# TECHNICAL SUMMARY OF RESULTS

## 2008-004605-34 [Debio 025-HCV-205]

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| **Sponsor:** Debiopharm S.A. | **Tabulated Study Report** | | **(For National Authority Use Only)** |
| **Name of Finished Product:** | | | |
| **Name of Active Ingredient:** Debio 025 | **Page:** | **Number:** | |

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| **Study Title** | A multicentre, randomised, double-blind, placebo-controlled, parallel-group phase II study on the efficacy and safety of Debio 025 combined with peg-IFNα2a and ribavirin in treatment naive chronic hepatitis C genotype 1 patients (2008-004605-34 [Debio 025-HCV-205]) |
| **Principal Investigators** | **Prof. Stefan Zeuzem**<br>**Prof. Robert Flisiak** |
| **Study Centres** | **Belgium**: Brussels, Gent.<br>**France**: Creteil, Lyon, Nice, Paris (2 sites), Pessac, Vandoeuvres-les-Nancy.<br>**Germany**: Berlin, Dusseldorf (2 sites), Essen, Frankfurt am Main, Freiburg, Hannover, Heidelberg, Mainz.<br>**Italy**: Bologna, Milan, Palermo.<br>**Poland**: Bialystok, Bydgoszcz, Chorzów, Kielce, Kraków, Lódz, Warszawa.<br>**Romania**: Bucharest (3 sites), Iasi.<br>**Spain**: Barcelona, Madrid, Sevilla. |
| **Publication (reference)** | Not applicable |
| **Clinical Phase** | IIb |
| **Study Dates** | First patient in: 06-Jan-2009<br>Last patient out: 06-Sep-2010 |
| **Objectives** | **Primary objective**<br>The primary objective was to evaluate whether 48-week triple therapy peg-IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day + Debio 025 600 mg significantly increases the proportion of patients who achieve SVR at Week 72 (i.e., HCV RNA < 10 IU/mL 72 weeks after treatment start), compared with standard 48-week peg IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day therapy (SOC) in treatment naïve chronic hepatitis C genotype 1 patients.<br>**Secondary objectives**<br>1. To evaluate whether 24-week triple therapy peg-IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day + Debio 025 600 mg significantly increases the proportion of patients who achieve SVR at Week 72 (i.e., HCV RNA < 10 IU/mL 72 weeks after treatment start) compared to SOC treatment. |

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| **Objectives (cont'd)** | 2. To evaluate whether the 24-/48-week response-guided triple therapy peg-IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day + Debio 025 600 mg significantly increases the proportion of patients who achieve SVR at Week 72 (i.e., HCV RNA < 10 IU/mL 72 weeks after treatment start) compared to SOC treatment.<br>3. To evaluate whether any of the different peg-IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day + Debio 025 600 mg triple therapies significantly increases the proportion of patients who achieve SVR 12 (i.e., HCV RNA < 10 IU/mL 12 weeks after treatment end), independently of treatment duration, compared to SOC treatment.<br>4. To evaluate whether any of the different peg-IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day + Debio 025 600 mg triple therapies significantly increases the proportion of patients who achieve SVR 24 (i.e., HCV RNA < 10 IU/mL 24 weeks after treatment end), independently of treatment duration, compared to SOC treatment.<br>5. To evaluate whether triple therapy peg-IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day + Debio 025 600 mg significantly increases the proportion of patients who achieve RVR (HCV RNA < 10 IU/mL after 4 weeks of treatment) compared to SOC treatment.<br>6. To evaluate whether triple therapy peg-IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day + Debio 025 600 mg significantly increases the proportion of patients who achieve cEVR (HCV RNA < 10 IU/mL after 12 weeks of treatment) compared to SOC treatment.<br>7. To evaluate whether triple therapy peg-IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day + Debio 025 600 mg significantly increases the proportion of patients who achieve EVR (HCV RNA decrease of > 2 $\log_{10}$ or < 10 IU/mL after 12 weeks of treatment) compared to SOC treatment.<br>8. To evaluate whether any of the different peg-IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day + Debio 025 600 mg triple therapies significantly increase the proportion of patients who achieve ETR (HCV RNA < 10 IU/mL at the end of treatment) compared to SOC treatment.<br>9. To explore if there is any difference in ETR (HCV RNA < 10 IU/mL at treatment end), SVR 24 (HCV RNA < 10 IU/mL 24 weeks after treatment end) or SVR at Week 72 (HCV RNA < 10 IU/mL 72 weeks after treatment start) between the three Debio 025 treatment arms.<br>10. To explore if there is any difference in relapse rate or safety between the 4 study treatment arms (relapser is defined as a patient with undetectable HCV RNA < 10 IU/mL levels at the end of treatment which become detectable again during post-treatment follow up).<br>11. To evaluate the proportion of patients that normalise ALAT as a result of any of the investigational treatments.<br>12. To evaluate the safety profile of Debio 025 in each of the treatment arms tested.<br>13. To explore the potential of HCV to develop resistance against the treatment regimens studied by repeated sequencing of HCV strains.<br>14. To collect Debio 025 plasma concentration and pharmacogenetic data (genetic polymorphisms of cytochrome P450, biliary canalicular transporters, basolateral hepatocyte transporters, P-gP and Cyps, as well as gene expression profiles) for further population PK data analysis aiming to explore interindividual variability in Debio 025 exposure and potential factors (demographic, pathophysiological, or other) affecting Debio 025 disposition, efficacy and toxicity. |

