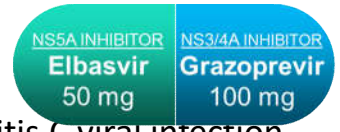
PP0214

Impact Of a 12-Week Oral Regimen of Elbasvir/Grazoprevir (EBR/GZR) On Health-related Quality of Life (HRQOL) and Fatigue In Treatment-Naïve Patients With Chronic Hepatitis C Virus (HCV) Genotype (GT) 1, 4, or 6 Infection: Data from the C-CORAL Study

Wendy Cheng[1], Abhasnee Sobhonslidsuk[2], Thuy Thi Thu Pham[3], Fu-Sheng Wang[4], Youn-Jae Lee[5], Chi-Jen Chu[6], Jidong Jia[7], Pauline Lindore[8], Liwen Liang[8], Barvara Evans[8], Joy Ginanni[8], Rohit Talwani[8], Jean Marie Arduino[8]

[1]Royal Perth Hospital, Perth, Australia; [2]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [3]Hoa Hao Medical Ltd Company, Hoa Hao Hospital, Ho Chi Minh, Vietnam; [4]Beijing 302 Hospital, Beijing, China; [5]Inje University Busan Paik Hospital, Busan, South Korea; [6]Taipei Veterans General Hospital, Taipei City, Taiwan; [7]Beijing Friendship Hospital, Capital Medial University, Beijing, China; [8]Merck & Co., Inc., Kenilworth, NJ, USA

Background



- Health-related quality of life (HRQOL) is diminished in patients with chronic hepatitis C viral infection
- As new IFN-and RBV-free direct-acting antiviral therapies for the treatment of chronic HCV infection are assessed, the impact of these therapies on the patients' HRQOL, including functional health, well-being and fatigue, is important to describe and evaluate
- EBR/GZR, a fixed-dose combination tablet administered once daily, without regard to food intake, is approved for the treatment of GT1 and GT4 HCV infections in a number of countries including the United States, Canada, and the European Union
  - Efficacious in treatment-naive & treatment-experienced compensated cirrhotic and non-cirrhotic patients with HCV, and in HIV/HCV co-infected patients [1,2]
  - Safety and efficacy also demonstrated in special populations including patients receiving opioid substitution therapy, patients with stage 4/5 chronic kidney disease and patients with inherited blood disorders. [3, 4, 5,6]
- A Phase 3, double-blind, placebo-control, randomized trial was conducted to assess the efficacy and safety profile of EBR/GZR in patients from China, Korea, Taiwan, Thailand, Vietnam, Russia and Australia
  - Data were presented for the ex-China cohort[7]:
    - SVR12 was 93% overall, and by genotype: 89% for GT1a, 99% for GT1b, 100% for GT4, 63% for GT6
    - The incidence of adverse events (AEs) was generally comparable between EBR/GZR and placebo including drug-related AEs (21% vs 20%) and serious AEs (1% vs 1%; none considered drug-related).
  - Updated efficacy and safety results, including data from the China cohort, to be presented on February 19th: Oral Presentation-Viral Hepatitis C-Therapeutics Approved Agents (OP248)
- An exploratory objective was to evaluate whether treatment with EBR/GZR impacts patient-reported outcomes (PRO) assessing HRQOL by
  - describing changes from baseline in HRQOL during treatment and follow-up within treatment groups and
  - comparing changes from baseline in HRQOL between treatment groups over time

