Telaprevir Treatment of HIV/HCV Genotype 1 Patients with Severe Fibrosis: Efficacy Results to Week 16

Poster 663

A. Gori,[1] M. Doroana,[2] O. Chernova,[3] J. Rockstroh,[4] D. Bánhegyi,[5] C. Bergin,[6] G. Verucchi,[7] A. Hill,[8] B. Hadacek,[9] M. Nelson[10]

[1]San Gerardo Hospital, Division of Infectious Diseases, Monza, Italy; [2]Hospital de Santa Maria, Serviço de Doenças Infecciosas, Lisbon, Portugal; [3]State Healthcare Institution, Tolyatti, Russian Federation; [4]University Hospital Bonn, Department of Internal Medicine, Bonn, Germany; [5]Szent László Hospital, Budapest, Hungary; [6]St James's Hospital, Department of Genitourinary Medicine and Infectious Diseases, Dublin, Ireland; [7]University of Bologna, Division of Infectious Disease, Bologna, Italy; [8]Janssen Research & Development, High Wycombe, UK; [9]Janssen Pharmaceuticals, Paris, France; [10]Chelsea and Westminster Hospital, London, UK

Background and Aims

- Telaprevir is a hepatitis C virus (HCV) NS3•4A protease inhibitor approved for the treatment of chronic HCV genotype 1 infection in combination with pegylated-interferon (Peg-IFN, P) and ribavirin (RBV, R) (PR).[1,2]
- HEP3005 is an ongoing, open-label, international clinical trial of telaprevir for patients with human immunodeficiency virus (HIV)/genotype 1 HCV co-infection and either severe fibrosis or compensated cirrhosis.
- This interim analysis investigated the safety and efficacy of telaprevir in patients reaching Week 16.

HEP3005 Interim Analysis

- Design: multicenter, open-label, early access program of telaprevir in combination with PR.
- Inclusion: genotype 1, severe fibrosis (F3) or compensated cirrhosis (F4), HIV/HCV co-infection.
- Recruitment: 118 patients are being treated with telaprevir plus PR for 12 weeks, followed by PR alone for 36 weeks. Data to Week 16 available for 102 patients were included in the interim analysis.

Methods

- To have been enrolled in the early access program, each patient must have satisfied the following criteria:
  - Male or female, between the ages of 18 and 70
  - Have HCV genotype 1 with a quantifiable plasma HCV RNA
  - Co-infection with HIV-1 and/or HIV-2
  - On a stable, permissible highly active antiretroviral therapy regimen for more than 8 weeks before Day 1 without switches (CD4+ count ≥200 cells/mm^3 and HIV viral load <50 copies/mL) or not on antiretroviral treatment (CD4+ count ≥500 cells/mm^3 and HIV viral load ≤50,000 copies/mL)
  - Severe fibrosis (Metavir F3 or Ishak 3–4) or cirrhosis (Metavir F4 or Ishak 5–6) assessed by liver biopsy or noninvasive test
  - Have compensated liver disease (Child-Pugh Grade A)
  - A platelet count of at least 90,000 cells/mm^3, hemoglobin concentration ≥12 g/dL in females or ≥13 g/dL in males.
- Patients were treated with telaprevir and PR for 12 weeks, followed by PR alone for an additional 36 weeks (Figure 1).

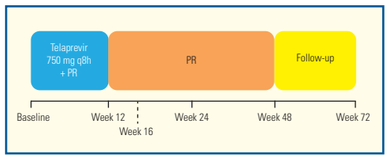

Figure 1. Schematic Overview of the Early Access Program.

Results

- This interim report describes the 16-week data available for 102 patients enrolled in to the program (intent-to-treat [ITT] population) (Figure 2).
- Overall, mean age was 44 years and mean weight was 75 kg; 82% were male and 100% White, 67% had HCV RNA levels ≥800,000 IU/mL, 59%/41% had bridging fibrosis/cirrhosis, 61% had genotype 1a, 34% were treatment naïve, 16% prior relapsers, 45% prior nonresponders and 4% had prior viral breakthrough (Table 1 and Figure 3). Baseline HIV RNA was <50 copies/mL in 96% of patients; mean baseline CD4+ count was 644 cells/μL (Table 1).

