



Clinical trial results:

A Phase 2, Open-Label Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Activity of Titrating-Dose Lonafarnib in Combination with Ritonavir in Patients Chronically Infected with Hepatitis Delta Virus (LOWR-4)

Summary

EudraCT number	2015-003077-15
Trial protocol	DE
Global end of trial date	09 February 2017

Results information

Result version number	v1 (current)
This version publication date	18 April 2022
First version publication date	18 April 2022
Summary attachment (see zip file)	AASLD 2016 Abstract (EIG-LNF-002 AASLD 2016 abstract.pdf) ILC 2017 abstract (EIG-LNF-002 ILC 2017 abstract.pdf) CSR Synopsis (Synopsis_2015-003077-15.pdf) protocol amendment 01 (Description of Amendment 01.pdf)

Trial information

Trial identification

Sponsor protocol code	EIG-LNF-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02527707
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eiger BioPharmaceuticals Inc
Sponsor organisation address	2155 Park Boulevard, Palo Alto, United States, CA 94306
Public contact	Matthew J. Bys, Senior Director of Operations, , Eiger BioPharmaceuticals, 1-(877) 899-2051, mbys@eigerbio.com
Scientific contact	David Apelian MD, PhD, MBA Chief Operating Officer and Executive Medical Officer, , Eiger BioPharmaceuticals, 1-(877) 899-2051, dapelian@eigerbio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 May 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- 1) Evaluate the safety and tolerability of the following dose-titration regimen of lonafernib (LNF) in combination with ritonavir (RTV) over a 24-week treatment period: LNF/RTV starting at 50 mg bid/100 mg bid, escalated to LNF/RTV 75 mg bid/100 mg bid, and then to 100 mg bid/100 mg bid as tolerated
- 2) Evaluate the pharmacodynamic activity (change in HDV viral load) of the dose-titration regimen of LNF in combination with RTV over a 24-week treatment period

Protection of trial subjects:

The study was conducted according to GCP, signed ICF was obtained before each patient's participation in the study. Gastrointestinal (GI) symptoms (diarrhea, nausea, dyspepsia, vomiting, and decreased appetite) are the most common AEs reported with lonafernib single-agent therapy. Ritonavir may be associated with diarrhea. Occurrence of diarrhea may reduce the absorption of lonafernib, ritonavir, and other medications from the GI tract. Diarrhea may result in loss of fluids and dehydration, which can be severe, and require hospitalization for supportive care. Patients were requested to receive therapy (antacids, anti-emetics, or anti-diarrheals) for GI symptoms at the earliest signs in order to avoid possible severe complications and prevent and distress associated with these symptoms. Electrolytes were requested to be monitored in cases of diarrhea and volume depletion to prevent further complications which could arise due to electrolyte loss.

Background therapy:

- 1) As the Hepatitis Delta patients are also infected with Hepatitis B virus, antivirals for HBV management such as Viread was allowed.
- 2) Ondansetron was used as a concomitant medication, on need basis, to prevent nausea and vomiting to an does not inhibit or induce enzymes in the CYP system. No interaction is expected with concomitant administration with lonafernib, therefore it was a safe concomitant medication recommended for use in this trial.
- 3) Famotidine is a histamine H receptor antagonist that inhibits stomach acid production was allowed to be used as a concomitant medication to prevent symptoms related to stomach acidity and Famotidine not been associated with any clinically significant drug-drug interactions. No significant interference with CYP system has been identified; thus, no interaction is expected with concomitant administration with lonafernib, therefore it was a safe concomitant medication recommended for use in this trial
- 4) Omeprazole inhibits CYP2C19 and P-glycoprotein (P-gp) and is completely metabolized, specifically by CYP3A4 and CYP2C19. This medication is another alternative for the reatment of gastrointestinal symptoms. Dose adjustments are typically not required when administering omeprazole with other medications metabolized by CYP2C19; however, dose adjustments are required for omeprazole when administered to patients with hepatic impairment (refer to the Prilosec Product Label for additional information). Therefore the use of this medication was only allowed for some patients who fitted the product label requirement.
- 4)

Evidence for comparator:

