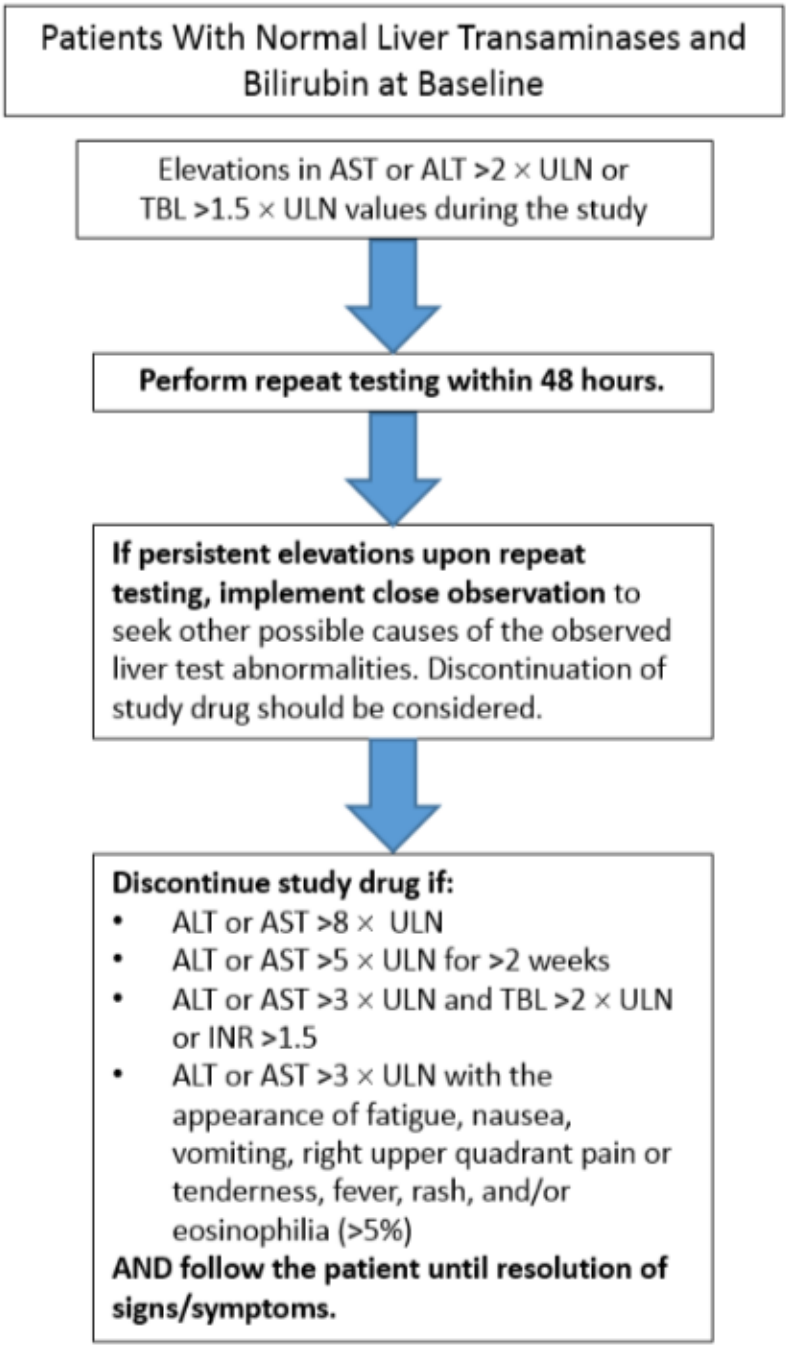
- ALT or AST >3 ULN and (TBL >2 ULN or international normalized ratio [INR] >1.5).

- ALT or AST >3 ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

For any patients who present with a constellation of syndromes indicative of liver disease as per the Investigator's overall assessment (i.e., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]), perform liver function tests to determine if liver disease is worsening.

Re-initiation of study drug may be considered after consultation with the Medical Monitor.

Figure 8 Normal liver transaminase and bilirubin at baseline



ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; TBL: total bilirubin; ULN: upper limit of normal.

8.3.2. Elevated values at baseline

Drug-induced liver injury (DILI) monitoring in patients with **elevations in liver transaminases or bilirubin at baseline** should be performed throughout the study according to the procedures summarized below:

- If patients with abnormal baseline liver indices develop elevations of AST or ALT >2 baseline average or TBL >1.5 baseline average values during the study, repeat testing should be performed within 48 hours.

- If there are persistent elevations (ALT or AST >2 baseline average or TBL>1.5 baseline average values) upon repeat testing, then close observation (testing and physical examination 2 to 3 times per week) should be implemented and discontinuation of study drug should be considered.

Study drug should be discontinued, and the patient should be followed until resolution of signs or symptoms, in the following situations:

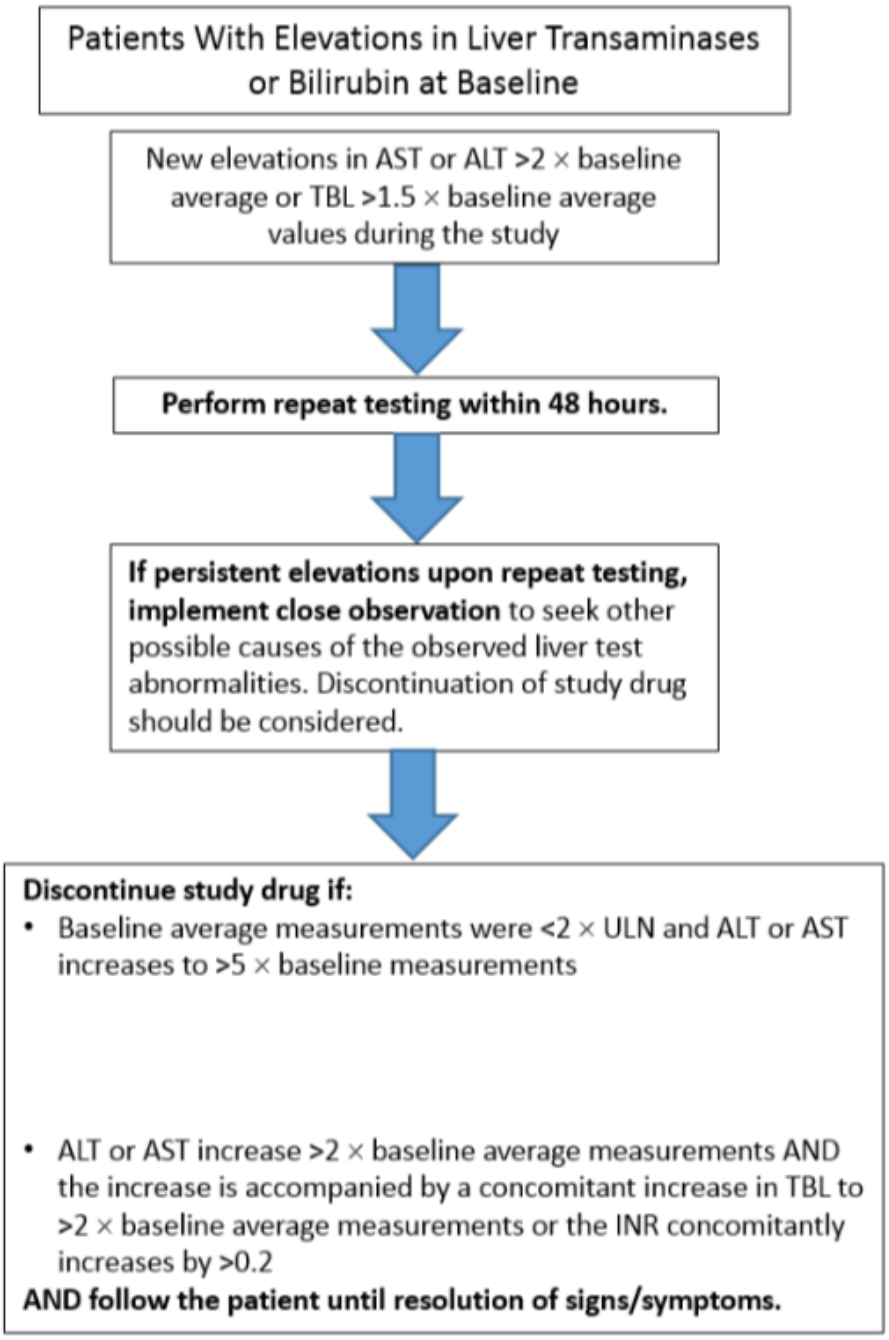
- Baseline average measurements were <2 × ULN and ALT or AST increases to >5 × baseline measurements.

