1. ABSTRACT

Title

An Observational Post-Authorization Safety Study (PASS) of Victrelis™ (boceprevir) among Chronic Hepatitis C patients.

Keywords

Victrelis™, Incivo™, Anemia, Neutropenia, Thrombocytopenia, Serious Rash.

Rationale and background

This post-authorization safety study (PASS) was assessing the utilization of Victrelis™ and the management of hematologic health outcomes of interest (HOIs - anemia, neutropenia, and thrombocytopenia) under conditions of routine clinical care among patients being treated with Victrelis™ in the real-world. [redacted]

Research question and objectives

Primary objectives:

The primary objectives of this study were:

- To describe drug utilization patterns among genotype-1 treatment-naive and/or previous treatment failure patients initiating treatment with Victrelis™ in combination with PR, Incivo™ in combination with PR, or PR alone (without other DAAs)
- To describe baseline patient and disease characteristics among genotype-1 treatment-naive and/or previous treatment failure patients initiating treatment with Victrelis™ in combination with PR, Incivo™ in combination with PR, or PR alone (without other DAAs)
- To describe the clinical management of pre-specified protocol-defined HOI: anemia, neutropenia, thrombocytopenia and rash in treatment-naive and/or previous treatment failure patients that are initiating treatment with Victrelis™ in combination with PR, Incivo™ in combination with PR, or PR alone (without other DAAs).

Subjects and study size, including dropouts

Patients

Inclusion criteria

All inclusion criteria were reviewed by the investigator or qualified designee to ensure that the subject qualified for the study.

The following patients were selected for the study:

1) CHC genotype-1 infection documented in the medical chart.
2) > 18 years of age.
3) Previously untreated before the current therapy; OR patient who failed his/her previous therapy.
4) Subject agreed to participate in the study by giving written informed consent.
5) Subject signed informed consent prior to the start of new treatment for Hepatitis C or within the first 8 weeks of treatment (Prospective enrollment is preferred, i.e. subject signed informed consent prior to the start of new treatment for Hepatitis C)

Exclusion criteria:

The following patients were not selected for the study:

1) Patients taking part in a clinical trial or in any study where a patient was receiving care outside of normal clinical practice for HCV.

Planned sample size

The sample size estimation was based on providing precision on the primary criteria "proportion of patients with an HCV genotype-1 infection treated with Victrelis™ in combination with PR".

Therefore, the study has targeted an overall recruitment of 1,000 treated CHC patients to yield approximately 200 Victrelis™ patients. This number was deemed as appropriate to provide a description of proportion of Victrelis™ patients with any of the protocol-defined HOIs with relatively good precision.

Results

This report presents the final results of the study.

A total of 713 patients were included in the study by 82 physicians between 29 May 2012 (1st patient enrolled) and 30 June 2014 (last patient enrolled): 156 in France, 174 in Germany, 258 in Spain, and 125 in the UK. The date of the last patient out was 6 July 2015.

Overall, 679 patients (95.2%) were included in the Analysis population and 34 (4.8%) were excluded from analyses because they did not meet the selection criteria.

In the analysis population, CHC treatment regimen was initiated before the signature of the informed consent in 26.4% of patients (1 to 8 weeks before informed consent signature), the day of the signature of the informed consent in 33.0% of patients and after the signature of the informed consent in 40.6% of patients (1 to 13 weeks after informed consent signature). Most of patients were included prospectively (73.6%) and before the first data collection point at week 8. The change in inclusion criteria (protocol amendment 3) allowing physicians to include patients until the first update visit at week 8 was made in order to improve prospective inclusions of patients.

At site level, 79 Drug Utilization Questionnaires (DUQ) were collected between 27 September 2012 and 30 October 2014.

Physician participation

Physicians were recruited in 4 European countries: France, Germany, Spain and the UK. Of the 827 physicians contacted, 89 participated and 738 did not participate in the study.

