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Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

DEB025

Trial Indication(s)

Hepatitis C and how biomarkers affect the response to treatment of the disease.

Protocol Number

CDEB025A2212

Protocol Title

A Retrospective Pharmacogenetic Analysis of Hepatitis C Patients treated with Alisporivir (DEB025) Alone or in Combination with Peg-IFN2a and/or Ribavirin

Clinical Trial Phase

Phase IIB

Phase of Drug Development

Phase II

Study Start/End Dates

28 Feb 2012 to 07 Nov 2012

Reason for Termination

Not applicable.

Study Design/Methodology

The study population consists of 7, 37, and 109 patients, who completed DEB-025-103, DEB-025-HCV-203 or DEB-025-HCV-205, respectively. These patients came back to the investigator site, signed informed consent and had blood drawn for this retrospective pharmacogenetic study.

Of note, two patients with HIV mono-infection in DEB025-025-103 were excluded from this analysis. DNA extraction did not yield sufficient DNA of quality for 1, 1 and 4 samples from studies DEB-025-103, DEB-025-HCV-203 or DEB-025-HCV-205, respectively, and these patients were therefore excluded from the present analysis. As only 1/37 and 2/109 (one without sufficient DNA of quality) are non-Caucasian in studies DEB-025-HCV-203 or DEB-025-HCV-205, these 3 non-Caucasians were also excluded from this analysis to avoid the effect of ethnic background. Of the remaining patients, 4, 30 and 86 subjects were treated with DEB025-containing regimens in studies DEB-025-103, DEB-025-HCV-203 or DEB-025-HCV-205, respectively, and were therefore included in the present analysis.

Centers

centers in 8 countries: Belgium, Canada, France, Germany, Italy, Poland, Romania, Spain

Objectives:

Primary objective(s)

• To examine the impact of IL28B genotype on early viral response after 2 weeks in patients treated with DEB025 alone (monotherapy) in DEB-025-103

• To examine the impact of IL28B genotype on rapid virologic response (RVR) after 4 weeks in patients treated with DEB025 alone or with Peg-IFN in DEB-025-HCV-203

• To examine the impact of IL28B genotype on sustained virologic response (SVR72) in patients treated with DEB025 in combination with Peg-IFN and RBV for 24 or 48 weeks in DEB-025-HCV-205

Test Product (s), Dose(s), and Mode(s) of Administration

This was a retrospective pharmacogenetic study; patients received DEB025 in previous studies.

Statistical Methods

- DEB-025-103: No statistical analysis was performed.
- DEB-025-HCV-203: Statistical analyses were conducted to evaluate association between IL28B genotype and rapid viral response (RVR) after 4 weeks of treatment, using logistic regression adjusting for body weight, treatment arm, baseline viral load and viral genotype (group A: genotype 1 and 4; group B: genotype 2 and 3). SNP was tested using dominant (comparing presence of one or two copies of the minor allele versus none), recessive (comparing presence of two copies of the minor allele versus none or one copy), and additive (none, one or two copies of the minor allele were coded 0, 1 and 2, respectively, inheritance. T is the minor allele of IL28B rs12979860.
- DEB-025-HCV-205: Statistical analyses were conducted to evaluate association between IL28B genotype and sustained virologic response 72 weeks after initiation of treatment (SVR72), using logistic regression adjusting for body weight, treatment arm, baseline viral load and viral genotype. SNP was also tested using additive, dominant and recessive model of inheritance.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Patients must have completed studies DEB-025-103, DEB-025-HCV-203 and DEB-025-HCV-205. Written informed consent must be obtained prior to any assessments being performed.

Exclusion criteria

- None

Participant Flow

In studies DEB-025-103, DEB-025-HCV-203 or DEB-025-HCV-205, 4, 30 and 86 subjects were treated with DEB025 respectively, and were therefore included in the present analysis.