- ALT or AST increase >2 × baseline average measurements AND the increase is accompanied by a concomitant increase in TBL to >2 × baseline average measurements or the INR concomitantly increases by >0.2.

For any patients who present with a constellation of syndromes indicative of liver disease as per the Investigator's overall assessment (i.e., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]), perform liver function tests to determine if liver disease is worsening.

Re-initiation of study drug may be considered after consultation with the Medical Monitor.

Figure 9 Elevated liver transaminase and bilirubin at baseline



ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; TBL: total bilirubin; ULN: upper limit of normal.

8.3.3. General Considerations

For all patients, close observation for suspected drug-induced liver injury includes the following:

- Repeating liver enzyme (ALT, AST, and alkaline phosphatase) and serum bilirubin tests 2 or 3 times weekly.
- The frequency of repeat testing can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g. INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

8.4. Pruritus Assessment

Pruritus will be assessed using a visual analog scale and a 5-D (degree, duration direction, disability, and distribution) itch scale (Refer Section 19.2, Appendix B) at each study visit after screening.

8.5. Pregnancy

Pregnancy testing must be performed in all WOCBP as specified in the Schedule of Assessments table, and the results of all pregnancy tests (positive or negative) are to be recorded on the eCRF. If the pregnancy test is positive, the patient will be immediately discontinued from study treatment.

In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g. missed or late menstrual period) at any time during the study. Male patients should contact the Investigator immediately if they suspect they may have fathered a child during the study. When possible, partner's pregnancies should be followed (to term) to determine the outcome.

If a patient becomes pregnant while enrolled in the trial, a Pregnancy Form should be completed and sent to the Sponsor Safety Representative expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Sponsor Safety Representative. Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed and will need to

be updated to reflect the outcome of the pregnancy. The Investigator must report any pregnancy (including the pregnancy of a male patient's partner), even if no AE has occurred, on a Pregnancy Report Form within 24 hours of the Investigator becoming aware of the pregnancy.

9. PK and PD Methods

9.1. Pharmacokinetics

EYP001a PK parameters to be determined include:

- Plasma concentration of EYP001a or any relevant active metabolites (as identified in an ongoing phase 1 study).

Fasting plasma samples will be collected at all study visits pre-dose in the morning on Day 1 and at Weeks 2, 4, 6, 8, 10, 12, 14 and 16 and in the morning at the ET Visit.

If by error patient has taken study medication on study Visit days prior to coming to the clinic the accurate time of last dosing and blood draw will be recorded.

Plasma will be stored at -80°C until analysis. Plasma samples will be analysed for EYP001a and any active metabolites using a validated liquid chromatography/mass spectrometry (LC-MS/MS) method.

9.2. Pharmacodynamics

EYP001a PD parameters to be determined include:

- Plasma C4 (7α-hydroxy-4-cholesten-3-one)
- FGF19
- Plasma primary and secondary BAs

Plasma C4, FGF19; BAs (total, primary, and secondary BAs (such as chenodeoxycholic acid [CDCA], deoxycholic acid [DCA], lithocholic acid, and/or others as appropriate) sampling will occur pre-dose paired with PK sampling at all visits during treatment period. A sample will also be collected at the Weeks 28 and 40 (EoS) or ET Visits.

Samples for BAs will be collected and stored centrally frozen for subsequent assessment after the EoS pending ongoing BA profiling related to EYP001a pharmacology.

10. Data Quality Assurance

The study may be audited by the Quality Assurance Department at CRO to assess adherence to the clinical study protocol and Quality System. During the conduct of the study, process related audits may be performed. An audit certificate will be provided in the appendices of the final CSR outlining any audits and other related activities performed.

The clinical research site will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study will be conducted according to the relevant regulatory requirements.

The eCRF entries will be verified with the source documentation.

The study monitor identifies any data to be recorded directly on the eCRF (i.e., no prior

written or electronic record of data), and to be considered to be source data.

Regulatory authorities, the IRB/IEC and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study. Review procedures will be followed by the CRO for all documents that are generated in relation with the study. Essential study activities of personnel will be checked by other CRO colleagues during execution, and each of them will sign off the documentation for execution or checking of the activities.

An explanation will be given for all missing, unused and spurious data in the relevant sections of the CSR.

11. Statistical Methods and Determination of Sample Size

11.1. Statistical Analysis Plan and General Statistical Methods

All data will be handled and processed according to the sponsor's representative (Novotech [Australia] Pty Ltd) SOPs, which are written based on the principles of GCP.

A Statistical Analysis Plan (SAP) containing the detailed planned statistical methods will be finalized prior to locking of the study database for the interim and final analysis and will form the basis for the programming of the displays and analyses of the final study data. All statistical calculations will be performed using SAS® (SAS Institute Inc., Cary, NC, USA) or similar software.

The statistical analyses will consist of both inferential and descriptive statistics. In general, the data will be presented by dose group. All collected and derived data will be included in the patient data listings.

All inferential analyses will be conducted at a one-sided 0.05 level of significance. Unless otherwise specified, all inferential testing will be one-sided in nature.

Continuous data, other than PK data, will be summarized by treatment group and time point using the number of observations, arithmetic mean, standard deviation, median, minimum and maximum. The coefficient of variance, geometric means and geometric coefficient of variance will also be presented for the concentration-related PK data. Categorical data will be summarized by the number and percentage of patients in each category. Unless specifically stated otherwise, the number of patients in the treatment group (for the specific analysis set) will be used as the denominator for all percentage calculations.