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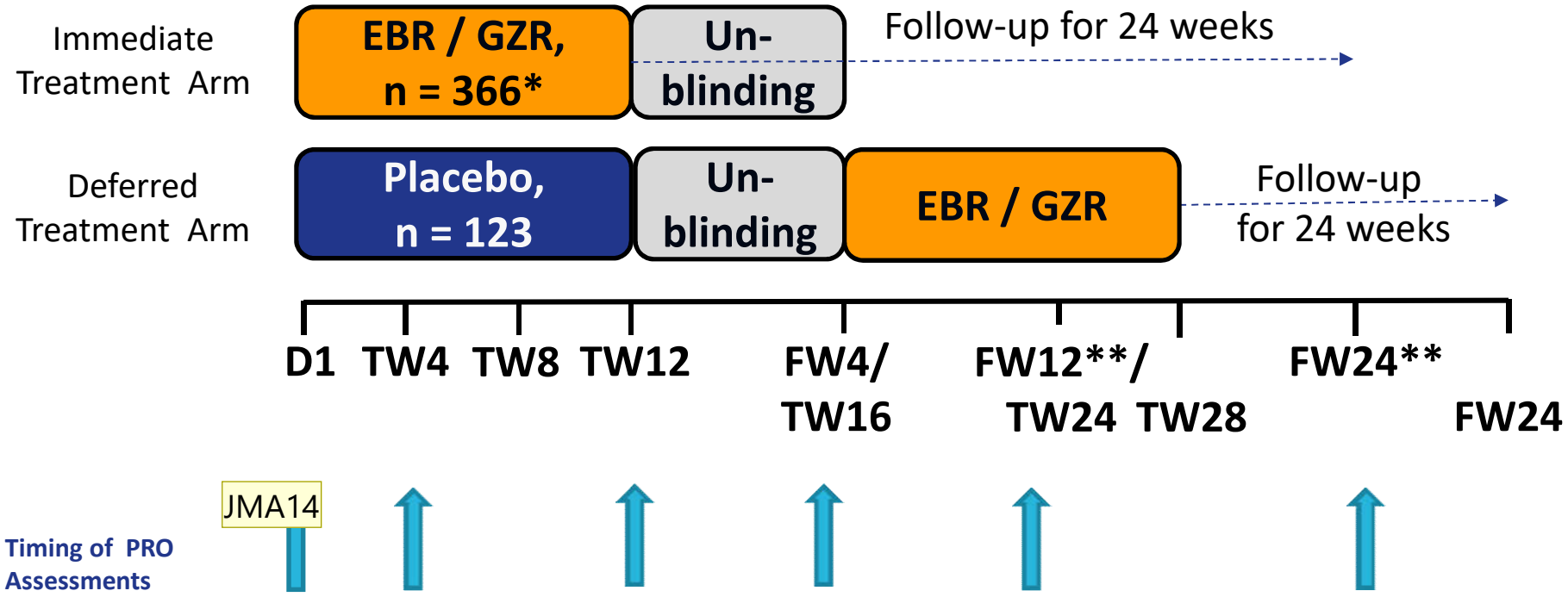
METHODS

Study Design

- Phase 3, randomized, parallel group, double blind placebo-controlled trial
- EBR/GZR fixed-dose combination tablet given once daily, without regard for food
- Randomized 3:1 into Immediate Treatment Group (ITG) vs Deferred Treatment Group (DTG)
  - ITG: EBR/GZR for 12 weeks + follow-up for 24 weeks
  - DTG: Placebo for 12 weeks + 4 weeks follow-up + 12 weeks of active treatment + follow-up for 24 weeks
- Stratification by cirrhosis status (non cirrhotic vs cirrhotic) and study site location (country)



*365 of 366 patients randomized to EBR/GZR received study drug
**PRO assessments only completed by subjects in ITG
D: Day, **TW:** Treatment Week, **FW:** Follow-up Week

Slide 3

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Jean Marie Arduino, 3/29/2016

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Jean Marie Arduino, 1/18/2017

- Patients completed three patient-reported outcome (PRO) questionnaires at clinic visits, on their own , using an electronic data capture tool. Every attempt was made for the patients to complete the PROs prior to receiving study treatment, discussing any medical conditions with the study personnel, or receiving any medical results
- Three PRO questionnaires were included in this study to assess general HRQOL and fatigue:
  - General Health-Related Quality of Life (HRQOL):
    - SF-36v2® Acute Health Survey (1-week recall) — to detect more recent changes in health status
    - EuroQol-5D-5L/Visual Analogue Scale [EQ-VAS]
  - Fatigue: FACIT-Fatigue Scale
- The PROs were scored for each patient at each measured time point according to the developer's scoring algorithm
  - Higher scores indicate better health status
  - SF-36v2® scores: 8 health domain scores range from 0 to 100, and contribute to the computation of the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. PCS and MCS scores were calculated using the individual domain scores linearly transformed using the United States population norms to the mean of 50 and a standard deviation of 10
  - EQ-VAS score: ranges from 0 to 100
  - FACIT-Fatigue Scale: Fatigue score ranges from 0-52
- The primary analysis approach was based on Full Analysis Set population, defined separately for each PRO. This population consists of all enrolled patients who had at least one dose of study medication and had completed at least one baseline or post-baseline PRO assessment.
- Pre-specified analyses focused on the following:
  - Within treatment group changes: estimating mean change (95% confidence intervals (CI)) from baseline in PRO scores at TW4, TW12 , FW4, FW12 by treatment group
  - Between treatment group differences: estimating difference in mean change from baseline in PRO scores (EBR/GZR group – Placebo group), with 95% CI, at TW4, TW12 and FW4