The main reasons for non-participation were 'non-responding physician' (53.6%), 'not qualified' (14.5%), 'not interested in study objectives' (8.9%), 'never accept to participate in studies' (8.7%) and 'lack of time' (8.4%). Of the 381 non-responding physicians, 305 never responded to the study-presentation letter and to the 3 rounds of phone calls conducted by CRAs. Other non-responding physicians corresponded to wrong addresses or contacts, or physicians no longer working at the site or absent for a long period.

Considering reachable and eligible physicians (practicing physicians with correct contact details and qualified), the participation rate was 12.7%.

Responding and non-responding physicians differed by country distribution. Germany was overrepresented (37.0% in responding vs. 11.5% in non-responding physicians) and the UK was underrepresented (16.1% in responding vs. 40.2% in non-responding physicians). This higher rate of responding physicians in Germany is explained by the fact that the MAH subsidiary in Germany provided more active support in recruitment compared to the other countries.

Most of responding and non-responding physicians were gastroenterologists and practiced at hospital. This is an expected finding since Chronic Hepatitis C is treated at hospital in most

The third primary and the secondary objectives were analyzed per CHC treatment groups of exposure (PR, PR + Victrelis™, PR + Incivo™ and PR + Incivo™ + Victrelis™). These groups are non mutually exclusive, meaning that patients could successively be assigned to different treatment groups of exposure depending on their treatment regimen. The total number of patient-days was 22061 in the PR group of exposure, 60443 in the PR + Victrelis™ group of exposure, 63259 in the PR + Incivo™ group of exposure, and 1458 in the PR + Incivo™+ Victrelis™ group of exposure.

- First primary objective: Drug utilization patterns
  - At site level (physician survey)

DUQ cross-sectional data collected from physicians at site level between 27 September 2012 and 30 October 2014 showed that overall, 15.5% of patients at the physician sites were treated with PR only, 33.4% with PR + Victrelis™ and 51.1% with PR + Incivo™. Several inter-country variations were also observed.

- At patient level (patient cohort)

The drug utilization patterns observed among the 679 patients included in the Analysis population were somewhat different than the DUQ data and showed that 10.9% of patients were treated with PR only, 43.9% with PR + Victrelis™ and 45.2% with PR + Incivo™ between 29 May 2012 (1st patient enrolled) and 30 June 2014 (last patient enrolled). The patient enrollment for both DAAs was therefore comparable.

The different estimates of utilization based on the DUQ versus that from enrolled patients are likely due to differences in methodology. While the DUQ represents data on all patients of the site receiving treatment at one point of time in clinical practice, the enrolled patients represent a prospective subset of patients receiving treatment that met the inclusion criteria and have consented to participate in the study since first patient enrolled (29 May 2012). The average market share of Victrelis™ between 2011-2013 in Europe was 54.7% (MAH internal data). Drug utilization patterns observed from enrolled patients were therefore closer to market-share data than estimates based on the DUQ.

The duration of the lead-in period was in accordance with Victrelis™ SmPC for the majority of patients (63.1%). However an off-label use of Victrelis™ lead-in period (<26 days or >30 days) was reported in 36.9% of patients, although this may be considered as a strict criterion.

In accordance with Victrelis™ SmPC, most patients of the PR + Victrelis™ group discontinued Victrelis™ between week 24 and week 40. Likewise, most patients of the PR + Incivo ™ group discontinued Incivo ™ before week 16.

Victrelis™ groups (8.6% and 5.6% of liver assessments respectively). Most of the patients did not have severe hepatic disease at baseline as indicated by the necroinflammatory, the steatosis and the Child-Pugh scores. No hepatic encephalopathies were reported among patients in the analysis population.

Comorbidities were reported at baseline in 51.1% of all patients. Cardiovascular diseases and diabetes were the most frequent comorbidities reported. Patients with at least one comorbidity were more frequently treated with PR + Victrelis™ (48.8%) than with PR + Incivo™ (39.2%) or PR only (11.9%). History of cardiovascular disease and diabetes was more frequent in the PR + Victrelis™ group (19.6% and 13.2% respectively) than in the PR only (12.2% and 6.8% respectively) and PR + Incivo™ groups (15.5% and 6.9% respectively). Diagnosis of HIV was reported in 3.7% of patients (8.1% in the PR only, 2.4% in the PR + Victrelis™ and 4.0% in the PR + Incivo™ group) and diagnosis of HBV in 2.5% of patients (2.7% in the PR only, 1.4% in the PR + Victrelis™ and 3.6% in the PR + Incivo™ group).