Baseline is defined as the last available non-missing value collected prior to the first administration of IP.

Change from baseline values will be calculated as the difference between the result at a specific time point, and the baseline value for the specific endpoint.

Missing, unused, or spurious data will be handling in the following manner:

- There will be no imputations or substitution made for missing safety data points.
- For the PK analyses, imputations will be made for missing data points.

11.2. Definition of Analysis Sets

The following analysis sets are defined for this study.

11.2.1. Intention-To-Treat (ITT) Set

The ITT set will include all randomized patients, irrespective of whether a patient receives any study drug. This set will be based on randomized treatment. The ITT set will be used for the baseline, demographic summaries and efficacy summaries.

11.2.2. Modified Intention-To-Treat (mITT) Set

The mITT set will include all randomized patients, who received any amount of study drug, have a measurable baseline HBsAg assessment and a 16-week post baseline efficacy assessment. This set will be based on randomized treatment. The mITT set will be used for efficacy analyses.

11.2.3. Per Protocol (PP) Set

The PP set is defined as the set of patients who meet the mITT set requirements and were not associated with a major protocol violation. This set will be identified before the start of the final analysis and will be used to support the analysis conducted for the primary efficacy endpoint. Patients will be analysed based on the actual treatment received.

11.2.4. Safety Analysis Set (SAS)

The Safety analyses set will be defined as all patients who receive at least one confirmed dose of the study drug and will be based on actual treatment received. The SAS will be used for all safety and tolerability analyses.

11.2.5. Pharmacokinetic Set

The PK set will consist of all patients who received any study drug administration and that have sufficient and interpretable EYP001a concentrations data. Patients with missing sample concentrations will be included in the PK set provided that the PK parameters can be adequately characterized based upon the remaining data. Protocol violations and individual patient profiles will be assessed on a case-by-case basis to determine if the patient, or specific concentration values, should be excluded from the PK set.

11.2.6. Pharmacodynamic Set

All patients included in the SAS with a measurable baseline PD assessment and at least one measurable post baseline PD assessment, will be included in the PD set.

11.3. Statistical Methods

11.3.1. Patient Disposition

Patient disposition will be summarised using counts and percentages. The number and percentage of enrolled patients, patients discontinued from the study, the primary reason

for discontinuation as well as the number and percentage of patients included in each analysis set will be summarised by treatment group.

11.3.2. Demographic and Baseline Characteristics

Demographic and baseline information including treatment history, HBV genotype, age, gender, BMI, weight, and height will be summarised by treatment group using the ITT set.

11.3.3. Efficacy Analyses

All Efficacy analyses will be based on the ITT set unless otherwise specified. All efficacy data will be summarised by study visit and treatment group.

11.3.3.1. Primary Efficacy

The primary endpoint, HBsAg decline ($\Delta \log_{10}$) from Day 1 to Week 16 of treatment will be analysed using a general linear model for repeated measures, using the stratification factors as independent variables in the model (A Genotype [yes, no] and HBeAg pos [yes, no]). The primary analysis will be based on the ITT set. The analysis will be repeated based on the mITT and PP sets, as sensitivity analyses.

The analysis will be based on a one-sided test at a 5% level of significance.

Note that the sample size calculations are based on a t-test, as power calculations based on a repeated measures model require information about within-patient correlation structures, which is not available. However, using a repeated measures model, better power is expected compared to a t-test. A t-test, imputing missing data at 16 weeks as zero difference versus baseline, will be carried out as a sensitivity analysis.

11.3.3.2. Secondary Efficacy

HBsAg responder rate (decrease from baseline ≥ 1.0 on the $\log_{10}$ scale and decrease from baseline ≥ 0.5 on the $\log_{10}$ scale) and HBsAg loss rate (proportion of HBsAg<LLOQ) at Week 16 of treatment and Week 20, Week 28 and Week 40 of follow-up will be analysed as key secondary endpoints at 16 weeks, and 40 weeks. Proportion of patients of Target not detected will be analysed as exploratory endpoint. HBsAg responder rate (decrease from baseline ≥ 0.5 on the $\log_{10}$ scale) will also be analysed at Week 12 of treatment. At 16 and 40 weeks, these endpoints will be analysed taking into account multiplicity by a combination of a hierarchical fixed test procedure and a Hochberg procedure (See Section 11.4.2), using a this Pearson Chi-square test. At other timepoints, analyses for these two endpoints will be descriptive.

Relapse rate HBsAg (% patients who became negative [HBsAg< LLOQ], then increased with HBsAg > LLOQ) at Week 16 of treatment period and Weeks 20, 28 and 40 during the follow-up period will be summarized by frequency counts and percentages.

Virologic failure rate (breakthrough) [17] of HBV DNA (% patients with a confirmed quantifiable HBV DNA increase of ≥ 1log10 HBV DNA copies/mL above LLOQ[18]) assessed at Weeks 16 of treatment, 20, 28 and 40 during follow up period will be summarized by frequency counts and percentages.

HBV-pgRNA decline ($\Delta \log_{10}$) and HBcrAg decline ($\Delta \log_{10}$) from Day 1 to Weeks 4, 8, 12 and 16 of the treatment period and Week 40 of maintenance period, HBeAg quantification for HBeAg positive patients and changes at Week 16 of treatment and Week 40 of follow-up and Fibroscan VCTE change from screening value to the Weeks 16 and 40 or ET visit will be summarized through descriptive statistics.

11.3.4. PK Analyses

The PK analysis will be based on the PK set.

Individual plasma concentrations and trough levels of EYP001a and any active metabolites will be listed for each patient and summarised by nominal sampling time point and treatment group with descriptive statistics. All concentrations below the limit of quantification will be labelled as such in the concentration data listings. Listings of individual patient plasma concentrations and actual blood sampling times and graphs of concentration versus time will be prepared. Plasma concentrations will be summarized using descriptive statistics. The actual PK sampling timepoints will be used for the PK analysis. Appropriate validated PK software (eg, Phoenix WinNonlin v6.3) will be used. A non-compartmental analysis will not be performed.

EYP001a PK parameters to be determined include:

- Plasma concentration of EYP001a or any relevant active metabolites (as identified in an ongoing phase 1 study).

PK parameters will be summarized by treatment group using descriptive statistics. Statistical analysis will be performed on the pharmacokinetic parameters using validated statistical software.

11.3.5. PD Analyses

The PD analysis will be based on the PD set.

PD marker parameters will be summarized using descriptive statistics and will also be presented graphically per treatment group.

The following PD markers will be assessed:

[17] Breakthrough samples will be further assessed for resistance assessments, including both for the nucleos(t)ide analogue as well as for EYP001a (e.g., sequence analysis of FXR response elements in HBV genome). Details will be described in the Laboratory manual.
[18] HBV DNA results <LLOQ will be reported as either <LLOQ/Detected (i.e. LLOQ/TD) or <LLOQ/Target Not Detected (i.e. LLOQ/TND), both are considered LLOQ.

