TITLE PAGE

CLINICAL STUDY REPORT NO: 1115700STUDY INFORMATION

TITLE:	**Peginterferon alfa-2a Non-Interventional Study (PAN)** - A Roche project in cooperation with the bng (Association of German Resident Gastroenterologists) for quality assurance in the dual combination respectively triple-therapy of chronic hepatitis C with Peg-(40kd)-Interferon alfa-2a (Pegasys®) at gastroenterology centers
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CLINICAL STUDY REPORT APPROVAL

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TABLE OF CONTENTS

1. SYNOPSIS / ABSTRACT

Title

Peginterferon alfa-2a Non-Interventional Study (PAN) – A Roche project in cooperation with the bng (Association of German resident gastroenterologists in German for quality assurance in the dual combination respectively triple-therapy of chronic hepatitis C with Peg-(40kd)-Interferon alfa-2a (Pegasys®) at gastroenterology centers

Keywords

Peginterferon alfa-2a; Chronic hepatitis C; Non-interventional study, Antiviral therapy

Research Question and Objectives

The primary objective of this non-interventional study (NIS) was to determine effectiveness of Peginterferon alfa-2a (Pegasys®) treatment – usually in combination with Ribavirin and in patients with Genotype-1 mutation additionally a serine protease inhibitor – in patients with chronic hepatitis C treated by gastroenterology specialists in a real-life setting.

Secondary objectives of this NIS were the evaluation of screening parameters and criteria for decision-making on the start of antiviral therapy as well as the assessment of treatment modalities of hepatitis C and patients' compliance in a real-world setting, in order to assess the quality of hepatitis C treatment on routine clinical care in Germany.

Safety objective was the systematic collection of information on the safety profile of Peginterferon alfa-2a (Pegasys®) in combination with other antiviral medication against hepatitis C.

Study Design

PAN was designed as a non-interventional single-arm study collecting data on routine clinical care of patients with chronic hepatitis C. The NIS was conducted by gastroenterologists in specialized practices or outpatient clinics and comprised a planned observation period of a maximum of 72 weeks per patient.

The study start date was 03 October 2011 and the NIS was planned to be completed on 31 December 2016 according to the observational plan v 2.0 (of 28 February 2013). Deviating from this plan, the observation period was shortened by 29.5 months. Although the observation period was shorter than planned, the planned number of patients were enrolled. The study was transferred to the German liver foundation (deutsche Leberstiftung) to broaden the NIS into a kind of registry.

PAN was initially managed by Roche and lasted until 15 July 2014. As of 15 July 2014, PAN was continued / taken-over by 'Deutsche Leberstiftung' as a Roche-funded NIS. Therefore, this clinical study report (CSR) reflects only those data collected under the responsibility of Roche as a study initiator (i.e. period between 03 October 2011 to 15 July 2014).

Target Population

It was planned to enroll at least 7500 patients with chronic hepatitis C infection in about 600 centers throughout Germany. The therapeutic decision was made at the sole discretion of the treating physician, irrespective of this NIS and prior to enrollment in this NIS.

Patients were enrolled, when they met the following inclusion criteria:

- Diagnosis of chronic hepatitis C
- ≥18 years of age
- Eligibility for treatment with Pegasys® (according to the current Summary of Product Characteristics, SmPC)
- Women of childbearing potential were required to use adequate contraception

  - Two contraceptive methods at the same time during Pegasys® treatment and four months after treatment discontinuation.
- Signed Informed Consent

Patients were not enrolled, when they met any of the following exclusion criteria:

- Contraindications for the use of Peginterferon alfa-2a (Pegasys®) or combination therapy with Ribavirin (according to the current SmPCs)
- Pregnant or breastfeeding women

Study Size

In this study, 9822 patients were enrolled at 510 sites. Overall 5199 patients were included in this final analysis.

Studied Medicinal Product

At the time of study start, Peginterferon alfa-2a (Pegasys®) was indicated in the treatment of chronic hepatitis C and had been authorized by the European Medicines Agency (EMA) in June 2002. Until 2011, Pegasys® was most commonly applied in combination with Ribavirin. Only in cases of intolerance or contraindications to Ribavirin, Pegasys® was administered as monotherapy. In patients with hepatitis C virus (HCV) Genotype 1, triple therapy with serine protease inhibitors was approved in combination with Pegasys® and Ribavirin.