Results

- Patients were enrolled from 49 trial centers from 7 countries:
  - 13 centers in China (N=152 patients), 6 in South Korea (N=50), 7 in Taiwan (N=85), 3 in Thailand (N=21), 3 in Vietnam (N=33), 15 in Russia (N=119) and 2 in Australia (N=28)

- Baseline characteristics:
  - Female: 55.7%
  - Mean age: 48.3 years (range 18-77 years)
  - Distribution of HCV genotype (GT): GT1a:7.6%, GT1b:80.1%, GT1-other:1.2%, GT4: 0.6%, GT6:10.5%
  - Cirrhosis: 18.4%

- Compliance rates for the PRO assessments were high across the timepoints (>94%)and comparable between treatment groups.

- Baseline mean PRO scores were comparable between treatment groups **(Figure 1)**

- **Figures 2a, 2b and 2c** presents changes from baseline in PRO scores within treatment groups.

- <u>On-treatment Period</u>
  - **EBR/GZR group:** significant improvements in General Health (TW4, TW12), Vitality (TW12), Social Functioning (TW4), Mental Component Summary (TW4, TW12), Overall HRQOL (TW12)
  - **Placebo group:** significant improvements in General Health (TW4)
- <u>Follow-up Period</u>
  - **EBR/GZR group:** significant improvements in Role-Limitations Physical (FW4), General Health (FW4, FW12), Vitality (FW4, FW12), Social Functioning (FW4), Role-Limitations Emotional (FW4), Mental Health (FW4), Physical and Mental Component Summary scores(FW4, FW12), Overall HRQOL (FW4, FW12), and Fatigue Score (FW4)
  - **Placebo group:** significant decline in Role-Limitations Emotional (FW4)

Results

- **Treatment differences in mean change scores**
  - In general, EBR/GZR group had more favorable mean change from baseline in PRO scores than the placebo group during treatment and follow-up
  - However, only significant differences (95% CI for treatment differences exclude 0) in mean change scores between treatment groups were noted at FW4 for the following PRO scores:

PRO	Domain	Difference in mean change scores (EBR/GZR – Placebo) (95% CI)
SF-36	Role-Limitations Physical	4.9 (1.0, 8.8)
	General Health	3.8 (0.1, 7.5)
	Vitality	5.6 (2.0, 9.3)
	Social functioning	6.1 (2.4, 9.8)
	Role-Limitations Emotional	8.1 (4.1, 12.0)
	Mental Component Summary	2.9 (1.3, 4.5)
EQ-VAS	Overall HRQOL	3.4 (1.0, 5.8)
FACIT-Fatigue Scale	Fatigue Score	1.5 (0.3, 2.8)