At least one HOI (anemia, neutropenia, thrombocytopenia or rash (all grades)) had previously been experienced by 116 patients (17.1%) within the 3 months preceding the initiation of the CHC treatment regimen. Among them, 11 patients had at least one protocol-defined HOI (anemia <10 g/dl, grade 3/4 neutropenia, grade 3/4 thrombocytopenia, or serious rash). Patients with HOI within the 3 months preceding the initiation of the CHC treatment regimen were more frequently treated with PR + Victrelis™ than patients with no baseline diagnosis of HOI (50.9% vs. 41.5%). The occurrence of HOIs in the 3 months preceding the initiation of the CHC treatment regimen was higher in the PR + Victrelis™ and in the PR only group (respectively 21.6% and 19.8% of patients with at least one previous HOI) than in the PR + Incivo™ group (13.4% with at least one previous HOI). At CHC treatment initiation, the majority of the HOIs at baseline were unresolved with the exception of rash episodes, which were predominantly resolved.

Table b (part 1 of 2): Baseline disease characteristics

	CHC treatment regimen			Total Analysis population N=679
	PR only N=74	PR+Victrelis™ N=298	PR+Incivo™ N=307	
Time since HCV infection diagnosis (yrs)				
Missing patients	25	109	105	239
Mean (SD)	5.6 (7.6)	8.3 (8.3)	8.9 (8.3)	8.3 (8.3)
Median	2.0	5.5	7.1	5.4
Patient status, N (%)				
Missing	0	0	0	0
Treatment naïve	53 (71.6%)	158 (53.0%)	145 (47.2%)	356 (52.4%)
Treatment failure	21 (28.4%)	140 (47.0%)	165 (52.8%)	323 (47.6%)
Viral load value, N (%)				
Not available	0	15	16	31
≥800,000 IU/mL or ≥2,000,000 RNA copies/mL)	39 (52.7%)	182 (64.3%)	197 (67.7%)	418 (64.5%)

A total of 763 protocol-defined HOI episodes were reported (377 anemia (<10 g/dL), 214 grade 3/4 neutropenia, 137 grade 3/4 thrombocytopenia, and 35 serious rash episodes):

- In the PR group of exposure, 29 anemia (<10 g/dL) episodes (including 6 serious episodes), 30 grade 3/4 neutropenia episodes (no serious episode), 26 grade 3/4 thrombocytopenia episodes (including 1 serious episode), and 1 serious rash episode (1 serious episode) were reported.
- In the PR + Victrelis™ group of exposure, 178 anemia (<10 g/dL) episodes (including 12 serious episodes), 116 grade 3/4 neutropenia episodes (including 3 serious episodes), 53 grade 3/4 thrombocytopenia episodes (including 1 serious episode), and 7 serious rash episodes (no serious episode) were reported.
- In the PR + Incivo™ group of exposure, 166 anemia (<10 g/dL) episodes (including 3 serious episodes), 65 grade 3/4 neutropenia episodes (no serious episodes), 56 grade 3/4 thrombocytopenia episodes (including 1 serious episode), and 27 serious rash episodes (including 4 serious episodes) were reported.
- In the PR + Incivo™ + Victrelis™ group of exposure, 4 anemia (<10 g/dL) episodes (no serious episodes), 3 grade 3/4 neutropenia episodes (no serious episodes), 2 grade 3/4 thrombocytopenia episodes (no serious episodes), and no serious rash episodes were reported.