- Plasma C4 (7α-hydroxy-4-cholesten-3-one)
- FGF19
- Plasma primary and secondary BAs

11.3.6. Safety Analyses

Listings and summaries for all safety data will be presented using the Safety Set. Safety endpoints will be summarised by treatment group.

The following data presentations and summaries will be performed. No formal inferential statistics will be performed on safety assessments.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). All AE summaries will be restricted to TEAEs only and will be summarised by treatment group. Summary tables will include the number of patients (%) experiencing an event and the number of events. Patients will be counted only once at each system organ class and preferred term (PT) level of summary.

The TEAE summaries may include but not be limited to:

- TEAE summary by SOC and PT
- TEAE summary of serious events by SOC and PT
- TEAE summary by severity by SOC and PT
- TEAE summary by causality by SOC and PT

All AEs will be listed and will include verbatim term, preferred term (PT), system organ class, treatment, severity, causality, seriousness, and action taken with regards to the study drug. Separate listings will be created for SAEs and events leading to treatment discontinuation.

Clinical laboratory results will be summarised by treatment group and will include changes from baseline and counts of number of values out of normal range at each scheduled time point. Shift tables (categorical parameters) may also be used, as appropriate. Individual vital signs assessments will be listed for each patient. Summaries of vital signs by treatment group will include changes from baseline for each parameter at each scheduled time point.

Individual ECG results will be listed for each patient. Summaries of ECGs by treatment group will include changes from baseline for each parameter at each scheduled time point.

Physical examination findings will be listed for each patient and any changes described in the text of the final report.

Exposure to study drug and concomitant medications will be listed by patient and coded using the most current WHO drug dictionary available at the Sponsor. The number and percentage of patients who used prior and/or concomitant medications will be summarised by Anatomic Therapeutic Chemical (ATC) classification levels and treatment group. At each level of ATC classification, patients will be counted once. Concomitant medications

are medications defined as any medications taken after first study drug administration. Prior medications are medications stopped prior to first study drug administration.

11.4. Determination of Sample Size

11.4.1. Sample size calculations for the primary endpoint

The primary endpoint is HBsAg reduction. Improvement of 1.0 on a $\log_{10}$ scale at 16 weeks is considered to be clinically significant. The expected accrual rate is 2 to 4 patients per week but does not affect sample calculation. Note that the accrual rate will not affect sample size calculations. All assumptions are given in Table 5.

The primary analysis will be performed using a general linear model for repeated measures, using the stratification factors as independent variables in the model (A Genotype [yes, no] and HBeAg pos [yes, no]). The primary analysis will be done on the ITT population. The mITT and PP population, will be analysed as a sensitivity analysis.

Table 5 Assumptions for primary endpoint

Primary Endpoint	HBsAg reduction vs baseline on a $\log_{10}$ scale ("Chg")
Null hypothesis	H_0: $Chg_{exp} - Chg_{ctrl} = 0$
Alternative hypothesis	H_a: $Chg_{exp} - Chg_{ctrl} = -1.0$
SD of change vs baseline in experimental arm	1.08
SD of change vs baseline in control arm	1.08
Drop-out	10% over total study duration
Randomization ratio	3:1 for experimental:control (i.e. nE/nC=3)
Power	80%
Type I error rate (1-sided)	0.05

Chg: Change vs baseline; Ctrl: Control arm; Exp: Experimental arm; H_0: Null Hypothesis; H_a: Alternative Hypothesis; SD: Standard Deviation

As the ITT population will be analysed, patients who have dropped out, will be assumed to have a zero-difference vs baseline for conservativeness. To take this into account, the assumed effect of -1.0 on a $\log_{10}$ scale, will be multiplied by 0.9, resulting in an assumed effect of -0.9. Using these assumptions, based on a test, 49 patients will need to be enrolled. Calculations are based on a t-test.

Note that the final analysis will be done, using a general linear model for repeated measures. Using this type of model, a better power is expected, thus sample size calculations can be considered conservative.

11.4.2. Testing strategy and power for key secondary endpoints

Multiplicity is taken into account by using a combination of a hierarchical fixed test procedure and a Hochberg procedure.

Only in case the primary endpoint is significant at 16 weeks, the key secondary endpoint "HBsAg loss rate" will be tested at the same one-sided α level of 0.05, using a Hochberg procedure. This procedure goes as follows: the p-values will be ordered from small to large

$p_{(1)} \leq p_{(2)}$. largest p-value $p_{(2)}$ will be compared to α=0.05. If significant, then both hypotheses will be rejected. If not, the smallest p-value is compared to $\alpha/2$=0.025. If significant, then only the hypothesis corresponding to the smallest p-value is rejected.

At 40 weeks, the key secondary endpoints HBsAg responder rate and HBsAg loss rate will be tested a one-sided α level of 0.05, using a Hochberg procedure.

To calculate the power to detect a difference in HBsAg loss rate, we assumed a proportion of 0.5% in the placebo arm, and of 10% in the experimental arm. A trial including 49 patients results in a power of about 55% for this endpoint (using an un-pooled estimate of the variance), using a one-sided α of 0.05.

11.5. Interim Analyses

An unscheduled interim analysis of all available unblinded preliminary safety study data will be conducted when any stopping rules (Section 4.6) are met in two or more subjects.

Two interim analysis are scheduled:

1. First interim analysis on all available unblinded preliminary safety study data:
   Safety assessment when 50% (n=25) patients reach week 8 resulting in a decision on continuation of the study based on safety (Go/No go decision); enrolment would remain ongoing during this review.
2. Second interim analysis on all available unblinded preliminary virology, safety, PK and PD study data:
   Safety and futility when 50% patients (n=25) reached week 12, resulting in a decision on continuation of the study (Go/No go decision) based on safety and evidence of a benefit of EYP001a (HBsAg, other secondary viral markers); enrolment is ongoing during this review.

The interim analyses will be performed on all available primary and secondary endpoints according to the SAP and DSMC charter, which describes the overall guidelines, composition, roles, and responsibilities of the independent DSMC for the EYP001-201 study, including the selection of DSMC members, timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings, data analysis recommendations, and DSMC relationships with other parties participating in the conduct of this study.

The futility assessment will be performed to determine if EYP001 has no benefit at a point when 50% of subjects have reached 12 weeks of dosing. The futility assessment will be performed by the DSMC according to the following rules:

- A treatment effect of -1.0 on a log10 scale of HBsAg for the primary endpoint at 16 weeks, and a common standard deviation of 1.08 was assumed and the treatment effect would be -0.5 after 12 weeks of treatment, with common standard deviation of 0.7 Using a one-sided alpha of 0.05 and 80% power, a group sequential design, incorporating a futility and efficacy O'Brien-Fleming analysis when 50% of patients have reached 12 weeks of treatment, needs inclusion of 49 patients.

- Table 6 gives the probability of stopping early under the null and alternative hypothesis, at the time of the interim analysis.
  The probability of stopping correctly for futility is 40%. The probability of stopping wrongly for futility is only 3.5%.