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| **Methodology** | The study compared three Debio 025/peg-IFNα2a/ribavirin regimens to SOC treatment in treatment naïve chronic HCV genotype 1 patients. Patients were randomised into one of 4 arms (see table below) for a fixed treatment duration of 48 weeks (Treatments A and D) or 24 weeks (Treatment B), or a response-guided treatment duration of 24 or 48 weeks (Treatment C). Follow up lasted up to Week 72 in all treatment arms (i.e., 24 or 48 weeks after treatment end, depending on the treatment arm).<br><br>**Treatment A** 48 weeks: Peg-IFNα2a 180 µg sc once weekly for 48 weeks; Ribavirin 1000 or 1200 mg orally daily (weight based) for 48 weeks; Debio 025 600 mg orally twice daily for 7 days (loading dose) followed by 600 mg orally once daily for 47 weeks<br>**Treatment B** 24 weeks: Peg-IFNα2a 180 µg sc once weekly for 24 weeks; Ribavirin 1000 or 1200 mg orally daily (weight based) for 24 weeks; Debio 025 600 mg orally twice daily for 7 days (loading dose) followed by 600 mg orally once daily for 23 weeks<br>**Treatment C** 24 or 48 weeks (response-guided*): Peg-IFNα2a 180 µg sc once weekly for 24 or 48 weeks; Ribavirin 1000 or 1200 mg orally daily (weight based) for 24 or 48 weeks; Debio 025 600 mg orally twice daily for 7 days (loading dose) followed by 600 mg orally once daily for 23 or 47 weeks<br>**Treatment D** 48 weeks: Peg-IFNα2a 180 µg sc once weekly for 48 weeks; Ribavirin 1000 or 1200 mg orally daily (weight based) for 48 weeks; Debio 025 placebo 3 soft gel placebo capsules twice daily for 7 days followed by 3 soft gel placebo capsules once daily for 47 weeks<br><br>*In **Treatment Arm C**, patients who achieved RVR, defined as having undetectable HCV RNA (Roche COBAS® TaqMan LOD < 10 IU/mL) at week 4) were treated for a total of 24 weeks, whereas the other patients continued up to week 48. |
| **Number of Patients** | Planned (272), Enrolled (290), Safety (289), ITT (288), PP (158), PG Subset (260), PK subset (216) |
| **Diagnosis and Main Inclusion Criteria** | Treatment naïve HbsAg and HIV-1 negative chronic hepatitis C patients aged ≥ 18 and ≤ 65 years with a serological diagnosis of chronic hepatitis C viral infection genotype 1 for > 6 months, chronic liver disease consistent with chronic hepatitis C infection on a biopsy or FibroScan® obtained within the past 24 months (36 months for patients with incomplete/transition to cirrhosis), a normal or compensated liver function, absence of complicated portal hypertension, and plasma HCV RNA level lower limit ≥ 100 IU/mL |
| **Test Product** | Debio 025 200 mg soft gel capsules with matching placebo. |
| **Treatment Duration** | Fixed treatment duration of 48 weeks (Treatments A and D) or 24 weeks (Treatment B), or a response-guided treatment duration of 24 or 48 weeks (Treatment C) |