Variables

Following parameters were to be documented:

	Variable	Comment
Primary Effectiveness	HCV response Early virological response (EVR) End of treatment-response (EoTR), Sustained virological response (SVR)	
Secondary Effectiveness	Demographic data	
	Anamnesis of hepatitis C	
	Concomitant diseases / medications / alcohol or drug abuse	
	Current clinical symptoms	
	HCV laboratory diagnostics incl. genotype and viral load	
	Treatment modalities of Pegasys®	
	Relevant laboratory parameters	
	Therapy-related sick leave	Not analyzed in this final analysis
	Patients' compliance and quality of life assessed with the questionnaire SF-36	Not analyzed in this final analysis
	Liver transplantation and pharmacoeconomics	Not analyzed in this final analysis
Primary Safety	All adverse events (AEs) and serious AEs (SAEs, SAEs) during treatment and follow-up period	
Secondary Safety	All laboratory values Vital signs Pregnancy	

Data Sources

Data on the patients' routine treatment and the Investigators' medical decisions were documented during regular visits at the study center, no visits or measurements were mandatory. Patient data were recorded on electronic Case Report Forms (eCRFs) by the Investigator or by a person authorized by the Investigator.

Statistical and Epidemiological Methods

As specified in the observational plan only descriptive analyses were performed.

Categorical data were analyzed by frequency tables (absolute and relative frequencies). The percentage basis was by default the individual genotype or the total sample size (analysis population). If no analysis was performed according to individual genotypes, this was indicated in a footnote of the analysis table with justification.

For continuous data, sample statistics (N, missing, mean, standard deviation, median, Q1 and Q3, minimum and maximum) were determined. For continuous variables collected multiple times over time, statistics with absolute differences between end of observation and baseline were calculated where appropriate.

Missing values were not be replaced.

Results

- **Results of Descriptive Data:**

This final analysis includes data of 5199 patients. Overall, 9822 patients were enrolled of whom 4623 patients (47.1%) were excluded from the analysis population (AP).

At study start, the median estimated duration of HCV infection was 11 years (range 1 - 60) and only one-third of the patients (33.6%) received previous antiviral therapy. The predominant HCV genotypes were Genotype 1 and Genotype 3 (68.5% and 24.1%, respectively). The median duration of HCV therapy in this study was 172.0 days (range 1 - 706). Approximately one-quarter of the patients (25.5%) discontinued Pegasys® therapy prematurely. The most common reasons for treatment discontinuation were lack of virological response (8.7%) and patients' wishes (5.7%).

- **Effectiveness Results:**

The key results regarding virological responses of total population are depicted in the table below.

Virological Response	Frequency, n (%) (N=5199)
Early virological Response (EVR)	**2623 (50.5%)**
Patients with measurement 74-94 days after start of treatment	4561 (87.7%)
End of Treatment-Response (EoTR)	**3161 (60.8%)**
Patients with measurement at/after End of Treatment	3603 (69.3%)
Sustained virological Response (SVR)	**1414 (27.2%)**
Patients with measurement >168 days after End of Treatment	1699 (32.7%)

The proportion of responders was the highest in triple therapy Group 2 (Genotype 1 mutation + Boceprevir: EVR: 56.3%; EoTR: 66.0% and SVR: 34.0%) and the smallest in triple therapy Group 1 (EVR: 44.2%, SVR: 14.0%) or Pegasys® monotherapy group (EoTR: 44.2%).

In the AP, HCV polymerase chain reaction (PCR) data was available for the assessment of virological response rates in 87.7% of the patients for EVR, 69.3% for EoTR and only 32.7% for SVR.

- **Safety Results:**

In the AP, 4161 patients (80.0%) experienced AEs during the course of the study. Of these, 71.5% experienced Pegasys®-related AEs, 62.9% experienced Ribavirin-related AEs, and 54.7% experienced AEs related to both Pegasys® and Ribavirin.

Overall, the majority of AEs were mild to moderate in severity (mild: 12810/22626 events, moderate: 8894/22626 events, severe: 785/22626 events). The most common system organ class (SOC) was general disorders and administration site conditions (57.9% of the patients) and the most common AE by preferred term (PT) was fatigue (50.8% of the patients). The most common treatment related AEs belonged also to

SOC general disorders and administration site conditions and the most common treatment related AE by PT was fatigue.