Table 6 Probability of different decisions at the interim analysis

Under H_0		Under H_a	
Efficacy	**Futility**	**Efficacy**	**Futility**
0.001	0.4	0.073	0.035

H_0: Null Hypothesis; H_a: Alternative Hypothesis

- The efficacy boundary is crossed when the 12-week p-value is less than 0.001, or the difference is less than -0.971 on a log scale. The futility boundary is crossed when the 12-week p-value is higher than 0.603, or the difference is more than 0.085 on a log scale.

The stopping of the study for futility will be considered by the DSMC by applying these rules. The study will not stop for efficacy at Week 12 interim analyses, even if efficacy boundary is crossed. The criteria are not binding and DSMC can overrule if other interim results show beneficial results.

Data will be summarized and presented by treatment group and time point in summary tables. Descriptive statistics including number of patients (N), means, standard deviations, medians, and minimum and maximum values will be presented for continuous variables. Counts and percentages will be presented for categorical variables. In addition, by- patient listing for all safety and efficacy data will be presented.

Note that all interim analyses will be descriptive. The study design does not include any formal statistical guidelines for use at interim analysis.

11.6. Other Analysis

ENYO is developing a mathematical computational HBV disease model. The results from EYP001-201 will serve as clinical data for the calibration of in silico HBV patients simulating the effect of combinational treatments that will eventually support designing later trials. With its different sub-models (HBV replication and excretion, BAs metabolism, cholesterol metabolism, immune system, fibrosis, blood virus related changes, and EYP001a, ETV and PEG-IFNα2a drug models) the disease model of chronic HBV infection will be used to predict quantitative efficacy on relevant endpoints (DNA HBV in blood, HBsAg) in a representative virtual population. The computational model is a system of ordinary differential equations (ODEs) which integrates more than 300 biological variables and more than 1000 parameters. It will be used to explore the effect of combinations of different treatments regimens including EYP001a, ETV and PEG-IFNα2a. Iterations of the validated model will serve for the exploration of alternative arms in the EYP001-203 study (conducted in parallel EYP001-201, with treatment naive or virologically non-suppressed patients treated with EYP001a combined with NA and peg-IFN), by simulating different doses and treatment regimens. Disease model simulations will support future explorations of development strategies, with the upcoming EYP001a pivotal study designs.

12. Protocol Amendments, other Changes in Study Conduct

12.1. Protocol Amendments

Any additional amendments proposed by the Sponsor will be submitted to the Investigator and IRB/IEC for review and approval prior to implementation by the Investigator. In addition, the Investigator must provide the signed protocol amendment page to the Sponsor.

If the protocol is amended to eliminate or reduce the risk to participants, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

12.2. Other Changes in Study Conduct

Protocol waivers will not be allowed.

Protocol deviations brought to the attention of the Sponsor after their occurrence will only be recognized and assessed for ethical, medical, scientific, and regulatory implications and for impact on the participant's participation in the study and will be documented. Such deviations cannot be waived.

Protocol violations (which are deviations that have a major impact on the participant's rights, safety, or well-being or the integrity and authenticity of the study data) can never be waived.

13. Ethical Considerations

13.1. Independent Ethics Committee/Institutional Review Board

It is the responsibility of the Investigator to obtain the approval of the IRB/IEC before the start of the study. A copy of the approval letter will be supplied to the Sponsor, along with a roster of IRB/IEC members. During the course of the study, the Investigator or designee will provide timely and accurate reports to the IRB/IEC on the progress of the study at appropriate intervals [not to exceed 1 year] and at the completion of the study. Investigator or designee will notify the IRB/IEC of SAEs or other important safety findings. The study protocol, ICF, information sheet advertisements (if any), and amendments (if any) will be approved by the IRB at each study centre in conformance Code of Federal Regulations (CFR), Title 21, Part 56.

13.2. Ethical Conduct of the Study

This study will be performed in accordance with the protocol, current ethical principles that have their origins in the Declaration of Helsinki, the ICH Harmonized Tripartite Guideline for GCP, and all applicable local regulatory requirements.

The procedures set out in this study protocol are also designed to ensure that the Sponsor and Investigator abide by the principles of the GCP guidelines of the ICH and in keeping with local legal requirements.

13.3. Participant Information and Consent

Before the start of any study-related procedures are undertaken, the Investigator or designee must obtain written, informed consent from each participant in accordance with US federal regulations (21 CFR §50) and the ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance". Informed consent will be obtained by discussing with the participant the purpose of the study, the risks and benefits, the study procedures, and any other information relevant to the participant.

The Investigator or designee must explain to the participant that for purposes of evaluating the study results, that participant's private health information obtained during the study may be shared with the Sponsor, regulatory agencies, and IRBs/IECs, before enrolling that participant into the study. The participant or his/her legal representative will document his/her informed consent by signing the current version of the written, IRB/IEC approved ICF. The person who conducted the informed consent discussion with the participant and/or participant's legal representative (if applicable) must also sign the ICF. The participant is given a fully executed copy of the ICF bearing all appropriate signatures, and the original must be maintained in the clinical master files at the site.

The Investigator, or designee, is responsible for the content of the ICF, but the original and any updated versions must be approved by the Sponsor prior to submission to the IRB/IEC. The ICF should also include any additional information required by local laws relating to institutional review. All active participants participating on the protocol must be re-consented each time the ICF is updated and re-approved by the IRB/IEC.

13.4. Compensation Arrangements

If the participant is physically injured as a direct result of this study or study procedure improperly performed under the plan for this study and it is not due to a pre-existing medical condition or underlying disease, the Sponsor will reimburse the participant for the reasonable medical expenses for the treatment of that injury which are not covered by another payor, their own insurance or health care program. No other compensation is available from the Sponsor if any injury occurs.

13.5. Protected Health Information

Data collected during this study may be used to support the development, registration or marketing of this investigational product. All data collected during the study will be controlled by the Sponsor (or designee) and the Sponsor will abide by all relevant data protection laws. After a participant has consented to take part in the study, their medical records and the data collected during the study will be reviewed by representatives of the Sponsor and/or the company organizing the research on the Sponsor's behalf to confirm that the data collected are accurate and for the purpose of analysing the results. These records and data may additionally be reviewed by auditors or by regulatory authorities. The participant's name, however, will not be disclosed outside the hospital. They will be known by a unique participant number. The results of this study may be used in other countries throughout the world that have ensured an adequate level of protection for personal data.

14. Data Handling and Record Keeping

Data collection will involve the use of the Sponsor Electronic Data Capture (EDC) system, to which only authorized personnel will have access.

In addition to periodic monitoring occurring within the system by Sponsor personnel or representative, programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study centre and answered electronically by that study centre. The identifying information (assigned username, date, and time) for both the originator of the query (if created during the monitoring process) and the originator of the data change (if applicable), as well as the Investigator's approval of all changes performed on his or her participants' data, will be collected.

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records. Data will be stored and evaluated in such a way as to guarantee participant confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g. patient diaries, copies of eCRFs, regulatory documents, etc.) will be retained at the study centre, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by the Sponsor, its authorized representatives, and FDA officials.

The PI must maintain the documentation relating to this study. If the Sponsor, the FDA, or another regulatory authority wishes to review any documentation relating to the study, the PI must permit access to such records.