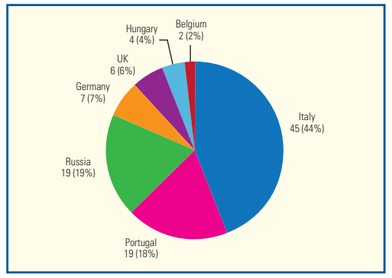

Figure 2. Recruitment by Country (ITT, N=102).

Table 1. Baseline Patient Demographics and HIV/HCV Disease Characteristics (ITT; N=102).

Baseline characteristic		Value
Age (years)	Mean (SD)	44 (8.0)
Sex	Male	84 (82%)
Race	White	102 (100%)
Body mass index (kg/m^2)	Mean (SD)	24.5 (3.5)
Weight (kg)	Mean (SD)	74.6 (13.0)
HCV RNA at baseline	<800,000 IU/mL	34 (33%)
	≥800,000 IU/mL	68 (67%)
Result of fibrosis assessment	Bridging fibrosis (F3)	60 (59%)
	Cirrhosis (F4)	42 (41%)
HCV genotype	1a	62 (61%)
	1b	27 (26%)
	Missing or unknown	13 (13%)
IL28B genotype	Missing or unknown	71 (70%)
	CC	10 (10%)
	CT	17 (17%)
	TT	4 (4%)
HIV RNA at baseline	<50 copies/mL	98 (96%)
	≥50 copies/mL	4 (4%)
CD4+ count at baseline (cells/mm^3)	<200	1 (1%)
	200–500	42 (41%)
	≥500	59 (58%)
	Mean (SD)	644 (319)
	Median (range)	571 (193–1854)

SD = standard deviation

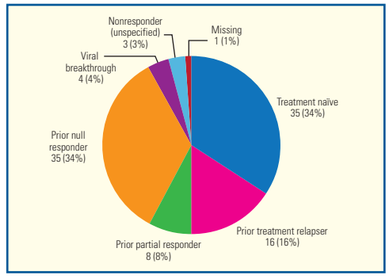

Figure 3. Baseline Characteristics: Prior Response (ITT, N=102).

- Overall, 99/102 patients continued antiretroviral treatment during the trial, while three were untreated. Nucleoside reverse transcriptase inhibitors (NRTIs) were tenofovir/emtricitabine for 62% and abacavir/lamivudine for 34% of patients. In addition, patients received either raltegravir (37%), efavirenz (21%) or atazanavir/ritonavir (46%) (Table 2).

Table 2. Concomitant Antiretroviral Therapies (ITT; N=102).

Concomitant mediation used		N (%)
Any use of antiretroviral medication		**99 (97)**
II	Raltegravir	38 (37)
NNRTI	Efavirenz	21 (21)
NRTI	TDF	63 (62)
	Emtricitabine	62 (61)
	Lamivudine	38 (37)
	Abacavir	35 (34)
PI	Atazanavir	47 (46)
	Ritonavir (low dose)	47 (46)
	Darunavir	1 (1)
Antiretroviral naïve		**3 (3)**

II = Integrase inhibitor
TDF = Tenofovir disoproxil fumarate

- The RBV dose was 1000–1200 mg/day in 94 patients (92%), and in 26% of patients the dose of RBV was reduced (Table 3).

Table 3. RBV Initial Dose and Dose Reductions (ITT; N=102).

RBV dose		Patients dose reduced, n (%)
Initial RBV dosage (mg/day)	800 (n=6)	2 (33)
	1000 (n=41)	13 (32)
	1200 (n=53)	12 (22)
	1400 (n=2)	0
	Total (N=102)	**27 (26)**

- Of the 18 patients who discontinued telaprevir, 15 patients also discontinued PR through Week 16 (Table 4).