The median time from start of treatment exposure to the first protocol-defined HOI was respectively 11.3 weeks for anemia (<10 g/dL) episodes, 11.6 weeks for grade 3/4 neutropenia episodes, 6.4 weeks for grade 3/4 thrombocytopenia episodes and 10.7 weeks for serious rash episodes. Overall, the median time from start of exposure to the first anemia (<10 g/dL) episode and to the first grade 3/4 neutropenia episode was shorter in the PR group of exposure (4.0 weeks and 3.4 weeks respectively) than in the PR + Victrelis™ (7.4 weeks and 8.4 weeks respectively) and PR + Incivo™ (7.8 weeks and 12.5 weeks respectively) groups of exposure. For grade 3/4 thrombocytopenia, the median time from start of exposure to the first episode was shorter in the PR and PR + Incivo™ groups of exposure (4.0 weeks in both groups) than in the PR + Victrelis™ group of exposure (8.5 weeks).

Table c (Part 1 of 2): HOI overview

	CHC treatment group of exposure				Total Analysis Population N=679
	PR N=394	PR + Victrelis™ N=298	PR + Incivo™ N=307	PR + Incivo™ + Victrelis™ N=6	
Anemia (<10 g/dL)					
Number of patients with at least one episode	27	133	126	4	281
Total number of episodes	29	178	166	4	377
Time to the 1st episode (weeks)					
Missing patients	0	0	0	0	0
Mean (SD)	8.9 (12.5)	9.8 (8.6)	8.4 (5.4)	12.4 (5.6)	11.3 (8.4)

respectively) than in the UK or in Germany (8.8% and 7.1% respectively). ESA was mainly administered in patients aged >50 years; the proportion of episodes treated with ESA was slightly higher in females (48.9%) than in males (42.1%). ESA was more frequently used in patients with previous treatment failure (52.8%) than in treatment-naïve patients (37.3%). ESA was more frequently administered in patients with comorbidity, in particular in patients with diabetes, cardiovascular disease or hypothyroidism. In addition, ESA was more frequently used in patients with fibrosis stage F3/F4 (56.0%) than in patients with fibrosis stage F1/F2 (36.2%).

Table d: Management of Anemia (<10 g/dL)

	CHC treatment group of exposure				Total number of anemia episodes (Analysis population)
	PR	PR + Victrelis™	PR + Incivo™	PR + Incivo™ + Victrelis™	
	N=29	N=178	N=166	N=4	N=377
At least one intervention to manage the HOI, N (%)					
Missing	0	0	0	0	0
Yes	23 (79.3%)	129 (72.5%)	116 (69.9%)	3 (75.0%)	271 (71.9%)
If yes:					
ESA					
Missing	2	5	2	0	9
N (%)	11 (52.4%)	57 (46.0%)	50 (43.9%)	2 (66.7%)	120 (45.8%)
Blood transfusion					
Missing	2	4	1	0	7
N (%)	11 (52.4%)	25 (20.0%)	28 (24.3%)	1 (33.3%)	65 (24.6%)
CHC treatment modification					
Missing	0	0	0	0	0
N (%)	19 (82.6%)	112 (86.8%)	91 (78.4%)	3 (100.0%)	225 (83.0%)

Of the 214 grade 3/4 neutropenia, 29.0% were managed and 71.0% were not managed. The management of grade 3/4 neutropenia consisted of CHC regimen modification and G-CSF (59.7% and 48.4% of managed episodes). No grade 3/4 neutropenia led to hospitalization or urgent care visit (Table e).

Grade 3/4 neutropenia episodes were more frequently managed in patients whose physician practiced in academic/non-academic hospital only (32.1%). The proportion of managed grade 3/4 neutropenia episodes was higher in the UK and in Germany (40.0% and 35.5% respectively) than in France or in Spain (24.6% and 24.4% respectively). Granulocyte colony-stimulating factor was frequently used in France (92.9% of managed grade 3/4 neutropenia episodes). The proportion of managed grade 3/4 neutropenia episodes tended to increase with age and was similar in males and in females. Grade 3/4 neutropenia episodes were more frequently managed in patients with previous treatment failure than in treatment-naïve patients (31.5% vs. 26.4% respectively). In particular, granulocyte colony-stimulating factor was more frequently used in patients with previous treatment failure than in treatment-naïve patients (61.8% vs. 32.1% of managed episodes). The proportion of managed grade 3/4 neutropenia episodes was similar in patients with low or high baseline viral load value, and