There was no comparator product used in this trial

Actual start date of recruitment	06 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	14
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open label non-randomized trial. Patients were recruited between 06-January-2016 until 09Mar2016

Pre-assignment

Screening details:

Patients were screened against the protocol defined inclusion/exclusion criteria. There were 18 patients screened and 15 were eligible and thus enrolled into the study. 2/3 screening failures were due to concomitant use of any prohibited medications or supplements and the remaining one was a screen failure due to significant renal dysfunction

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Study arm
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Arm description:

This is a open label single arm study

Arm type	Single Arm
Investigational medicinal product name	Ionafarnib Capsules, 50 mg, for oral administration
Investigational medicinal product code	L262-01A005BOT35
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

50 mg bid (1 capsule twice daily) as a starting dose and after 4 weeks if the patients can also tolerate 2 weeks of 75 mg bid (different capsule) 100 mg bid (2 times 50 mg capsules once in the morning and once in the evening) as tolerated in patients - the 50mg capsules were used for 50 mg BID and 100 mg BID

Investigational medicinal product name	Ionafarnib Capsules, 75 mg, for oral administration
Investigational medicinal product code	L262-01A006BOT35
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

After the first 4 weeks of 50mg BID, if the patients could tolerate 50 mg BID they were escalated for 2 weeks to 75 mg BID. The 75 mg capsule was to be administered once in the morning and once in the evening

Investigational medicinal product name	Novir, Ritonavir Tablets, 100 mg
Investigational medicinal product code	Lot no: 1039671
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg BID, one 100 mg Tablet twice daily, once morning and once in the evening

Number of subjects in period 1	Study arm
Started	15
Completed	13
Not completed	2
Adverse event, non-fatal	2

Baseline characteristics

Reporting groups

Reporting group title	overall trial
Reporting group description: -	

Reporting group values	overall trial	Total	
Number of subjects	15	15	
Age categorical			
Units: Subjects			
Adults (18-64 years)	14	14	
From 65-84 years	1	1	
Gender categorical			
Units: Subjects			
Female	4	4	
Male	11	11	
Ethnic group			
Units: Subjects			
white	12	12	
black or african american	1	2	
Asian	2	1	

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis population will consist of all patients who receive at least one dose of study drug.

Subject analysis set title	The primary PD/efficacy population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The primary PD/efficacy population will consist of patients who receive study drug throughout the entire 24 week treatment period and for whom viral load data are available from baseline and end-of-treatment (Week 24) study visits

Subject analysis set title	The PK population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population will include patients who received at least 2 weeks of study drug at a stable dose level, and in whom a sufficient number of blood samples were collected, plasma samples were analyzed, concentration data were analyzed, and PK parameter values were derived

Reporting group values	Safety Population	The primary PD/efficacy population	The PK population
Number of subjects	15	13	15
Age categorical			
Units: Subjects			
Adults (18-64 years)	14	12	14
From 65-84 years	1	1	1

Gender categorical Units: Subjects			
Female	4	3	4
Male	11	10	11
Ethnic group Units: Subjects			
white	12	11	12
black or african american	1	1	1
Asian	2	1	2

End points

End points reporting groups

Reporting group title	Study arm
Reporting group description: This is a open label single arm study	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis population will consist of all patients who receive at least one dose of study drug.	
Subject analysis set title	The primary PD/efficacy population
Subject analysis set type	Sub-group analysis
Subject analysis set description: The primary PD/efficacy population will consist of patients who receive study drug throughout the entire 24 week treatment period and for whom viral load data are available from baseline and end-of-treatment (Week 24) study visits	
Subject analysis set title	The PK population
Subject analysis set type	Sub-group analysis
Subject analysis set description: The PK population will include patients who received at least 2 weeks of study drug at a stable dose level, and in whom a sufficient number of blood samples were collected, plasma samples were analyzed, concentration data were analyzed, and PK parameter values were derived	