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| **Criteria for Evaluation** | **Primary efficacy endpoint**<br>Proportion of patients achieving SVR at Week 72 (HCV RNA < 10 IU/mL 72 weeks after treatment start)<br><br>**Secondary efficacy endpoints**<br>1. Proportion of patients achieving RVR (HCV RNA < 10 IU/mL after 4 weeks of treatment);<br>2. Proportion of patients achieving cEVR (HCV RNA < 10 IU/mL after 12 weeks of treatment);<br>3. Proportion of patients achieving EVR (HCV RNA decrease by > 2 $\log_{10}$ or undetectable [< 10 IU/mL] after 12 weeks of treatment);<br>4. Proportion of patients achieving ETR (HCV RNA < 10 IU/mL at treatment end);<br>5. Proportion of patients achieving SVR 12 (HCV RNA < 10 IU/mL 12 weeks after treatment end);<br>6. Proportion of patients achieving SVR 24 (HCV RNA < 10 IU/mL 24 weeks after treatment end);<br>7. Patients who develop a mutant viral strain selecting for resistance against treatment regimens;<br>8. Proportion of patients with abnormal ALAT at baseline who improve and/or normalise ALAT levels at treatment end.<br><br>**Additional efficacy endpoints**<br>o Proportion of patients with virological relapse defined as a patient with undetectable HCV RNA < 10 IU/mL levels at the end of treatment which become detectable again during post-treatment follow up<br>o Proportion of patients with virological breakthrough defined as a patient with a HCV RNA increase of > 1 log10 IU/mL from nadir during treatment or becoming detectable after previously being undetectable.<br><br>**Safety endpoints**<br>1. Incidence of AEs;<br>2. Change in vital signs;<br>3. Change in haematology, coagulation, biochemistry, and urinalysis;<br>4. Change in 12-lead ECG parameters (RR, PR, QRS, QT, QTcB, and QTcF intervals);<br>5. Changes in bone metabolism and bone density<br><br>**Pharmacogenetic endpoint**<br>The association between any of the investigated genetic polymorphisms and any of the predefined quantitative and qualitative phenotypes of virological response or phenotypic traits of serum bilirubin and bile acid increase. |

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| **Statistical Methods** | **Sample size**<br>Sample size was calculated to assess a difference in SVR at week 72 between the triple combination therapy regimen (Treatment A) and SOC treatment. For a comparison of two independent binomial proportions using Pearson's Chi-square statistic with a two-sided significance level of 0.05, a sample size of 61 patients per treatment group achieved a power of at least 0.8 when the proportions were 45% and 70%. To adjust for an anticipated withdrawal rate of 10%, 272 patients (68 per arm) were to be enrolled to achieve 244 patients.<br>**Randomisation**<br>Randomisation was performed by stochastic minimisation technique to balance study treatment groups using the factors baseline HCV RNA level ($\leq$ or > 600'000 IU/mL) and thrombocyte count ($\leq$ or > 120000/$mm^3$).<br>**Statistical analysis**<br>The global null hypothesis (Ho) is that there is no difference between study treatments and the alternative hypothesis (Ha) is that there is a true difference. Unless otherwise stated, the $\alpha$ risk p-values reported were two-sided and the statistical significance experiment-wise limit was set to 0.05.<br>The proportion of patients achieving RVR, cEVR, EVR, ETR, SVR 12, SVR 24, SVR at Week 72, the breakthrough and relapse rate, the proportion of patients with abnormal ALAT at baseline that normalise ALAT levels at the end of treatment were assessed by treatment arm and compared between treatment arms using Pearson's chi-square test or Fisher exact test when expected cell frequencies were < 5. *Adverse events*: Study TEAE frequencies were summarised by system organ class and preferred term by treatment arms, and analysed by the chi-square test, or by the Fisher exact test when expected cell frequencies were < 5. Adverse events were also tabulated by study treatment and by system organ class, along with severity grade and relationship to treatment. *Laboratory parameters and vital signs*: Change from baseline to last on-treatment was compared between treatment arms by ANOVA. Shift tables and scatter plots were provided. *ECG*: Change in 12-lead ECG parameters were analysed by ANOVA and by shift tables based on normal/abnormal classification. *Bone metabolism and bone density*: Changes in bone metabolism (CTX-1 and OC) and bone density of the spine and hip (BMD, t-score, and z-score) were analysed by ANOVA and shift tables.<br><br>*Pharmacogenetics analysis:* Frequency of genetic polymorphisms of CypA and B, IL28B and metabolic enzymes/transporters were calculated by treatment arm. General association between genetic polymorphisms and clinical phenotypes were analysed after adjustment for treatment by using CMH method or logistic regression. The relationship between SVR at Week 72 and the SNPs was analysed by treatment arm by using Pearson's chi-square test or Fisher exact test. |