Table f: Management of Grade 3/4 Thrombocytopenia

	CHC treatment group of exposure				Total number of thrombocytopenia episodes (Analysis population)
	PR	PR + Victrelis™	PR + Incivo™	PR + Incivo™ + Victrelis™	
	N=26	N=53	N=56	N=2	N=137
At least one intervention to manage the HOI, N (%)					
Missing	0	0	0	0	0
Yes	11 (42.3%)	19 (35.8%)	18 (32.1%)	0 (0.0%)	48 (35.0%)
If yes:					
Thrombopoietin					
Missing	1	0	0	0	1
N (%)	3 (30.0%)	8 (42.1%)	2 (11.1%)	-	13 (27.7%)
Platelet transfusion					
Missing	1	0	0	0	1
N (%)	0 (0.0%)	1 (5.3%)	2 (11.1%)	-	3 (6.4%)
CHC treatment modification					
Missing	0	0	0	0	0
N (%)	11 (100.0%)	10 (52.6%)	15 (83.3%)	-	36 (75.0%)

Of the 35 serious rash episodes, 34 were managed (97.1%) and 1 episode was not managed. Most frequent treatments consisted of antihistamines, topical corticosteroids, and emollients/moisturizers. Additionally, 19 serious rash episodes were managed by drug discontinuation. Nine (9) serious rash episodes led to hospitalization or urgent care visit (Table g).

Most of HOIs were resolved at time of analysis (98.1% of anemia (<10 g/dL) episodes, 97.2% of grade 3/4 neutropenia episodes, 97.1% of grade 3/4 thrombocytopenia episodes and 88.6% of serious rash episodes). Median durations of resolved HOI episodes was longer in PR + Victrelis™ than in PR + Incivo™ group for anemia (<10 g/dL) (66.0 days vs. 43.0 days), grade 3/4 neutropenia (43.0 days vs. 29.0 days) and grade 3/4 thrombocytopenia episodes (82.0 days vs. 43.5 days). Longer event resolution in patients treated with Victrelis™ may be explained by the longer duration of Victrelis™ exposure as compared to Incivo™.

- The point estimate of serious rash incidence was higher in the PR + Incivo™ group of exposure (0.4 per 1000 patient-days, 95%CI: [0.281;0.630]) than in the PR + Victrelis™ and in the PR groups of exposure (0.1 per 1000 patient-days, 95%CI: [0.047;0.242] and 0.05 per 1000 patient-days, 95%CI: [0.001;0.253] respectively), with no overlap in the 95% confidence intervals.

The total number of patient-days was similar in PR + Victrelis™ and PR + Incivo™ groups, except for grade 3/4 neutropenia (respectively 48920 and 56974 patient-days).

Table h: Incidence of protocol-defined HOIs over the overall follow-up period

	CHC treatment group of exposure				All patients (Analysis population)
	PR N=394	PR + Victrelis™ N=298	PR + Incivo™ N=307	PR + Incivo™ + Victrelis™ N=6	N=679
Anemia (<10 g/dL)					
Incidence per 1000 patient-days	1.185	3.302	3.001	5.122	2.714
95% CI	[0.767;1.749]	[2.760;3.918]	[2.499;3.572]	[1.395;13.113]	[2.404;3.052]
Grade 3/4 Neutropenia					
Incidence per 1000 patient-days	1.305	1.656	0.807	3.195	1.194
95% CI	[0.860;1.899]	[1.315;2.058]	[0.591;1.077]	[0.659;9.337]	[1.010;1.402]
Grade 3/4 Thrombocytopenia					
Incidence per 1000 patient-days	0.835	0.757	0.596	1.556	0.701
95% CI	[0.495;1.319]	[0.544;1.027]	[0.413;0.832]	[0.188;5.622]	[0.566;0.859]
Serious Rash					
Incidence per 1000 patient-days	0.045	0.117	0.430	0	0.237
95% CI	[0.001;0.253]	[0.047;0.242]	[0.281;0.630]		[0.164;0.332]