The PI must retain a copy of all records that support the CRFs for this study (e.g. ICFs, clinical laboratory reports, source documents, investigational product dispensing records) for a period of at least 15 years after study completion unless local regulations or study centre policies require a longer retention period or otherwise notified in writing by the Sponsor.

If the PI retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the study centre or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian before such transfer is made.

No study records shall be destroyed without notifying and giving the Sponsor the opportunity to arrange long-term storage for such study records or to authorize in writing the destruction of records after the required retention period.

15. Financing & Insurance

In the event of injury resulting from participation in this study, any medical treatment deemed necessary will be provided to study participants to assist in recovery from the injury.

Study participants will not be charged for this care beyond that covered by the study

participant's health insurance. This agreement to provide free medical treatment does not include treatment for illnesses experienced during the study if the illness is not the direct result of study participation. No compensation will be provided for study-related injury other than free medical treatment.

16. Financial Disclosure

The Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study; any significant payments of other sorts from the Sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any proprietary interest in the study; any significant equity interest in the Sponsor, as defined in the US CFR (21 CFR 54 2[b]).

In consideration of participation in the study, the Sponsor will pay the Investigator, study site or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

17. Reporting & Publication

17.1. Clinical Study Report

The data and information collected during this study will be reported in a study report prepared by the CRO. The final report may be used for the further development of the investigational product as considered necessary by the Sponsor.

17.2. Confidentiality and Intellectual Property Rights of Study Data

Any confidential information relating to the investigational product or the study, including any data and results from the study will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to the Sponsor.

17.3. Publication Policy

The Sponsor encourages publication of results derived from the clinical research. Publications include a paper in a peer reviewed medical journal, abstract submission with a poster or oral presentation at a scientific meeting or making results public by some other means. The Sponsor will retain the right to review all material prior to presentation or submission for publication and neither institution(s) nor Study Co-chairs/PI(s) are permitted to publish/present the results of the study, in part or in their entirety, without the written authorization of the Sponsor. The review is aimed at protecting the Sponsor's pre-existing proprietary information and commercial interests.

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19. Appendices

19.1. Appendix A - Schedule of Assessment*

Assessment	Screening Visit[1]	Treatment Period (Week 1 to Week 16)									Follow-up Period (Week 17 to Week 40)			ET Visit[2]
	Week -12 to -1 (Day -90 to Day -1)	Treatment Visit 1 Week 1 (Day 1)	Treatment Visit 2 Week 2 (Day 14 ± 3 days)	Treatment Visit 3 Week 4 (Day 28 ± 3 days)	Treatment Visit 4 Week 6 (Day 42 ± 3 days)	Treatment Visit 5 Week 8 (Day 56 ± 3 days)	Treatment Visit 6 Week 10 (Day 70 ± 3 days)	Treatment Visit 7 Week 12 (Day 84 ± 3 days)	Treatment Visit 8 Week 14 (Day 98 ± 3 days)	Treatment Visit 9 Week 16 (Day 112 ± 3 days)	Follow-up Visit 1 Week 20 (Day 140 ± 7 days)	Follow-up Visit 2 Week 28 (Day 196 ± 7 days)	Follow-up Visit 3 Week 40 (Day 280 ± 7 days) (EoS)	
Informed Consent	X													
Eligibility criteria	X	X[3]												
Demographics	X													
Medical History[4]	X													
Prior and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drugs of abuse screen[5]	X	X												
Height[6] and body weight	X	X		X		X		X		X	X	X	X	X
BMI Calculation	X	X		X		X		X		X	X	X	X	X

Assessment	Screening Visit[1]	Treatment Period (Week 1 to Week 16)									Follow-up Period (Week 17 to Week 40)			ET Visit[2]
	Week -12 to -1 (Day -90 to Day -1)	Treatment Visit 1 Week 1 (Day 1)	Treatment Visit 2 Week 2 (Day 14 ± 3 days)	Treatment Visit 3 Week 4 (Day 28 ± 3 days)	Treatment Visit 4 Week 6 (Day 42 ± 3 days)	Treatment Visit 5 Week 8 (Day 56 ± 3 days)	Treatment Visit 6 Week 10 (Day 70 ± 3 days)	Treatment Visit 7 Week 12 (Day 84 ± 3 days)	Treatment Visit 8 Week 14 (Day 98 ± 3 days)	Treatment Visit 9 Week 16 (Day 112 ± 3 days)	Follow-up Visit 1 Week 20 (Day 140 ± 7 days)	Follow-up Visit 2 Week 28 (Day 196 ± 7 days)	Follow-up Visit 3 Week 40 (Day 280 ± 7 days) (EoS)	
Physical Examination[7]	X	X		X		X		X		X	X	X	X	X
Vital Signs[8,9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AUDIT-C[10]	X	X												
Randomization[11]		X												
Pruritus assessment		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X
Viral serology[12]	X													
Chemistry	X[13]	X	X[23]	X	X[23]	X	X[23]	X	X[23]	X	X	X	X	X
Haematology, coagulation, lipid and metabolic profile	X	X	X[23]	X	X[23]	X	X[23]	X	X[23]	X	X	X	X	X
Pregnancy test (for WOCBP only)[14]	X	X		X		X		X		X				X

Assessment	**Screening Visit[1]**	**Treatment Period (Week 1 to Week 16)**									**Follow-up Period (Week 17 to Week 40)**			**ET Visit[2]**
	Week -12 to -1 (Day -90 to Day -1)	**Treatment Visit 1 Week 1 (Day 1)**	**Treatment Visit 2 Week 2 (Day 14 ± 3 days)**	**Treatment Visit 3 Week 4 (Day 28 ± 3 days)**	**Treatment Visit 4 Week 6 (Day 42 ± 3 days)**	**Treatment Visit 5 Week 8 (Day 56 ± 3 days)**	**Treatment Visit 6 Week 10 (Day 70 ± 3 days)**	**Treatment Visit 7 Week 12 (Day 84 ± 3 days)**	**Treatment Visit 8 Week 14 (Day 98 ± 3 days)**	**Treatment Visit 9 Week 16 (Day 112 ± 3 days)**	**Follow-up Visit 1 Week 20 (Day 140 ± 7 days)**	**Follow-up Visit 2 Week 28 (Day 196 ± 7 days)**	**Follow-up Visit 3 Week 40 (Day 280 ± 7 days) (EoS)**	
TSH intermittent monitoring	X			X		X		X		X				
Dipstick Urinalysis all male and females[15]	X	X		X		X		X		X				X
12-Lead ECG[9]	X	X		X		X		X		X				X
HBV response markers[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD biomarker sampling[17]		X	X	X	X	X	X	X	X	X	X	X	X	X
Liver fibrosis and inflammation assessment[18]		X		X		X		X		X	X	X	X	X
Fibroscan VCTE	X									X			X	X
Liver imaging	X[19]												X[19]	
PK Sampling		X	X	X	X	X	X	X	X	X				X
Dispense patient diary and review[20]		X	X	X	X	X	X	X	X	X	X	X	X	