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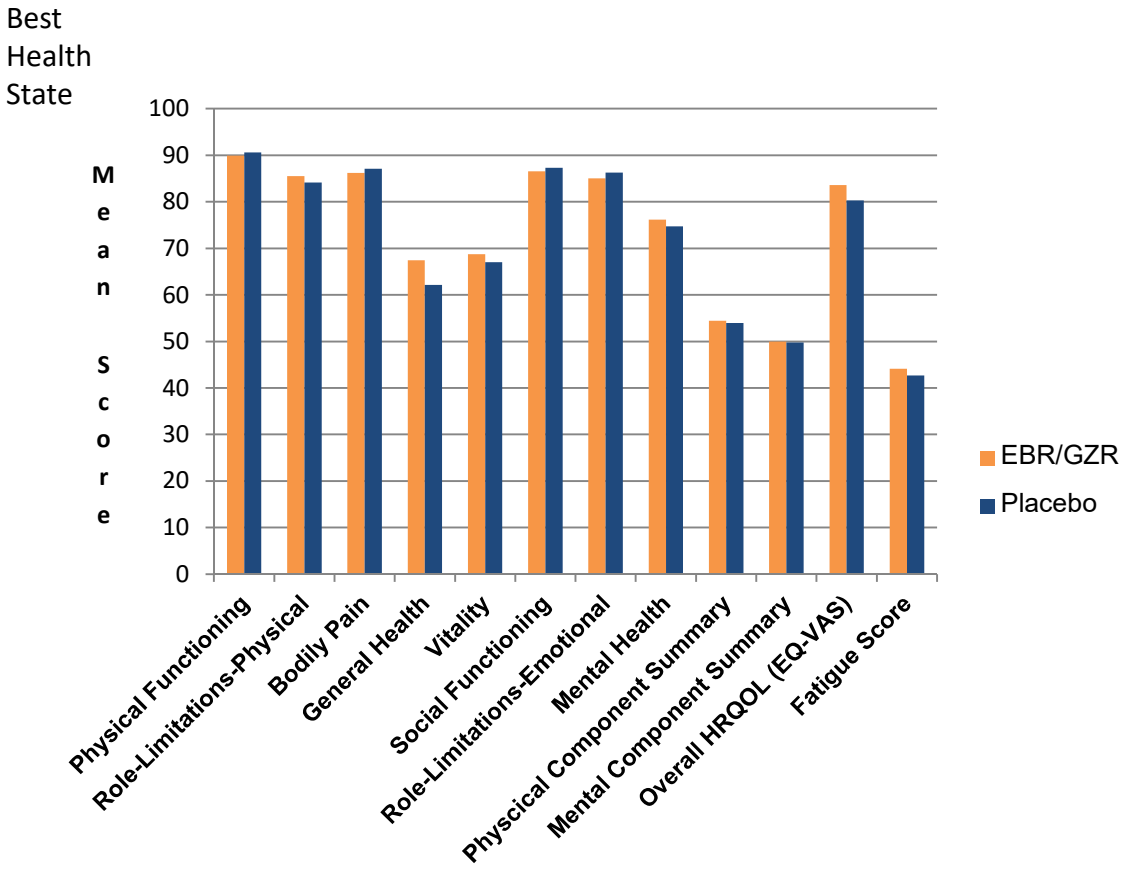
Figure 1 Comparable Baseline Mean Scores Between Treatment Groups



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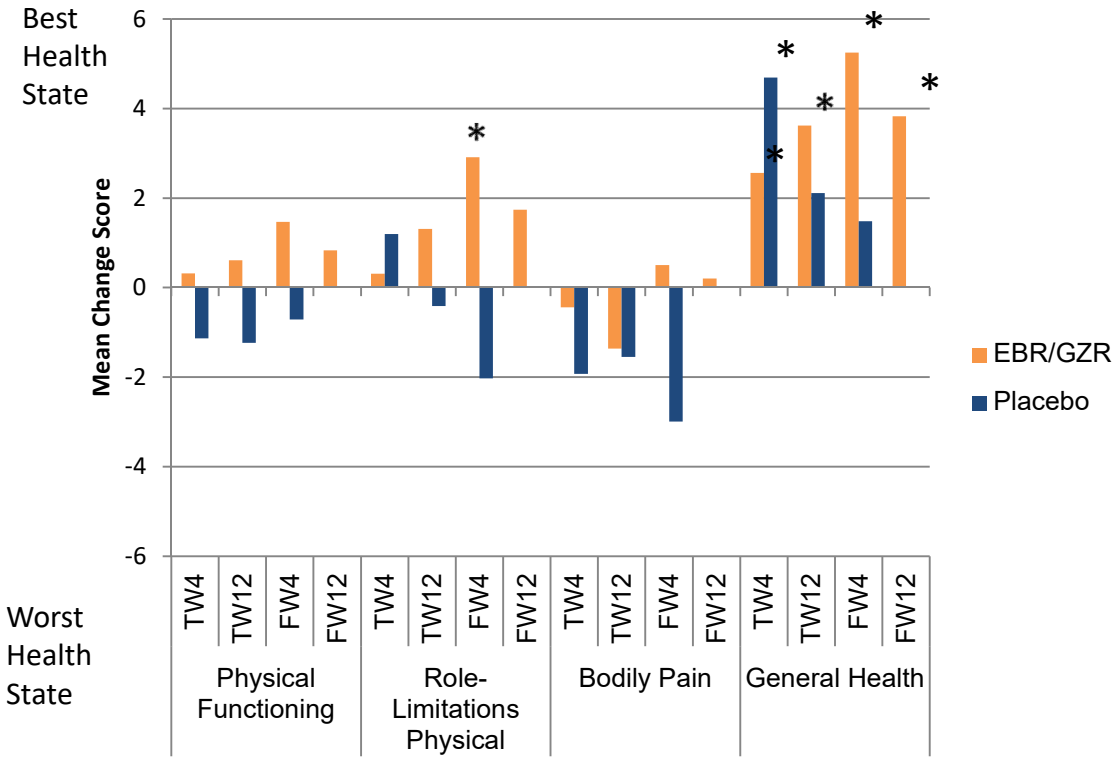
Jean Marie Arduino, 3/21/2016