It should be pointed out that the number of patient-days considering DAA exposure only was smaller in the PR + Incivo™ group of exposure than in the PR + Victrelis™ group of exposure. In order to assess the numerical imbalance, further incidence rate analyses were performed accounting for exposure of DAAs only. The results showed incidences of protocol-defined HOIs remained similar in patients exposed to Victrelis™ and tended to increase significantly in patients exposed to Incivo™ (Table i):

- Incidence of anemia (<10 g/dL) was lower in patients exposed to Victrelis™ than in patients exposed to Incivo™ (3.5 per 1000 patient-days, 95%CI: [2.883;4.097] vs. 4.9 per 1000 patient-days, 95%CI: [3.963;5.923]), with a slight overlap between 95% confidence intervals.
- Incidence of grade 3/4 neutropenia was higher in patients exposed to Victrelis™ (1.7 per 1000 patient-days, 95%CI: [1.346;2.118]) than in patients exposed to Incivo™ (0.9 per 1000 patient-days, 95%CI: [0.521;1.318]), with no overlap between 95% confidence intervals.
- Incidence of grade 3/4 thrombocytopenia was higher in patients exposed to Incivo™ (1.3 per 1000 patient-days, 95%CI: [0.854;1.831]) than in patients exposed to Victrelis™ (0.8 per 1000 patient-days, 95%CI: [0.563;1.073]), with overlapping 95% confidence intervals.

- Safety

All SAEs, solicited NSAEs (HOIs) and spontaneously reported NSAEs (non-HOI) that were related to Victrelis™, Incivo™, pegylated interferon and ribavirin (Merck or non-Merck manufactured) were collected in the e-CRF. All HOIs were reported as AEs to the health authorities.

Adverse events were described per CHC treatment regimen groups (mutually exclusive) with the same method used for the 1st and 2nd primary objective. As such, an event occurring during the PR lead-in period before Victrelis™ initiation, is still assigned to the PR + Victrelis™ group (unlike the methodology used for the third primary objective and for the second objective). The incidence of serious adverse events was analyzed per CHC treatment group of exposure (not mutually exclusive) with the same method used for the 3rd primary objective and the secondary objective.

- PR + Victrelis™ and PR + Incivo™ groups:

Among the 605 patients of the PR + Victrelis™ and PR + Incivo™ groups, 108 patients (17.9%) experienced at least one SAE (HOIs and AEs other than HOIs) and a total of 165 SAEs were reported (93 in the PR + Victrelis™ group and 72 in the PR + Incivo™ group) (Table j).

Most frequent SAEs (serious HOIs and other SAEs) were blood and lymphatic system disorders (25 patients), infections and infestations (25 patients) and gastrointestinal disorders (18 patients). One patient from the PR + Incivo™ group experienced a chronic obstructive pulmonary disease, which led to patient death ([redacted]

Overall, the incidence of SAEs (HOIs and AEs other than HOI) was similar in the PR + Victrelis™ and in the PR + Incivo™ groups: respectively 0.98 per 1000 patient-days (95% CI [0.737;1.280]) and 0.84 per 1000 patient-days (95% CI [0.625;1.110]).

In addition, 337 patients (55.7%) experienced at least one non-serious drug related HOI and a total of 681 non-serious drug related HOIs were reported (371 in the PR + Victrelis™ group and 310 in the PR + Incivo™ group). The proportion of patients who experienced at least one non-serious drug related anemia episodes (<10 g/dL) was similar in the PR + Victrelis™ group and in the PR + Incivo™ group (42.6% and 41.0% respectively). The proportion of patients who experienced at least one non-serious drug related grade 3/4 neutropenia episode and the proportion of patients who experienced at least one non-serious drug related grade 3/4 thrombocytopenia episode was higher in the PR + Victrelis™ group than in the PR + Incivo™ group (respectively 29.2% vs. 16.0% and 17.1% vs. 12.1%). Conversely, the proportion of patients who experienced at least one non-serious drug related serious rash episode was higher in the PR + Incivo™ group than in the PR + Victrelis™ group (6.8% vs. 2.3%).

Furthermore, 165 non-serious drug related AEs other than HOIs were reported in a total of 71 patients (11.7%).

Overall, the AEs reported in this study were consistent with the Victrelis™ safety profile.

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)