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Baseline Characteristics

Age Range

Trial has subjects under 18	No
In Utero	No
Preterm newborn infants (up to gestational age < 37 weeks)	No
Newborns (0-27 days)	No
Infants and toddlers (28 days-23 months)	No
Children (2-11years)	No
Adolescents (12-17 years)	No
Adults (18-64 years)	Yes
Elderly (>=65 years)	Yes

Gender

Female	Yes
Male	Yes

Primary Outcome Result(s)

IL28B genotype and clinical data of patients from DEB-025-103

Subject number	Body weight	Baseline Viral load	Viral load change	HCV genotype	IL28B (rs129798960)
1	76.5	4.50	-4.50	1B	CT
2	80	7.63	0.29	4C/4D	CT
3	55.5	5.09	-5.09	4C/4D	CC
4	79	6.06	-2.69	1B	CT

P values of logistic regression evaluating association between IL28B genotype and viral responses in DEB-025-HCV-203

Model	DEB-025-HCV-203
	RVR
Additive	0.020
Recessive	0.544
Dominant	0.021

P values of logistic regression evaluating association between IL28B genotype and viral responses in DEB-025-HCV-205

Model	DEB-025-HCV-205
	SVR72
Additive	0.016
Recessive	0.270
Dominant	0.011

Safety Results

Not reported in this retrospective pharmacogenetic analysis.

Other Relevant Findings

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IL28B genotype and clinical data of patients from DEB-025-HCV-203

Subject Number	Body Weight	Baseline Viral load	*Treatment	RVR	Genotype	IL28B
1	79.5	5.837	C	Y	3	C,C
2	51	6.599	A	N	1A	C,T
3	55	6.325	D	N	1B	C,C
4	66	6.640	D	Y	1B	C,C
5	66	4.465	B	Y	3	C,T
6	76.8	6.183	C	Y	3	C,C
7	73.5	5.156	B	Y	1B	C,T
8	71	7.372	B	Y	1A	C,T
9	83	3.928	D	Y	3A	C,C
10	65	6.221	D	N	1B	C,T
11	74	6.345	D	N	2B	C,T
12	72	5.312	D	N	1B	C,T
13	64	6.370	D	N	1B	T,T
14	75	6.488	B	N	3	C,T
15	68.3	6.634	A	N	3	C,C
16	74.5	4.509	D	Y	1B	C,C
17	68.1	6.358	C	Y	3	T,T
18	73	6.229	B	N	1B	C,T
19	74	6.058	A	N	1B	C,T
20	63	5.689	A	N	1B	C,T
21	85	6.435	C	Y	1B	C,C
22	81.8	5.288	A	N	3	C,T
23	65	6.606	B	N	1B	C,T
24	84	6.945	A	Y	3	C,C
25	73	5.906	A	N	1B	C,T
26	67	4.995	C	Y	1B	C,C
27	88	6.095	B	N	1B	C,T
28	77.5	6.025	D	N	1B	C,T
29	76	6.007	A	N	1B	C,C
30	89	5.317	A	Y	1B	C,T

* Treatment group A: DEB025 200 mg BID (Day 1 to Day 7) and DEB025 200mg QD (Day 8 to Day 29)/Peg-IFN180 µg QS; group B: DEB025 600 mg BID (Day 1 to Day 7) and DEB025 600mg QD (Day 8 to Day 29)/Peg-IFN180 µg QS; group C: DEB025 1000 mg BID (Day 1 to Day 7) and DEB025 1000mg QD (Day 8 to Day 29)/Peg-IFN180 µg QS; group D: DEB025 200 mg BID (Day 1 to Day 7) and DEB025 200mg QD (Day 8 to Day 29).

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IL28B genotype and clinical data of patients from DEB-025-HCV-205

Subject Number	Body weight	Baseline Viral load	*Treatment	SVR72	Genotype	IL28B
1	70	4.816	A	Y	1a	C,T
2	69	6.681	C1	Y	1b	C,C
3	60	7.017	A	Y	1a	C,C
4	60	6.420	C2	Y	1a	C,T
5	79	6.865	A	Y	1b	C,C
6	67	6.795	B	Y	1b	C,C
7	72	6.883	A	Y	1b	C,T
8	97	6.686	C2	Y	1a	T,T
9	50	6.245	A	Y	1b	C,C
10	73	6.127	A	Y	1b	C,T
11	60	6.167	A	Y	1a	C,T
12	73	3.149	B	Y	1a	C,C
13	57	4.724	C1	Y	1b	C,C
14	70	6.639	C2	Y	1b	C,T
15	70	5.808	B	Y	1b	C,T
16	68	5.220	A	Y	1b	C,T
17	68	7.057	B	Y	1b	C,C
18	55	4.700	C1	Y	1b	C,C
19	64	5.299	B	Y	1b	C,T
20	65	6.267	B	Y	1b	C,T
21	65.5	6.600	B	Y	1b	C,T
22	90.5	7.037	A	Y	1b	C,T
23	112.1	6.486	C2	Y	1a	T,T
24	59.8	5.439	C2	Y	1b	T,T
25	75	6.486	B	N	1a	C,T
26	91	7.143	A	Y	1a	C,C
27	75	7.057	B	Y	1a	C,T
28	60	5.874	B	N	1a	C,T
29	55	6.262	C2	Y	1a	C,C
30	70	6.356	C1	Y	1b	C,T
31	69	5.671	C1	Y	1a	T,T
32	67	6.114	A	Y	1b	C,C
33	64	5.953	C2	Y	1a	T,T
34	85	6.470	A	Y	1b	C,T
35	52	6.286	A	Y	1b	T,T
36	87	6.471	B	N	1b	C,T
37	81.8	6.867	A	Y	1b	C,T
38	76.7	5.978	C2	Y	1b	T,T
39	77.6	6.386	B	N	1b	C,T