Primary: Safety Endpoint - Clinical Lab results

End point title	Safety Endpoint - Clinical Lab results ^[1]
End point description: Blood samples were analyzed for hematology, clinical chemistry, and coagulation analytes, and urine samples were analyzed for urinalysis analytes/tests (all analytes/tests are listed in Section 4.1.7 of the study protocol). Laboratory results were summarized using summary statistics (absolute and change-from-baseline values) by dose level and time point. All Grade 3 and Grade 4 laboratory values were summarized categorically by dose level. Liver enzyme results (ALT, AST, total bilirubin, and alkaline phosphatase) were summarized by Common Terminology Criteria for Adverse Events (CTCAE; Version 4.03) grade. All laboratory results were listed by patient, with values outside the normal ranges flagged.	
End point type	Primary
End point timeframe: Enrollment to end of follow up	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Clinical laboratory data were summarized at each measurement time point and for eachpatient's final postbaseline measurement in the following ways: (1) with descriptive statistics (mean, standard deviation, median, and range) for each measurement time point and (2) with descriptive statistics for the change from baseline in the measurements at each postbaseline time point. Summary of the clinical laboratory data are attached.

End point values	Study arm	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: Clinical Laboratory Tests				
number (not applicable)	0	0		

Attachments (see zip file)	Laboratory Summary - Clinical Chemistry 14.4.3.1-
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Statistical analyses

No statistical analyses for this end point

Primary: Safety Endpoint - Vital Signs

End point title	Safety Endpoint - Vital Signs ^[2]
End point description: Actual and change-from-baseline vital sign values (BP, HR, respiration rate, and body temperature) were summarized at each time point by dose level. Vital signs were listed by patient.	
End point type	Primary
End point timeframe: From study enrollment including treatment follow up period	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Actual values for vital signs and changes from baseline were summarized for each patient in the attached document

Mean vital signs in the safety analysis set did not show any clinically significant changes during the study. Both systolic and diastolic BP (SBP and DBP) showed slight mean reductions from baseline, up to 8.5 and 11.5 mmHg, respectively. Mean HR also showed minor reductions from baseline, up to 5.1 bpm.

End point values	Study arm	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: vital sign units				
number (not applicable)	0	0		

Attachments (see zip file)	Vital Sign/Vital Sign Summary 14.4.4.1.pdf
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Statistical analyses

No statistical analyses for this end point

Primary: Safety Endpoint - ECG Results

End point title	Safety Endpoint - ECG Results ^[3]
End point description: ECG intervals were summarized by visit and dose level using summary statistics for actual values and change-from-baseline values (average of 3 readings). ECG data and clinical interpretations were listed by patient.	
End point type	Primary
End point timeframe: From study enrollment including study follow up	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Actual values for ECG intervals and changes from baseline were summarized by study visit using descriptive statistics. Clinical interpretation of ECG results are summarized in the attached document.

End point values	Study arm	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: msec				
number (not applicable)	0	0		

Attachments (see zip file)	QTcF Interval/Summary of QTcF Interval by Dose Level and
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Statistical analyses

No statistical analyses for this end point

Primary: Safety Endpoint - Concomitant medication use

End point title	Safety Endpoint - Concomitant medication use ^[4]
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End point description:

Concomitant medications were defined as non-study medications that were used during the study (ie, had a stop date on or after the first dose of study drug). New concomitant medications were those concomitant medications that were started on or after the day of first study drug dose. Prior medications were those non-study medications with a stop date prior to the day of first study drug dose. Prior, concomitant, and new concomitant medications were mapped to drug classes and generic terms using the World Health Organization Drug Dictionary Enhanced (WHO-DD Enhanced), Version WHO2015SEP and summarized by dose level. Prior and concomitant medications were also listed by patient.

End point type	Primary
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End point timeframe:

Since study enrollment including follow up

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Concomitant medications were summarized based on mapping to drug classes and generic terms in the World Health Organization Drug Dictionary Enhanced (WHO-DD Enhanced) in the attached document.