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| **Summary and Conclusions** | **Efficacy:**<br><br>In the ITT population, 48-week triple therapy peg-IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day + Debio 025 600 mg (arm A) was significantly superior with respect to the proportion of patients who achieve SVR at Week 72 (75%) compared with standard (arm D) 48-week peg-IFNα2a 180 µg once weekly + ribavirin 1000 or 1200 mg/day therapy (54.9%) in treatment naïve chronic hepatitis C GT1 patients (p=0.013, Chi-square).<br><br>The proportion of patients achieving SVR 24 (HCV RNA < 10 IU/mL 24 weeks after treatment end) was respectively 76.1%, 53.1%, 69.0% and 54.9% in arm A, B, C and D. The difference between arm A and D was statistically significant (p=0.008, Chi-square).<br><br>Absence of EVR (viral reduction <2 log10 IU/mL or undetectable at week 12) in the triple-therapy arms was only observed in patients who discontinued Debio 025 treatment in the first weeks of treatment. The proportion of patients with virological breakthrough was small and not significantly different between the Debio 025 and control treatment arms.<br><br>**Pharmacogenetics:**<br><br>Strong associations were observed between IL28B polymorphisms and the viral responses and the viral load reduction starting from week 1 of treatment.<br><br>**Safety:**<br><br>**Adverse events:**<br>Overall, the incidence of adverse events (AE) was evenly distributed between the different Debio 025 and the SOC treatment arms. The most frequent AEs reported were: neutropenia, anaemia, headache, asthenia, influenza like illness, nausea, pyrexia and hyperbilirubinaemia. Anaemia, headache, nausea and hyperbilirubinaemia were more frequent in the triple therapy arms, while pyrexia was more frequent in the standard of care arm.<br><br>Thyroid dysfunction, a known complication of interferon based treatment, was more frequently reported in all Debio 025 treatment arms. The frequency of reversible Hyperbilirubinaemia and Jaundice are increased during Debio 025 treatment.<br><br>Increases in blood fibrinogen concentrations were observed in all treatment arms, but the effect size was larger in the treatment arms with Debio 025. The changes are reversible after treatment.<br><br>No death occurred during the study and no specific pattern of SAEs emerged that could have suggested a causal relationship with Debio 025 treatment.<br><br>**Laboratory parameters**:<br><br>Very small, but statistically significant differences between Debio 025 and placebo arms were observed for a number of biochemical parameters. Platelet reductions were significantly larger in the Debio 025 treatment arms compared to SOC + placebo.<br><br>**Vital signs and ECG**:<br><br>Debio 025 induces a small but statistically significant reduction in QTcB and QTcF interval.<br><br>**Bone metabolism and Bone mineral density**<br><br>Results of serum OC and CTX-1 indicate that treatment with peg-IFN alpha2a and ribavirin has a clear influence on serum parameters of bone turn-over. The addition of Debio 025, affect the changes observed in bone serum markers, with attenuation of the changes in osteocalcin and a larger increase in CTX-1. The changes seem reversible after treatment, but recovery time is prolonged. Sequential bone mineral density assessment did not reveal any significant effect of Debio 025 on bone mineralisation after 24 or 48 weeks of treatment. |

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| **Report Date** | 28-Mar-2011 |
| **Protocol Amendments:** | There were no global substantial amendments to the protocol during this study. |
| **GCP Conformance** | This study was performed in compliance with GCP including archiving of documents. |