Table 4. Discontinuation of Study Drugs for Any Reason (ITT; N=102).

Study drug	Number of discontinuations (%)
Telaprevir	18 (18)
RBV	17 (17)
Peg-IFN	17 (17)
Trial termination	6 (6)

Efficacy data

- Of the 102 patients enrolled, 65 (64%) had undetectable HCV RNA by Week 4, with 86 (84%) undetectable at Week 12 and extended rapid virologic response (eRVR) was 65/102 patients (64%). Responses for sub-groups of patients are shown in Figures 4 and 5. Of the other 16 patients at Week 12, three discontinued for a virologic endpoint, two had detectable HCV RNA levels (<25 IU/mL), six had HCV RNA levels >1000 IU/mL, two discontinued for adverse events and three discontinued for other reasons.
- The mean reduction in CD4+ count to Week 12 was 267 cells/mm^3 (Figure 6). At Week 12, 78 out of 81 patients (96%) had HIV RNA <50 copies/mL (on-treatment analysis) (Figure 7).

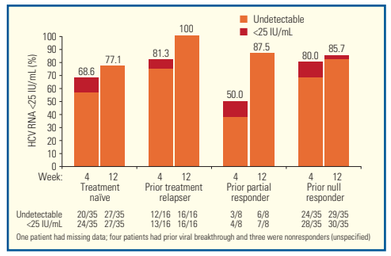

Figure 4. HCV RNA <25 IU/mL (Detectable and Undetectable) at Week 4 and 12: Main Subgroups.

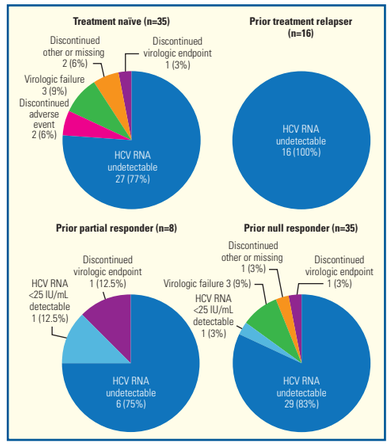

Figure 5. Outcome of Treatment at Week 12, by Prior Treatment.

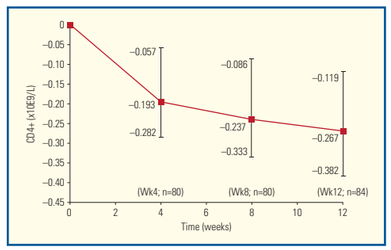

Figure 6. Changes from Baseline in Mean (Interquartile Range) CD4+ Count Over Time.

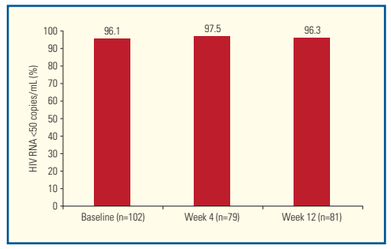

Figure 7. Percentage of Patients with HIV RNA <50 copies/mL.

Safety data

- The most common Grade 2–4 treatment related adverse events were anemia (12%), thrombocytopenia (8%), asthenia (7%), and rash (6%) (Table 5, Figures 8 and 9). Anemia was treated primarily with ribavirin dose reduction and epoetin (Tables 3 and 6).

Table 5. Grade 2–4 Adverse Events Reported by at Least 2% of Patients (Telaprevir Related).

Adverse event, n (%)	All (N=102)
Patients with one or more Grade 2–4 AE	**37 (36)**
Anemia SSC	12 (12)
Thrombocytopenia SSC	8 (8)
Asthenia	7 (7)
Rash SSC	6 (6)
Nausea	6 (6)
Neutropenia SSC	4 (4)
Fatigue	4 (4)
Hyperbilirubinemia	3 (3)
ECG/QT SSC	2 (2)
Pruritus SSC	2 (2)
Hypophosphatemia	2 (2)
Headache	2 (2)

SSC = special search category
ECG = electrocardiogram

Table 6. Concomitant Therapies: Anti-anemics and Blood Substitutes (ITT; N=102).