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Subject Number	Body weight	Baseline Viral load	*Treatment	SVR72	Genotype	IL28B
40	68	5.456	C1	Y	1b	C,T
41	87.5	5.645	A	Y	1b	T,T
42	65	5.763	A	N	1b	T,T
43	60	6.100	A	Y	1b	C,T
44	76.5	5.884	A	Y	1b	C,T
45	71.3	6.286	C2	N	1b	C,T
46	60	6.158	A	Y	1b	C,C
47	92	4.582	A	Y	1b	C,C
48	66	7.417	A	Y	1b	C,C
49	83	6.053	B	N	1b	T,T
50	51	5.607	A	Y	1b	T,T
51	73	6.283	B	N	1b	C,T
52	64	5.730	B	Y	1b	C,C
53	63	6.648	C2	N	1b	C,T
54	69	5.607	C2	Y	1b	T,T
55	84	6.949	C2	Y	1b	C,T
56	90	5.640	B	Y	1b	T,T
57	59	5.688	A	Y	1b	C,T
58	66.3	5.587	C2	Y	1a	T,T
59	84	6.182	C1	Y	1b	C,C
60	90	7.083	B	Y	1b	C,C
61	83	5.998	A	Y	1b	C,T
62	102	6.806	B	N	1b	C,T
63	82.5	6.834	C2	N	1b	C,T
64	97.5	6.611	A	N	1b	T,T
65	70	6.580	B	Y	1b	C,C
66	92	6.550	A	N	1b	C,T
67	81.5	6.629	C1	Y	1b	C,C
68	67	6.161	A	Y	1b	C,C
69	90	6.155	C2	Y	1b	T,T
70	62	7.021	A	Y	1b	C,C
71	77	6.725	C2	Y	1b	C,C
72	74	5.829	C2	N	1b	T,T
73	75	5.324	A	Y	1b	C,T
74	50	6.632	B	N	1b	C,C
75	69	6.620	B	Y	1b	C,T
76	80	5.500	B	Y	1b	C,C
77	65	6.561	B	Y	1b	C,C
78	58	5.498	B	Y	1b	C,T
79	61	5.734	C2	Y	1b	T,T

Subject Number	Body weight	Baseline Viral load	*Treatment	SVR72	Genotype	IL28B
80	77	5.903	B	Y	1b	C,T
81	78.4	6.763	C2	Y	1b	C,C
82	71	5.913	C2	Y	1b	C,T
83	78	6.310	C2	Y	1b	C,C
84	85	6.993	A	Y	1a	C,T
85	83	6.487	C2	Y	1b	C,C
86	66	5.680	A	Y	1b	C,T

* Treatment group A: DEB025 600 mg BID/600 mg QD plus Peg-IFN/RBV fixed-duration 48 weeks; group B: DEB025 600 mg BID/600 mg QD plus Peg-IFN/RBV fixed-duration 24 weeks; group C1: DEB025 600 mg BID/600 mg QD plus Peg-IFN/RBV response-guided treatment 24 weeks; group C2: DEB025 600 mg BID/600 mg QD plus Peg-IFN/RBV response-guided treatment 48 weeks.

Conclusion:

Consistent with previous findings, this targeted pharmacogenetic analysis supports that HCV patients of IL28B CC genotype, compared to patients of CT/TT genotype, responded better to DEB025-containing regimens in DEB-025-HCV-203 and DEB-025-HCV-205, reflected by greater rates of RVR and SVR72 respectively.

Date of Clinical Trial Report

25-Oct-2013