Assessment	Screening Visit[1]	Treatment Period (Week 1 to Week 16)									Follow-up Period (Week 17 to Week 40)			ET Visit[2]
	Week -12 to -1 (Day -90 to Day -1)	Treatment Visit 1 Week 1 (Day 1)	Treatment Visit 2 Week 2 (Day 14 ± 3 days)	Treatment Visit 3 Week 4 (Day 28 ± 3 days)	Treatment Visit 4 Week 6 (Day 42 ± 3 days)	Treatment Visit 5 Week 8 (Day 56 ± 3 days)	Treatment Visit 6 Week 10 (Day 70 ± 3 days)	Treatment Visit 7 Week 12 (Day 84 ± 3 days)	Treatment Visit 8 Week 14 (Day 98 ± 3 days)	Treatment Visit 9 Week 16 (Day 112 ± 3 days)	Follow-up Visit 1 Week 20 (Day 140 ± 7 days)	Follow-up Visit 2 Week 28 (Day 196 ± 7 days)	Follow-up Visit 3 Week 40 (Day 280 ± 7 days) (EoS)	
Check amount of study medication and dispense accordingly EYP001a/placebo and/or NA[21]		X		X		X		X		X	X	X		
Collect used/unused study drug and assess compliance[22]			X	X	X	X	X	X	X	X	X	X	X	X

AUDIT-C: Alcohol Use Disorders Identification Test-Concise; BMI: Body Mass Index; ECG: Electrocardiogram; EoS: End of Study; ET: Early Termination; HIV: Human Immunodeficiency Virus; VCTE: Vibration Controlled Transient Elastography; WOCBP: Women of Childbearing Potential

* 3-day window is acceptable for treatment visits and a 7 days window for Follow-Up visits.

[1] Patient who is first designated as a screen failure prior to being randomized may be rescreened upon Sponsor or designee approval.

[2] **Patients who discontinue early** from the study for any reason, will be requested to return to the clinic for a follow-up Visit approximately one week after administration of their final last dose of any study medication, regardless of how many days the patient was in the study.

[3] Confirm eligibility prior to randomization

[4] Genotype information will be collected from medical history. Genotyping will be requested via central lab only if information is not available through medical history.

[5] Drugs of abuse test at Screening and Day 1 pre-dose only for drugs such as amphetamines, methamphetamine, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tricyclic antidepressants and THC (cannabis).

[6] Height to be recorded only on Screening visit

[7] A complete physical examination (including general appearance; eyes, ears, nose, and throat; head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatological; neurological systems; mental status; and extremities) will be performed at screening. Brief, symptom-directed physical examinations will be performed on all other study visits.
[8] Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature and will be performed with the patient in the sitting position after 5 minutes of rest and before any blood draws. Site staff will use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centred over the brachial artery. Site staff will record the arm used for the measurement and use the same arm throughout the study. Site staff will measure and record the blood pressure. Blood pressure will be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device..
[9] The following schedule will be utilized to measure vital signs (Heart Rate, Blood Pressure, Temperature): Blood pressure and pulse:
screening, pre-dose on Week 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 28 and 40 (EoS) or ET. Blood pressure will be taken in a sitting position after 5 minutes rest. ECG will be performed prior to vital signs assessments.
[10] Patients with AUDIT-C scores 3 points at screening will receive the full AUDIT and will be excluded if they score 8 points on the full AUDIT. Patients with AUDIT C scores <3 points will not receive the full AUDIT.
[11] Can occur after eligibility check on Day -3 at the earliest and prior to dosing on Day 1 at the latest
[12] Anti-HIV, anti-HCV, anti-HDV, quantitative HBV-DNA, quantitative HBsAg, anti-HBs, anti-HBe on screening visit. For positive HCV antibody-test results only, a PCR-based quantitative HCV viral load assessment will also be performed.
[13] Alpha Foeto Protein (AFP) at screening normal
[14] A serum hCG test will be performed at Screening and ET Visits in WOCBP only. Urine hCG tests will be performed at all other visits. If a urine hCG test is positive, a serum hCG test will be performed.
[15] Urinalysis will be evaluated from a fresh urine sample by dipstick. Further analysis for urine sediment or urine microscopy will be performed when there are any abnormalities on any of the following 3 dipstick results: leukocyte esterase, blood, or nitrite, and if judged clinically significant by the Investigator.
[16] HBV DNA, HBsAg, HBV RNA, HBcrAg, HBeAg and anti-HBe.
Analysis of HBV response markers:

- Samples for analysis of quantitative HBsAg and quantitative HBV-DNA will be collected at pre-dose on all study visits during treatment period and Weeks 20, 28 and 40 of follow-up or at the ET visit.
- Samples for analysis of quantitative HBV pgRNA and HBcrAg will be collected at pre-dose on all study visits during treatment period and at week 40 of follow-up or at the ET visit.
- Sample for analysis of HBeAg, anti-HBe and anti-HBs will be collected at screening or Day 1, then pre-dose at Week 16, Week 40 (EoS visit) or ET Visit.

• A subject who experiences a breakthrough (defined by quantifiable HBV DNA increase of ≥ 1log10 HBV DNA copies/mL above LLOQ) should return to the study site for a confirmatory measurement within two weeks. If virologic breakthrough is confirmed stopping rule (Section 4.6. applies)
[17] PD biomarker samples:
Plasma C4, FGF19; BAs (total, primary, and secondary BAs [such as CDCA, DCA, LCA, and/or others as appropriate {Samples for BAs will be collected and stored centrally frozen for subsequent assessment after the EoS pending ongoing BA profiling related to EYP001a pharmacology}]) sampling will occur pre-dose paired with PK sampling at all visits during treatment period. A sample will also be collected at the EoS or ET Visits.

[18] Liver fibrosis and inflammation parameters include ALT, AST, AST/ALT ratio, high sensitivity C-reactive protein, interleukin 6, tumour necrosis factor alpha, procollagen type III N terminal peptide (Pro C3), tissue inhibitor of metalloproteinases-1 (and derived enhanced liver fibrosis score). This is a provisional list with some fibrosis markers that can be added.

[19] Unless done within 6 months prior screening liver imaging is performed at screening. For liver imaging ultrasonography (US) is preferred, alternately computed tomography (CT) or magnetic resonance imaging (MRI) can be used. For patients with risk factors for of hepatocellular carcinoma (HCC), i.e. any of these: family history with HCC, >40 years of age, male sex, born in Sub-Saharan Africa, Metabolic syndrome (obesity, diabetes), smoking, ALT>ULN, HBV DNA (>2,000 IU/mL), HBeAg-negative, Genotype C) during follow-up phase liver imaging is performed at week 40, i.e. after 6 months of follow-up maintenance treatment..

[20] During the treatment period, patient diary will be dispensed to record study drug (EYP001a/Placebo and NA) administration and will be reviewed to assess compliance to study drug. During the follow-up period, patient diary will be dispensed to record NA administration and will be reviewed to assess compliance to NA.