Concomitant medication used	n (%)
Any of the following	**12 (12)**
Epoetins (all types)	10 (10)
Any blood transfusion (including red blood cells)	3 (3)
Other	1 (1)

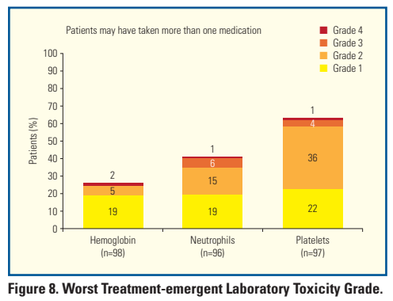

Figure 8. Worst Treatment-emergent Laboratory Toxicity Grade.

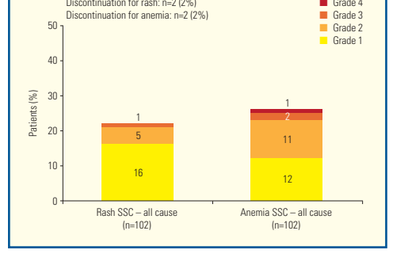

Figure 9. Summary of Rash and Anemia (SSC) by Grade.

- Five patients discontinued telaprevir for adverse events (two for anemia, two for rash, one for asthenia) (Table 7).

Table 7. Discontinuation of Telaprevir Due to Adverse Events Reported by at Least 1% of Patients.

Adverse event, n (%)	All (N=102)
Patients with one or more adverse events leading to discontinuation	**5 (5)**
Anemia SSC	2 (2)
Rash SSC	2 (2)
Asthenia	1 (1)
Apathy	1 (1)
Suicidal ideation	1 (1)

Conclusions

- In this interim analysis of the telaprevir early access program for HIV/HCV co-infected patients with severe fibrosis or compensated cirrhosis (N=102): 67% had baseline HCV RNA ≥800,000 IU/mL; 41% had F4, 59% had F3 and 46% were prior partial responders, null responders or viral breakthroughs.
- A total of 64% of patients had HCV RNA <25 IU/mL undetectable at Week 4 (RVR); 64% had HCV RNA <25 IU/mL undetectable at Weeks 4 and 12 (eRVR) and 84% had HCV RNA <25 IU/mL undetectable at Week 12 (ITT). HIV RNA remained suppressed in patients continuing on HCV treatment. The most common adverse events were hematological; 3% developed Grade 3 or 4 anemia (all cause; 2% discontinued telaprevir) and 1% developed Grade 3 rash (all cause; 2% discontinued telaprevir).

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A. Gori has received consultant honoraria, grant and research support from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp and Dohme and ViiV Healthcare; **M. Doroana** has received consultant honoraria and served on advisory boards for Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals and Merck Sharp and Dohme; **O. Chernova** has received research support from GlaxoSmithKline and Janssen Pharmaceuticals; **J. Rockstroh** has received honoraria for participating in educational events or consulting from Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Bionor, Gilead Sciences, Janssen Pharmaceuticals, Merck. Novartis, Tibotec, Vertex and ViiV Healthcare; **D. Bánhegyi** has received research support, consultant honoraria and travel grants from Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp and Dohme and Janssen Pharmaceuticals; **C. Bergin** has received research support, consultant honoraria or travel grants from Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp and Dohme, Gilead Sciences, Abbvie and Janssen Pharmaceuticals; **G. Verucchi** has received consultant honoraria, grant and research support from Bristol-Myers Squibb, Janssen Pharmaceuticals, Merck Sharp and Dohme and Roche; **A. Hill** is a consultant for Janssen Pharmaceuticals; **B. Hadacek** is an employee of Janssen Pharmaceuticals; **M. Nelson** has served on advisory boards and received honoraria and research grants from Janssen Pharmaceuticals, Merck Sharp and Dohme, Boehringer Ingelheim, Bristol-Myers Squibb, Abbott Pharmaceuticals and Gilead Sciences.