In total, 8.1% of the patients experienced SAEs. The proportion of patients with SAEs related to either Pegasys® or Ribavirin were similar (Pegasys®-related: 4.1%, Ribavirin-related: 3.8%). The most common treatment related SAEs belonged to SOC blood and lymphatic system disorders and the most common treatment related SAE by PT was anemia according to SOC and PT in this study. Seventeen patients died during NIS participation. In total, four pregnancy cases werereported during the observational period, 3 cases with paternal exposure and 1 case with maternal exposure.

AEs **SOC** **PT**	**Total (N=5199)** **Patients, n (%) – Events, n**
AEs	**4161 (80.0%) - 22626**
General disorders and administration site conditions	3008 (57.9%) - 4608
Fatigue	2642 (50.8%) - 2870
AEs related to Pegasys®	**3715 (71.5%) - 16291**
AEs related to Ribavirin	**3271 (62.9%) - 12847**
AEs related to Pegasys® and Ribavirin	**2846 (54.7%) - 10748**
SAEs	**420 (8.1%) - 667**
Blood and lymphatic system disorders	122 (2.3%) - 135
Anemia	79 (1.5%) - 84
SAEs related to Pegasys®	**215 (4.1%) - 310**
Blood and lymphatic system disorders	76 (1.5%) - 83
SAEs related to Ribavirin	**196 (3.8%) - 275**
Blood and lymphatic system disorders	98 (1.9%) - 106
Anemia	67 (1.3%) - 70
SAEs related to Pegasys® and Ribavirin	**152 (2.9%) - 207**
Blood and lymphatic system disorders	63 (1.2%) - 67
AEs leading to death	**15 (0.3%) - 28**

AE, adverse event; PT, preferred term; SOC, system organ class.

Conclusions

Virological response was the effectiveness endpoint in this final analysis of PAN. Virological response in terms of EVR and EoTR and SVR was achieved by 50.5% and 60.8 of the patients, respectively, in the AP. It is not possible to draw conclusions about SVR, because HCV PCR data were available in one-third of patients (32.7%) only during the given timeframe.

This final analysis revealed no new concerns for safety.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AIDS/	Acquired Immunodeficiency Syndrome
AMG	Alanine Aminotransferase / Glutamate Pyruvate Transaminase
AMA	Antimitochondrial Antibody
ANA	Antinuclear Antibody
AP	Analysis Population
AST / GOT	Aspartate Aminotransferase / Glutamic Oxaloacetic Transaminase
BMI	Body Mass Index
bng	Association Of German Resident Gastroenterologists (German: Berufsverband Der Niedergelassenen Gastroenterologen)
CDB	Clinical Database
CRO	Clinical Research Organization
CSR	Clinical Study Report
DAA	Direct-Acting Antivirals
DAM	Data Analysis Meeting
DNA	Desoxyribonucleic Acid
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EoT	End Of Treatment
EoTR	End Of Treatment-Response
EVR	Early Virological Response
GGT / Gamma-GT	Gamma-Glutamyltransferase
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamate Pyruvate Transaminase
HBc	Hepatitis B Core Antigen
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IC	Informed Consent
IgM	Immunoglobulin M
INF	Interferon

Abbreviation	Definition
IRT	Interactive Response System
LKM	Anti–Liver-Kidney Microsomal Antibody
LSU	Local Safety Unit
MAK	Microsomal Antibody
MedDRA	Medical Dictionary For Regulatory Activities
NIS	Non-Interventional Study
QC	Quality Control
PCR	Polymerase Chain Reaction
PegINF	Pegylated Interferon
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDB	Safety Database
SF-36	36-Item Short Form Survey
SLA	Soluble Liver Antigen Antibody
SMA	Smooth Muscle Antibody
SmPC	Summary Of Product Characteristics
SOC	System Organ Class
SVR	Sustained Virological Response
Trak	TSH-Receptor Antibody

3. MILESTONES

Milestone	Planned Date	Actual Date	Comments, if any
Start of data collection	01 October 2011	03 October 20211	
Interim analysis			During the course of the study database extracts were produced twice per year and various manuscripts have been published
End of data collection	31 December 2016	15 July2014	Study was transferred to German liver foundation (Leberstiftung)
Final report of study results		13 July 2022	

4. RATIONALE AND BACKGROUND

Until 2011, the existing standard chronic hepatitis C therapy consisted of pegylated Interferon (PegINF, Pegasys®) in combination with Ribavirin and, in patients with hepatitis C virus (HCV) Genotype 1, as triple therapy with an additional combination partner, a serine protease inhibitor (Boceprevir or Telaprevir). Monotherapy with Pegasys® was mainly indicated in cases of intolerance or contraindications to Ribavirin.

