TITLE PAGE

REPORT NO. 1060779

PASS INFORMATION

Title	A Post Approval Safety Study (PASS): **G**lobal Observational Cohort Study on the Prediction of **U**nwanted **A**dverse Effects in Indivi**d**uals Infected with Chronic Hepatitis **C** Receiving a Long-Acting Interferon plus Ribavirin (GUARD-C)
Version identifier of the final study report	v1
Date of last version of the final study report	26 June 2014
EU PAS register number	ENCEPP/SDPP/6725
Active substance	Pegylated interferon (alpha 2a or alpha 2b) + ribavirin
Medicinal product	Pegylated interferon: Pegasys (alpha 2a) or PegIntron (alpha 2b) Ribavirin
Product reference	Pegasys: EU/1/02/221/001-017 PegIntron: EU/1/00/131/001-050
Procedure number	EMEA/H/C/395/II/036
Marketing authorisation holder(s)	Roche Registration Ltd (Pegasys) Schering-Plough (PegIntron) MAH of ribavirin was not recorded
Joint PASS	No
Research question and objectives	The primary objective was to assess the following in routine clinical practice in subjects with CHC receiving combination therapy with a long-acting interferon plus ribavirin according to local label: 1) Baseline predictors for safety related dose reductions / treatment discontinuations and 2) The impact of safety-related dose reductions / treatment discontinuations on SVR Secondary objectives included 1) Assessment in routine clinical practice of on-treatment predictors for safety related dose reductions / treatment discontinuations 2) Assessment of the association between the degree of dose reductions / treatment interruptions and SVR 3) Evaluation and comparison of the predictive value of on-treatment virological response (rapid virological response [RVR], early virological response [EVR]) in naïve and treatment experienced subjects

Title	A Post Approval Safety Study (PASS): **G**lobal Observational Cohort Study on the Prediction of **U**nwanted **A**dverse Effects in Indivi**d**uals Infected with Chronic Hepatitis **C** Receiving a Long-Acting Interferon plus Ribavirin (GUARD-C)
	4) Assessment of the safety profile of extended treatment duration (in particular beyond 48 weeks) in subjects with CHC
Country(-ies) of study	Albania, Algeria, Bahrain, Belgium, Bosnia and Herzegovina, Brazil, Egypt, Greece, Hungary, India, Iran, Italy, Kuwait, Lebanon, Macedonia, Morocco, Pakistan, Poland, Portugal, Qatar, Romania, Serbia, Slovakia, South Korea and United Arab Emirates
Author	Clinical responsible: International Medical Director, Pegasys, Roche, Basel, Switzerland (George Bakalos since 01.10.2013; Fernando Tatsch 25.3.2010 to 16.08.2013; Andreas Tietz 01.03.2009 to 24.03.2010) Project Statistician Silke Ahlers (IST, Mannheim, Germany)

MARKETING AUTORISATION HOLDER(S)

Marketing authorisation holder(s)	Roche Registration Ltd Hexagon Place 6 Falcon Way Shire Park Welwyn Garden City Herts AL7 1TW UK
MAH contact person	Stephane Andre

1. ABSTRACT

Title

A Post Approval Safety Study (PASS): Global Observational Cohort Study on the Prediction of Unwanted Adverse Effects in Individuals Infected with Chronic Hepatitis C Receiving a Long-Acting Interferon plus Ribavirin (GUARD-C)

Keywords

Post-approval safety study (PASS), non-interventional observational study, adverse effects, pegylated interferon plus ribivarin, chronic hepatitis C

Rationale and background

Data available from controlled clinical trials in chronic hepatitis C (CHC) demonstrate that adherence to therapy is an important factor for achieving sustained virological response (SVR). However, the known side effect profile of interferon-based therapy often requires dose reductions/interruptions. Awareness of the side effect profile and early interventions can avoid dose reductions. A review at the time of study initiation showed a lack of data on patient adherence in the field of hepatitis C virus (HCV) therapy.

The rationale of the present study was to collect information from real world daily clinical practice on dose modifications doses and discontinuations due to side effects and to correlate these with treatment outcome.