End point values	Study arm	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: The amount of conmed used	0	0		

Attachments (see zip file)	Concomitant Medications/Concomitant Medications 14.1.4.1.pdf
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Statistical analyses

No statistical analyses for this end point

Primary: Safety Endpoint - Physical Examination Findings

End point title	Safety Endpoint - Physical Examination Findings ^[5]
End point description: Physical examination findings (comprehensive exam at screening, brief exams at each subsequent visit, and genital exams at screening and Week 24 or early termination) were listed by patient	
End point type	Primary
End point timeframe: From screening until end of follow up period	

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Actual values for physical examination and changes from baseline were summarized and listed for each patient in the attached document

End point values	Study arm	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: Units used for measuring physical exam				
number (not applicable)	0	0		

Attachments (see zip file)	Physical Exam findings/16.2.8 eig-Inf-002-ecg-vitals.pdf
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Statistical analyses

No statistical analyses for this end point

Primary: Safety Endpoint - Ophthalmic Test Results

End point title	Safety Endpoint - Ophthalmic Test Results ^[6]
End point description: Results of the slit lamp and dilated fundus examinations and retinal photography were summarized as normal or abnormal (nonclinically significant or clinically significant) using number (%) of patients by dose level and time point. Results of the visual acuity examination provided number (%) of patients with discrete visual acuity values (eg, 20/15, 20/20) by dose level and time point.	
End point type	Primary
End point timeframe: Screening until end of treatment	

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Actual values for ophthalmic examination and changes from baseline were summarized for each patient in the attached document

End point values	Study arm	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: differs for each parameter analysed				
number (not applicable)	0	0		

Attachments (see zip file)	Slip Lamp; Visual Acuity; Dilated Fundus/Table 14.4.4.5-
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Statistical analyses

No statistical analyses for this end point

Primary: Efficacy Endpoint - Change in HDV viral load

End point title	Efficacy Endpoint - Change in HDV viral load ^[7]
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End point description:

Change from baseline to Week 24 in HDV RNA (log10 IU/mL) (viral load).

End point type	Primary
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End point timeframe:

From BL to week 24

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The changes from baseline in HDV viral load is presented in the attached document

End point values	Study arm	The primary PD/efficacy population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	13		
Units: log10 IU/mL				
number (not applicable)	15	13		

Attachments (see zip file)	Summary of Hepatitis D RNA (log10 IU/mL) by Dose
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Statistical analyses

No statistical analyses for this end point

Primary: Safety Endpoint - AEs

End point title	Safety Endpoint - AEs ^[8]
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End point description:

Any AEs that occurred before administration of the first dose of study drug were recorded on the Medical History CRF. AEs that started after administration of the first dose of study drug up to and including 28 days after administration of the last dose of study drug were considered treatment emergent (TEAE). Any AEs that started more than 28 days after the last dose of study drug were considered posttreatment AEs.

End point type	Primary
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End point timeframe:

AEs that started after administration of the first dose of study drug up to and including 28 days after administration of the last dose of study drug were considered treatment emergent (TEAE)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This was an open-label single-arm study with no comparator group.

End point values	Study arm	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: number of AEs	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety Endpoint - Reproductive hormone test results

End point title	Safety Endpoint - Reproductive hormone test results ^[9]
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End point description:

Results of male and female reproductive hormone tests were summarized by dose and time point and listed by patient.

End point type	Primary
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End point timeframe:

From enrollment to the end of follow-up

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This was an open-label single-arm study with no comparator group.

End point values	Study arm	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: differs for each parameter measured				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoints - Change in pharmacokinetic parameters

End point title	Secondary Endpoints - Change in pharmacokinetic parameters
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End point description:

Peak plasma concentration as observed, Time of the peak plasma concentration, Area under the plasma concentration versus time curve during the dosing interval calculated by the linear trapezoidal rule,

Average plasma drug concentration during multiple-dose administration, Minimum plasma concentration, Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve, Apparent total volume of distribution, Apparent total body clearance and Apparent first-order terminal elimination half-life

End point type	Secondary
End point timeframe:	
Collect trough PK blood samples at Weeks 2, 4, 6, 8, 12, and 16. Trough PK sample is collected. At either Week 8, 12, or 16 if the patient is on a stable dose for the prior 2 weeks, full PK sampling should be performed	

End point values	The PK population			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: All respective PK parameter units				
number (not applicable)	0			

Attachments (see zip file)	PK results/PK data summary tables and figures.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Change in HBV DNA levels