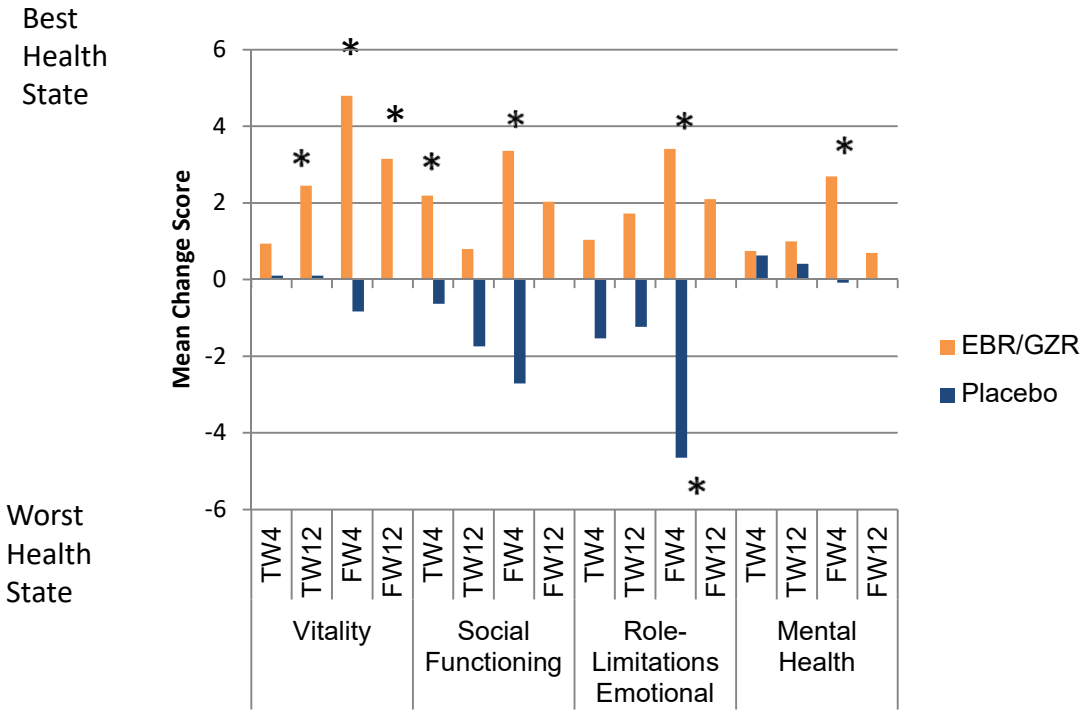
Figure 2. Comparison in mean change from baseline PRO scores between EBR/GZR and placebo

2a.