A further rationale was to identify baseline or on-treatment predictors for dose rmodifications/discontinuations due to side effects thus assisting physicians in the future to make treatment decisions for individual patients. The database was also to provide valuable insight on how side effects were managed in clinical practice.

Finally this study intended to document (in an international non-interventional cohort) the adverse event profile of prolonged treatment duration of up to 72 weeks in treatment-experienced subjects.

Research question and objectives

Primary objectives were to assess 1) baseline predictors for safety-related dose reductions / treatment discontinuations and 2) the impact of safety related dose reductions / treatment discontinuations on SVR, in subjects with CHC receiving combination therapy with a long-acting (pegylated) interferon plus ribavirin according to local label.

Secondary objectives were to 1) assess on-treatment predictors for safety-related dose reductions / treatment discontinuations, 2) assess the association between degree of dose reductions / treatment interruptions and SVR, 3) evaluate and compare the predictive value of on-treatment virological response in naïve and treatment experienced subjects, and 4) assess the safety profile of extended treatment duration (in particular beyond 48 weeks) in subjects with CHC.

Study design

The study was a prospective, international, multicenter, observational, non-interventional cohort study. Dosing and treatment duration of the long-acting interferon plus ribavirin were at the discretion of the investigator in accordance with local clinical practice and local labeling.

Setting

Clinical practice.

Subjects and study size, including dropouts

A total of 4453 subjects were enrolled from 301 centers, globally. Adult subjects who were receiving treatment for CHC with a long-acting interferon (alfa-2a or alfa-2b) plus ribavirin according to local standard-of-care and labeling with no contra-indication to long-acting interferon and ribavirin therapy were eligible provided they had quantifiable serum HCV RNA by polymerase-chain reaction before initiation of treatment.

Variables and data sources

Data on demographics, HCV disease characteristics including HCV genotype and HCV RNA, medical history, liver assessment, prior medication for HCV, laboratory parameters derived from standard-of-care visits were collected using a standard case report form.

Results

Of the 4453 subjects enrolled, 3181 treatment-naïve and 880 pretreated subjects were included in the core population (subjects with information on type of interferon and intended treatment duration [24, 48 and 72 weeks]).

Primary objective 1)

Baseline prognostic factors for earlier occurrence of safety-related dose reduction/discontinuation were: female gender, higher age, lower BMI, genotype 1 or 4, cardiovascular disease, pulmonary disease, lower hemoglobin concentration, lower number of platelets and lower number of neutrophils. These factors are known to be associated with a lower probability of achieving SVR.

Primary & secondary objective 2)

Early safety-related dose reduction/discontinuation (by week 4 and/or 12) were found to be associated with lower SVR in treatment-naïve subjects and pretreated subjects treated with PEG-IFN alfa-2a compared with no safety-related dose reduction/discontinuationThere was no impact from safety-related dose reductions/discontinuations which occurred > week 12.

Secondary objective 1)

On-treatment predictors for safety-related dose reductions/discontinuations were identified as early decreases in hemoglobin, neutrophils or platelets in treatment-naïve subjects and pretreated subjects.

Secondary objective 3)

Most of the known predictors for SVR were confirmed. The earlier VR was achieved clearly improved the chance of SVR.

Secondary objective 4)

There were no new safety findings and the safety data is consistent with the known safety profile for pegylated interferon alfa-2a/ribavirin for the treatment of CHC, including the data from subjects treated for >48 weeks, Treatment beyond 48 weeks resulted in a slight increase in the risk of time-dependent hematological adverse events (AEs), weight loss, severe AEs, discontinuation and dose modification rates, but there was no increase in serious AEs nor differences in laboratory nadir values, all of which are consistent with the current label.

Discussion

There were no new safety findings in this study and the safety data is consistent with the known safety profile for pegylated interferon alfa-2a/ribarivin for the treatment of CHC, including the data from subjects treated for >48 weeks. The prognostic factors associated with SVR, that were identified are well established. The benefit risk of treating treatment naïve for 48 weeks or less and treatment-experienced subjects with CHC for longer than 48 weeks remains positive. As a result no label changes are required.

Marketing Authorisation Holder(s)

F.Hoffmann-La Roche Ltd

Names and affiliations of principal investigators

No principal investigators were assigned.