End point title	Secondary Endpoint - Change in HBV DNA levels
End point description:	
HBV DNA (log10 IU/mL) absolute and change-from-baseline values were summarized using descriptive statistics (mean, SD, median, minimum, and maximum) by dose level at each time point. HBV DNA (log10 IU/mL) mean levels were presented graphically over time. Individual patient plots of HBV DNA over time were also presented graphically.	
End point type	Secondary
End point timeframe:	
From BL until end of study	

End point values	The primary PD/efficacy population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: log10 IU/mL				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Change in viral serology

End point title	Secondary Endpoint - Change in viral serology
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End point description:

Viral serology data (HBeAb, HBeAg, HBsAg, and HDV antibody) were listed by patient.

End point type	Secondary
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End point timeframe:

From BL at each visit until End of study including study follow up

End point values	Study arm	The primary PD/efficacy population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: IU/L				
number (not applicable)	0	0		

Attachments (see zip file)

Laboratory Results - ALT/16.2.7 eig-Inf-002-ind-lab-results.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From day 1 until EoT including post treatment follow up

Adverse event reporting additional description:

Any AEs that occurred before administration of the first dose of study drug were recorded on the Medical History CRF. AEs that started after administration of the first dose of study drug up to and including 28 days after administration of the last dose of study drug were considered treatment emergent (TEAE). Any AEs that started more than 28 day

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Treatment: 50 mg/100 mg
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Reporting group description:

Integral to this study was the titration of the LNF dose from the starting dose of 50 mg bid, up to 75 mg bid, and then to 100 mg bid, if tolerated.

LNF/RTV dosing started on Day 1 (baseline, Week 0) at 50 mg bid/100 mg bid. On or after Day 29, if the LNF/RTV dosage of 50 mg bid/100 mg bid had been tolerated for at least 4 weeks and with approval of the investigator, the LNF/RTV dosage could have been escalated to 75 mg bid/100 mg bid. On or after Day 43, if the LNF/RTV dosage of 75 mg bid/100 mg bid had been tolerated for at least 2 weeks and with approval of the investigator, the LNF/RTV dosage could have been escalated to 100 mg bid/100 mg bid

Reporting group title	Treatment: 75 mg/100 mg
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Reporting group description:

Integral to this study was the titration of the LNF dose from the starting dose of 50 mg bid, up to 75 mg bid, and then to 100 mg bid, if tolerated.

LNF/RTV dosing started on Day 1 (baseline, Week 0) at 50 mg bid/100 mg bid. On or after Day 29, if the LNF/RTV dosage of 50 mg bid/100 mg bid had been tolerated for at least 4 weeks and with approval of the investigator, the LNF/RTV dosage could have been escalated to 75 mg bid/100 mg bid. On or after Day 43, if the LNF/RTV dosage of 75 mg bid/100 mg bid had been tolerated for at least 2 weeks and with approval of the investigator, the LNF/RTV dosage could have been escalated to 100 mg bid/100 mg bid

Reporting group title	Treatment: 100 mg/100 mg
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Reporting group description:

Integral to this study was the titration of the LNF dose from the starting dose of 50 mg bid, up to 75 mg bid, and then to 100 mg bid, if tolerated.

LNF/RTV dosing started on Day 1 (baseline, Week 0) at 50 mg bid/100 mg bid. On or after Day 29, if the LNF/RTV dosage of 50 mg bid/100 mg bid had been tolerated for at least 4 weeks and with approval of the investigator, the LNF/RTV dosage could have been escalated to 75 mg bid/100 mg bid. On or after Day 43, if the LNF/RTV dosage of 75 mg bid/100 mg bid had been tolerated for at least 2 weeks and with approval of the investigator, the LNF/RTV dosage could have been escalated to 100 mg bid/100 mg bid