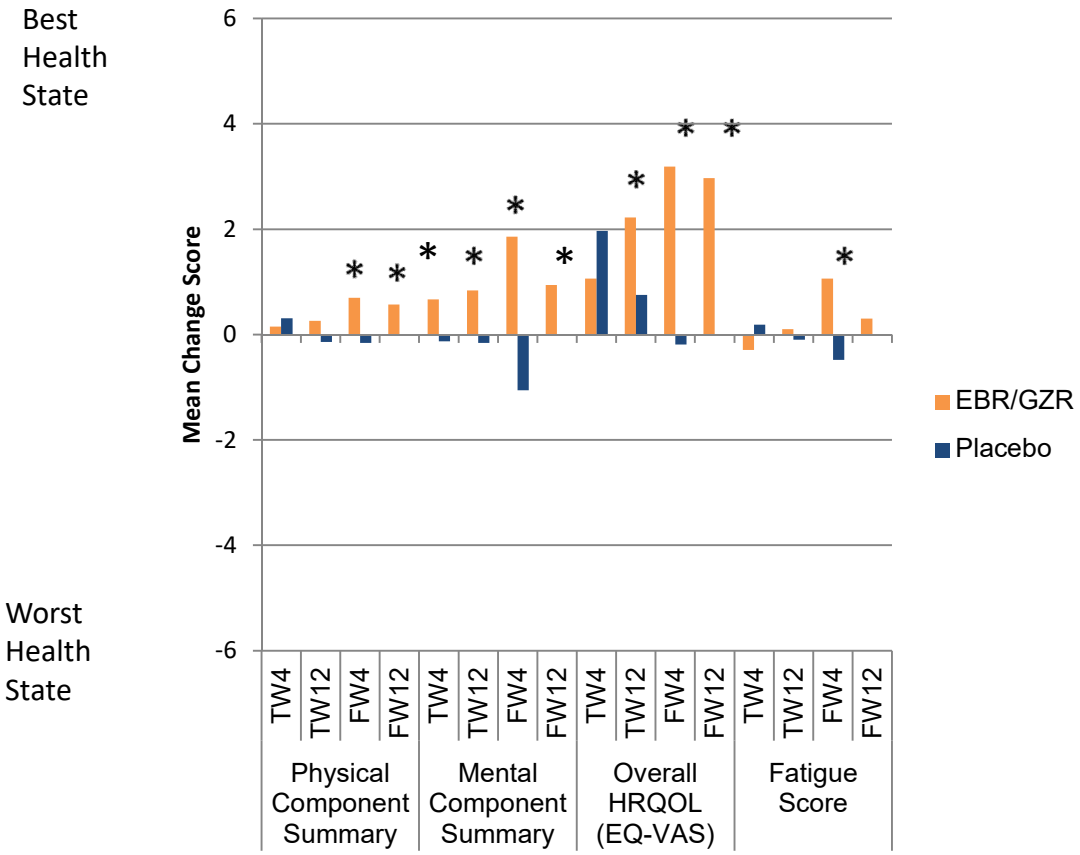


*Significant changes from baseline PRO scores with 95% CI of mean excludes 0:

2b.


Best Health State
Worst Health State
Mean Change Score
6
4
2
0
-2
-4
-6
TW4
TW12
FW4
FW12
Vitality
Social Functioning
Role-Limitations Emotional
Mental Health
EBR/GZR
Placebo

2c.


Best Health State
Worst Health State
Mean Change Score
6
4
2
0
-2
-4
-6
TW4
TW12
FW4
FW12
Physical Component Summary
Mental Component Summary
Overall HRQOL (EQ-VAS)
Fatigue Score
EBR/GZR
Placebo

Conclusion

- Patient-reported outcomes provide meaningful information which comes directly from the patients', giving their own perception on their overall health, including functional and well-being, during the course of the study.
- Treatment with EBR/GZR had a positive impact on patients' HRQOL and fatigue levels due to HCV infection during treatment and/or follow-up period
- Treatment with EBR/GZR had more favorable changes in health status than treatment with placebo, which was most evident at FW4
- Overall, the changes in PRO scores in this study were substantially more favorable than the large declines in PROs historically associated with interferon and ribavirin-containing regimens.
- A randomized, placebo-controlled, blinded trial design, such as used in this study, is the "gold" standard design for evaluating PROs. Reporting bias is minimized by the blinding of both investigators and patients to treatment assessment and clinical outcomes.
- In contrast, open-label trials, both investigators and patients are aware of the patients' treatment regimen and possibly the clinical outcomes. This knowledge may influence the investigators interaction with the subjects and the subjects' responses to the PROs, resulting in a possible bias (e.g., over-estimation) in the treatment benefit.

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Acknowledgments

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Disclosures

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- Clinicaltrials.gov Identifier for Protocol 067: NCT02251990
- PL, LL, BE, JG, RT and JMA are current employees of and/or own stock in Merck & Co., Inc., Kenilworth, NJ, USA

Contact

- Jean Marie Arduino, jeanmarie.arduino@merck.com