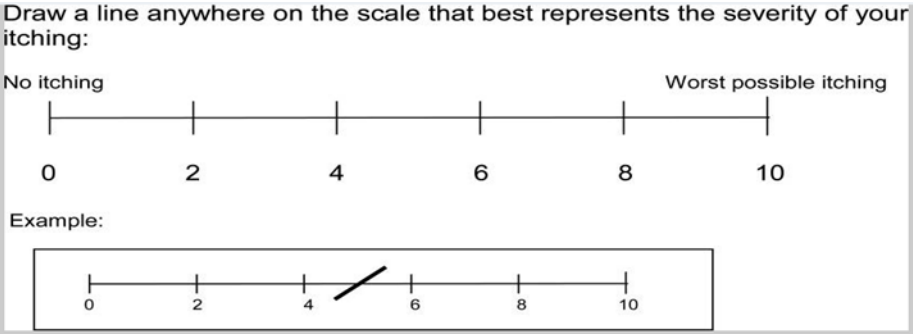
[21] EYP001a/Placebo will be dispensed throughout the treatment period. NA will be dispensed throughout the treatment period and follow-up Visits 1 and 2 (Weeks 20 and 28, respectively). Please note 16 weeks of treatment (EYP001a/Placebo and NA) with 4 weeks treatment units will be dispensed. This implies that no extra treatment units will be dispensed. Should patient “loose” treatment units the check on sufficient treatment can be made at each fortnightly visit.
On each treatment visit study drug (EYP001a/Placebo and NA) should be administered after PK/PD blood sampling.

[22] During the treatment period, used/unused study drug (EYP001a/Placebo and NA) will be collected to assess compliance to study drug. During the follow-up period, used/unused NA will be collected to assess compliance to NA.

[23] Liver safety testing: ALT, AST, Alkaline Phosphatase, Gamma Glutamyl Transferase (GGT), Total Bilirubin, Thrombocytes and Albumin.

19.2. Appendix B: Pruritus Scale

Pruritus Visual Analog Scale



5-D Pruritus Scale

1. **Duration**: During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree**: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction**: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability**: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

19.3. Appendix C: Alcohol Use Disorders Identification Test-Concise

The Alcohol Use Disorders Identification Test-Concise (AUDIT-C) has 3 questions and is scored on a scale of 0 to 12. Read the questions as written and circle the letter that corresponds to the answer. Each AUDIT-C question has 5 answer choices valued from 0 to 4 points. In men, a score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. In women, a score of 3 or more is considered positive. Generally the higher the score, the more likely it is that a person's drinking is affecting his or her safety.

AUDIT-C Questionnaire

Patient ID _____ Visit date _____

1. **How often do you have a drink containing alcohol?**
   a. Never
   b. Monthly or less
   c. 2-4 times a month
   d. 2-3 times a week
   e. 4 or more times a week

2. **How many standard drinks containing alcohol do you have on a typical day?**
   a. 1 or 2
   b. 3 or 4
   c. 5 or 6
   d. 7 to 9
   e. 10 or more

3. **How often do you have six or more drinks on one occasion?**
   a. Never
   b. Less than monthly
   c. Monthly
   d. Weekly
   e. Daily or almost daily

See answer module on the next page.

Answer Module

Question 1: How often do you have a drink containing alcohol?

Valid Values

Value	Value Meaning	Description	Display Order
Never	Never	Not ever; at no time in the past (or future).	0
Monthly or less	Monthly or less	Monthly or less	1
2 to 4 times a month	Two To Four Instance Per Month	A natural number greater than 1 and less than 3 and the quantity that it denotes: the sum of one and one.: Used as a function word to indicate direction, purpose, or movement.: A natural number greater than 3 and less than 5 and the quantity that it denotes: the sum of three and one.: An occurrence of something.: For each, generally denoting a ratio.: One of the 12 divisions of a year as determined by a calendar. It corresponds to the unit of time of approximately to one cycle of the moon's phases, about 30 days or 4 weeks.	2
2 to 3 times a week	Two To Three Instance Per Week	A natural number greater than 1 and less than 3 and the quantity that it denotes: the sum of one and one.: Used as a function word to indicate direction, purpose, or movement.: A natural number greater than 2 and less than 4 and the quantity that it denotes: the sum of two and one.: An occurrence of something.: For each, generally denoting a ratio.: Any period of seven consecutive days.	3
4 or more times a week	Four Or Greater Than Integer::4 Instance Per Week	A natural number greater than 3 and less than 5 and the quantity that it denotes: the sum of three and one.: An article used to connect words, phrases, or clauses representing alternatives; used to connect alternative terms for the same thing; used in correlation; used to correct or rephrase what was previously said; otherwise.: A statement about the relative size or order of two objects specifying that an object of interest exceeds another object in quantity or measure or value or status.: A number with no fractional part.::4: An occurrence of something.: For each, generally denoting a ratio.: Any period of seven consecutive days.	4

Question 2: How many standard drinks containing alcohol do you have on a typical day?

Valid Values

Value	Value Meaning	Description	Display Order
1 or 2	1 or 2	1 or 2	0
3 to 4	3 to 4	3 to 4	1
5 to 6	5 to 6	5 to 6	2
7 to 9	7 to 9	7 to 9	3
10 or more	10 or more	10 or more	4

Question 3: How often do you have six or more drinks on one occasion?

Valid Values

Value	Value Meaning	Description	Display Order
Never	Never	Not ever; at no time in the past (or future).	0
Less than monthly	Less Than Monthly	A statement about the relative size or order of two objects specifying that an object of interest is smaller than another object in quantity or measure or value or status.: Every month.	1
Monthly	Monthly	Every month.	2
Weekly	Weekly	Every week.	3
Daily or almost daily	Daily	Occurring or done each day.	4

19.4. Appendix D: The Alcohol Use Disorders Identification Test: Interview Version

Read questions as written. Read answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks." Place the correct answer number in the box at the right. Total scores of ≥8 are recommended as indicators of hazardous and harmful alcohol use.

1. How often do you have a drink containing alcohol? (0) Never [Skip to Qs 9-10] (1) Monthly or less (2) 2 to 4 times a month (3) 2 to 3 times a week (4) 4 or more times a week ☐	6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐
2. How many drinks containing alcohol do you have on a typical day when you are drinking? (0) 1 or 2 (1) 3 or 4 (2) 5 or 6 (3) 7, 8, or 9 (4) 10 or more ☐	7. How often during the last year have you had a feeling of guilt or remorse after drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐
3. How often do you have six or more drinks on one occasion? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily *Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0* ☐	8. How often during the last year have you been unable to remember what happened the night before because you had been drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐
4. How often during the last year have you found that you were not able to stop drinking once you had started? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐	9. Have you or someone else been injured as a result of your drinking? (0) No (2) Yes, but not in the last year (4) Yes, during the last year ☐
5. How often during the last year have you failed to do what was normally expected from you because of drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐	10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down? (0) No (2) Yes, but not in the last year (4) Yes, during the last year ☐
Record total of specific items here ☐ *If total is greater than recommended cut-off, consult User's Manual.*	