Serious adverse events	Treatment: 50 mg/100 mg	Treatment: 75 mg/100 mg	Treatment: 100 mg/100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Injury, poisoning and procedural complications			
Jaw fracture/mandibular fracture	Additional description: This patient was already withdrawn from treatment according to the patients own consent due to decreased appetite. Near the end of the follow-up period, the patient was involved in a fight where the patient sustained a mandibular fracture.		
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment: 50 mg/100 mg	Treatment: 75 mg/100 mg	Treatment: 100 mg/100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	10 / 13 (76.92%)	9 / 10 (90.00%)
Investigations			
Weight decreased			
subjects affected / exposed	2 / 15 (13.33%)	3 / 13 (23.08%)	4 / 10 (40.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 15 (13.33%)	0 / 13 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	3 / 15 (20.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 15 (20.00%)	2 / 13 (15.38%)	1 / 10 (10.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	2 / 15 (13.33%)	2 / 13 (15.38%)	2 / 10 (20.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

Anemia subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 0	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	15 / 15 (100.00%) 0	5 / 13 (38.46%) 0	2 / 10 (20.00%) 0
Nausea subjects affected / exposed occurrences (all)	6 / 15 (40.00%) 0	2 / 13 (15.38%) 0	5 / 10 (50.00%) 0
Vomiting subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 0	1 / 13 (7.69%) 0	5 / 10 (50.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 0	2 / 13 (15.38%) 0	1 / 10 (10.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 0	1 / 13 (7.69%) 0	1 / 10 (10.00%) 0
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 0	0 / 13 (0.00%) 0	1 / 10 (10.00%) 0
Acne subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 0	0 / 13 (0.00%) 0	0 / 10 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 0	0 / 13 (0.00%) 0	1 / 10 (10.00%) 0
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 0	1 / 13 (7.69%) 0	0 / 10 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 0	0 / 13 (0.00%) 0	1 / 10 (10.00%) 0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 15 (26.67%)	4 / 13 (30.77%)	3 / 10 (30.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2015	As the amendment description is longer than the characters allowed, it is included in the index as a separate summary attachment
03 November 2015	- Change in Sponsor Medical monitor - Change in clinical program manager - Addition of inclusion criterion for ALT Inclusion criterion # 7 - Change to exclusion criterion # 8e: From "Prothrombin time >2 seconds" to "Prothrombin time >12 seconds" - Change to exclusion criterion # 19 to include: pegylated interferon alfa-2b - Change to ALT value in management of flares from "ALT of $\geq 5 \times$ the ULN" to "ALT of $\geq 10 \times$ the ULN" - Change to description of COBAS test to change wording "The assay can quantitate HBV DNA levels with an upper limit of detection" to say "The assay can quantitate HBV DNA levels with an upper limit of quantification" - Change in SAE reporting information
22 December 2015	1. Removing prothrombin time (PT): Results for prothrombin time (PT) will vary depending on the method used, with results measured in seconds and compared to the normal range established and maintained by the laboratory that performs the test. This normal range represents an average value of healthy people who live in that area and will vary somewhat from lab to lab. The International Normalized Ratio (INR), provides a consistent way of expressing the prothrombin test results, which had previously suffered from a large degree of variation between centers using different reagents. Therefore, to allow for consistency of results and comparison with other studies, INR will be the test result used for inclusion/exclusion of subjects into the study 2. Changes in thyroid test: Most patients with chronic HDV infection may have received previous therapy with interferon alfa or peg-interferon alfa. Some patients may have developed hypothyroidism due to interferon therapy and are currently receiving thyroid hormone replacement therapy (THRT). All studies that investigate therapies for chronic HDV allow for inclusion of such patients as long as they are stable on THRT. As it is unnecessary to exclude patients who are stable on THRT, the restriction was removed from the exclusion criteria. 3. Removing the upper limit of BMI: The main concern related to patients with high BMI is the presence of Non-Alcoholic Fatty Liver Disease (NAFLD) in patients with chronic hepatitis Delta. Since liver biopsy is the gold standard for the diagnosis of NAFLD and the eligible patients will have a liver biopsy, the BMI limit is not. 4. Protocol time points are expressed in weeks and not in months 5. The following wording added at follow up: Alpha-interferon treatments will be allowed during the 20 weeks of the FU period (that is, starting 4 weeks after last dose of study treatment) "if considered by the investigator to be required for patient safety"

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported