SYNOPSIS OF RESEARCH REPORT PROTOCOL ML 28470

COMPANY: Roche S.p.A. NAME OF FINISHED PRODUCT: Not applicable NAME OF ACTIVE SUBSTANCE(S): Not applicable	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY: / REPORT No.:	Cross-sectional multicenter study evaluating the IL28B polymorphism in patients with HBeAg-negative chronic hepatitis B treated with pegylated interferon alfa-2a in the course of Peg.Be.Liver study
DATE OF REPORT:	10 January 2014
INVESTIGATORS / CENTERS AND COUNTRIES:	12 investigational study sites in Italy
PUBLICATION (REFERENCE):	Not applicable
PERIOD OF TRIAL:	08 Nov 2012 – 21 Jun 2013
CLINICAL PHASE:	IIIB
OBJECTIVES:	The primary objective of this study was to evaluate the association between interleukin 28B (IL28B) polymorphism and sustained virological response (SVR) observed in the predecessor ML18253 study. The secondary objectives of this study were: • To evaluate the association between IL28B polymorphism and HBsAg clearance observed at the end of treatment (EoT) and at the end of follow-up (EoF) in the predecessor ML18253 study; • To evaluate the association between IL28B polymorphism and HBsAg ≤ 10 IU/ml at EoT and EoF in the predecessor ML18253 study; • To evaluate the association of IL28B polymorphism and HBsAg kinetic in the predecessor ML18253 study.
STUDY DESIGN:	This was a phase IIIb, interventional, cross sectional, national, multicenter study. The study was carried out in one single visit, in which patients who took part in the predecessor ML18253 study and were eligible for participation in the present study underwent a blood sample for the determination of the IL28B polymorphism. A phone follow-up took place one week after the visit for the assessment of adverse events.
NUMBER OF SUBJECTS	88 enrolled and evaluable for safety, 86 evaluable for efficacy
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Inclusion criteria: This study included adult male or female patients with HBeAg-negative CHB, previously enrolled in ML18253 study (local sponsored study) during which they were treated with either with Peg-IFN alfa-2a given as single agent for 48 or 96 weeks (arm A and B), or with Peg-IFN alfa-2a + lamivudine for 48 weeks followed by Peg-IFN alfa-2a given as single agent for other 48 weeks (arm C). Inclusion criteria were: 1. Signing of the informed consent form for participation in this study; 2. Previous participation in ML18253 study; 3. Administration of at least one dose of the study drug in ML18253 study.
TRIAL DRUG / STROKE (BATCH) No.	Not applicable for this study.
DOSE / ROUTE / REGIMEN / DURATION	Not applicable for this study.
CRITERIA FOR EVALUATION EFFICACY:	Primary endpoint: Association between IL28B genotypes at rs12979860 (CC vs. TC+TT) and rs8099917 (TT vs. GT+GG) and SVR (No vs. Yes) at EoF. SVR is defined as HBV DNA ≤ 2.000 IU/ml. Secondary endpoints: • Association between IL28B genotypes at rs12979860 (CC vs. TC+TT) and rs8099917 (TT vs. GT+GG) and HBV DNA ≤ 2.000 IU/ml at EoT; • Association between IL28B genotypes at rs12979860 (CC vs. TC vs. TT) and rs8099917 (TT vs. GT vs. GG) and HBsAg clearance, defined as HBsAg < 0.05 IU/ml, at EoT; • Association between IL28B genotypes at rs12979860 (CC vs. TC vs. TT) and rs8099917 (TT vs. GT vs. GG) and HBsAg clearance, defined as HBsAg < 0.05 IU/ml, at EoF; • Association between IL28B genotypes at rs12979860 (CC vs. TC vs. TT) and rs8099917 (TT vs. GT vs. GG) and HBsAg ≤ 10 IU/ml at EoT; • Association between IL28B genotypes at rs12979860 (CC vs. TC vs. TT) and rs8099917 (TT vs. GT vs. GG) and HBsAg ≤ 10 IU/ml at EoF; • Kinetic of HBsAg during treatment and follow-up by IL28B genotypes at rs12979860 (CC vs. TC vs. TT) and rs8099917 (TT vs. GT vs. GG). EoT, as defined in the predecessor study, was Week 48 for arm A and Week 96 for both arm B and C.

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	EoF, as defined in the predecessor study, was at Follow-up 48 for all arms (i.e. 48 weeks after the end of treatment).
PHARMACODYNAMICS:	Not applicable for this study
PHARMACOKINETICS:	Not applicable for this study
SAFETY:	Adverse Events (AEs) and Serious Adverse Events (SAEs) related to study-specific procedures (i.e. blood drawing for genotyping).
STATISTICAL METHODS:	The following populations were considered for data analysis: the all subjects enrolled set (ENR), which included all subjects who provided informed consent for this study; the full analysis set (FAS), which included all subjects in the ENR having valid data for the determination of the interleukin 28B (IL28B) genotypes; the safety analysis set (SAF), which included all subjects in the ENR set who performed the blood drawing for genotyping. The default summary statistics for quantitative variables were the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). For qualitative variables, the number (n) and percentage (%) of subjects per category were calculated. The association between IL28B genotypes at rs12979860 (CC vs. TC+TT) and rs8099917 (TT vs. GT+GG) and the SVR was analyzed by means of a univariate logistic analysis using the SVR (No vs. Yes) as outcome variable and the IL28B genotypes at rs12979860 (CC vs. TC+TT) and rs8099917 (TT vs. GT+GG) as covariate. Odds ratios and 95% confidence intervals (CI) were also calculated. A sensitivity analysis excluding subjects with missing data on primary end point was performed to verify sensitivity to missing data assumptions. The other secondary variables were analyzed analogously to the primary end-point. AEs due to study procedures (i.e. the blood sample) were to be coded using MedDRA dictionary (version 16.0) and summarized by presenting the number and percentage of patients having at least one AE by primary system organ class (SOC) and preferred term (PT).

EFFICACY RESULTS:

Primary variable (proportions of patients with SVR at EoF by IL28B genotypes)

The summary of the distribution of SVR (HBV DNA ≤ 2000 IU/ml) at EoF by IL28B genotypes at rs12979860 and rs8099917 in the FAS is presented in the table below.

	IL28B genotypes at rs12979860				
	CC (N=35)	TC (N=41)	TT (N=10)	TC+TT (N=51)	Overall (N=86)
HBV DNA ≤ 2000 IU/ml					
No, N (%)	28 (80.0%)	34 (82.9%)	8 (80.0%)	42 (82.4%)	70 (81.4%)
Yes, N (%)	7 (20.0%)	7 (17.1%)	2 (20.0%)	9 (17.6%)	16 (18.6%)
	IL28B genotypes at rs8099917				
	TT (N=52)	GT (N=31)	GG (N=3)	GT+GG (N=34)	Overall (N=86)
HBV DNA ≤ 2000 IU/ml					
No, N (%)	40 (76.9%)	27 (87.1%)	3 (100.0%)	30 (88.2%)	70 (81.4%)
Yes, N (%)	12 (23.1%)	4 (12.9%)	0 (0.0%)	4 (11.8%)	16 (18.6%)

No statistically significant associations between IL28B genotypes and SVR at EoF were observed at both rs12979860 and rs8099917. In the comparison of TC+TT vs. CC genotypes at rs12979860, the OR was 0.86 (95% CI: 0.29 to 2.57; p value = 0.7831). In the comparison of TT vs. GT+GG genotypes at rs8099917, the OR was 2.25 (95% CI: 0.66 to 7.67; p value = 0.1951).

The results of the univariate logistic sensitivity analysis, in which subjects with missing data were excluded, were consistent with those observed in the primary analysis.

Secondary variables

HBV DNA ≤ 2000 UI/ml at EoT, HBsAg clearance and HBsAg ≤ 10 IU/ml at EoT/EoF

At rs12979860, the proportion of patients with HBV DNA ≤ 2000 UI/ml at EoT was higher in patients with CC genotype (74.3%) than in those with TC (65.9%) or TT (50.0%) genotype. Few patients with CC or TC genotype, and none of patients with TT genotype, had HBsAg clearance or HBsAg ≤ 10 IU/ml at EoT/EoF (except for none of patients with CC genotype that had HBsAg clearance at EoF).

At rs8099917, the proportion of patients with HBV DNA ≤ 2000 UI/ml at EoT was also higher in patients with TT genotype (75.0%) than in those with GT (54.8%) or GG (66.7%) genotype. Few patients with TT genotype, and none of patients with GT or GG genotype, had HBsAg clearance or HBsAg ≤ 10 IU/ml at EoT/EoF.

No statistically significant associations between IL28B genotypes and HBV DNA ≤ 2000 UI/ml at EoT were observed at both rs12979860 and rs8099917. In the comparison of TC+TT vs. CC genotypes at rs12979860, the OR was 0.58 (95% CI: 0.23 to 1.50; p value = 0.2642). In the comparison of TT vs. GT+GG genotypes at rs8099917, the OR was 2.37 (95% CI: 0.94 to 5.96; p value = 0.672).

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The results of the univariate logistic sensitivity analysis did not show statistically significant associations between IL28B genotypes and HBV DNA ≤ 2000 UI/ml at EoT at rs12979860. At rs8099917, a statistically significant association between IL28B genotypes and HBV DNA ≤ 2000 UI/ml R at EoT was observed. In the comparison of TT vs. GT+GG genotypes, the OR was 4.11 (95% CI: 1.34 to 12.62; p value = 0.0137), thus indicating that TT patients had 4.11 times higher probability than GT+GG patients of having a HBV DNA ≤ 2000 UI/ml at EoT.

Kinetic of HBsAg during treatment and follow-up

At rs12979860, the mean Log_{10} HBsAg levels declined from baseline up to week 96 in patients with all genotypes. The extent of the mean decline from week 48 up to week 96 was more marked in patients with genotype TC and TT than in those with genotype CC. The mean Log_{10} HBsAg levels from week 96 up to the end of follow-up did not substantially change in patients with the CC genotype and slightly increased in patients with genotype TC and TT. The same trend was observed with the grouped data of TC and TT patients.

At rs8099917, the mean Log_{10} HBsAg levels declined from baseline up to week 96 in patients with all genotypes. The extent of the mean decline was more marked in patients with genotype TT than in those with genotype GT and GG. The mean Log_{10} HBsAg levels from week 96 up to the end of follow-up did not substantially change in patients with all genotypes, except for a small further decrease in patients with genotype GG. The same trend was observed with the grouped data of GT and GG patients.

PHARMACODYNAMIC RESULTS: Not applicable for this study.

PHARMACOKINETIC RESULTS: Not applicable for this study.

SAFETY RESULTS:

No AEs related to study-specific procedures were reported in any patient.

CONCLUSIONS:

- The assessment of IL28B polymorphism in patients who took part in ML18253 study showed that the proportion of patients with SVR at end of follow-up did not substantially differ between the CC, TC and TT genotypes at rs12979860, and was higher in TT patients than in GT or GG patients at rs8099917. There were no statistically significant associations between IL28B genotypes and SVR end of follow-up.
- At end of treatment, the proportion of patients with HBV DNA ≤ 2000 UI/ml was higher in CC patients than in TC or TT patients at rs12979860, and was higher in TT patients than in GT or GG patients at rs8099917. No statistically significant associations between IL28B genotypes and HBV DNA ≤ 2000 UI/ml at end of treatment were observed. . In the same comparison evaluated in the univariate logistic sensitivity analysis (in which patients with missing data were excluded), the association was statistically significant: TT patients had more than 4 times higher probability than GT+GG patients of having a HBV DNA ≤ 2000 UI/ml at EoT.
- HBsAg clearance or HBsAg ≤ 10 IU/ml at EoT/EoF was observed in few patients with CC or TC genotype, and none of patients with TT genotype, at rs12979860, and were observed in few patients with TT genotype, and in none of patients with GT or GG genotype, at rs8099917.
- The mean Log_{10} HBsAg levels declined from baseline up to week 96 more markedly in TC and TT patients than in CC patients at rs12979860, and declined more markedly in TT patients than in GT and GG patients at rs8099917.