With the launch of direct-acting antivirals (DAA) in 2014 / 2015, the first Interferon (INF)-free treatments became available. Nowadays, INF-based therapy regimes are no longer indicated in HCV treatment (Sarrazin et al. 2018 and 2020). However, combination therapies of DAAs, Ribavirin, and early PegINF continue to be approved for the treatment of HCV infection.

Preceding non-interventional studies (ML17071, ML19464 and ML21645) enabled evaluation and documentation of the routine patient care in chronic hepatitis C in daily practice. Different from these previous studies, PAN also included patients with triple therapy and allowed a more comprehensive analysis of treatment modalities (monotherapy, combination therapy and/or triple therapy).

PAN was designed as a non-interventional single-arm study to collect data on routine clinical care of patients with chronic hepatitis C.

5. RESEARCH QUESTIONS AND OBJECTIVES

In the original observation plan (v 2.0, 28 February 2013), the main objective of PAN was defined as the determination of effectiveness and safety of Pegasys® treatment in patients with chronic hepatitis C treated by gastroenterology specialists in a real-life setting.

For this final analysis, the primary objective was further specified.

The primary objective of this final analysis of PAN was:

- To determine effectiveness of Pegasys® treatment - most commonly in combination with Ribavirin and in patients with Genotype-1 mutation additionally a serine protease inhibitor - in patients with chronic hepatitis C treated by gastroenterology specialists in a real-life setting.

Secondary objectives of this NIS were the evaluation of screening parameters and criteria for decision-making on the start of antiviral therapy as well as the assessment of treatment modalities of hepatitis C and patient compliance in a real-world setting, in order to assess the quality of hepatitis C treatment in routine clinical care in Germany.

The safety objective was the systematic collection of information on the safety profile of Pegasys®) in combination with other antiviral medication against hepatitis C.

For some of these additional objectives aspects, results are displayed in this clinical study report (CSR).

6. AMENDMENTS AND UPDATES TO PROTOCOL

Number	Date	Section of Study Protocol	Amendment or Update
1	28 February 2013 v. 2.0	Contact Data	Contact details for safety reporting further specified
		List of Abbreviations	Further abbreviations included
		Safety Reporting for Pregnancies	Exposition of the father included in safety variables
		Safety Reporting of Adverse Events (AEs)	Further specified that AEs were to be documented for 90 days after premature discontinuation of therapy
		Safety Reporting Expedited Reporting	Added to expedited reporting: - Quality / Product complaints - Drug counterfeiting / suspected counterfeiting - Occupational exposure

7. RESEARCH METHODS

7.1 STUDY DESIGN

PAN was designed as a non-interventional single-arm study collecting data on routine clinical care of patients with chronic hepatitis C. All treatments and therapeutic decisions were up to the Investigator and were taken irrespective of this NIS. The NIS was conducted by gastroenterologists in specialized practices or outpatient clinics and comprised a planned observation period of a maximum of 72 weeks per patient.

7.2 SETTING

The study aimed at documenting overall 7500 patients in specialized practices and outpatient clinics experienced in treating patients with HCV infection over a duration of five years with a planned recruitment period of three years. A return rate of 80%, i.e. approx. 6000 patients within three years or 2000 patients per year were expected to be available for evaluation of effectiveness and tolerability. The planned patient numbers were already achieved by the time the study was handed over to the German liver foundation (Leberstiftung), where the study was continued. Therefore, a recalculation of the sample size was not necessary.

The study start date was 03 October 2011 and the NIS was planned to be completed on 31 December 2016 according to the observational plan v 2.0 (of 28 February 2013). Deviating from the original observational plan the observation period was shortened by 29.5 months and the study was transferred to the German liver foundation to broaden the NIS into a kind of registry. Due to various reasons, in particular in the context of handover to German liver foundation and the immanent change in type of NIS (Roche-managed into Roche-funded), a timely finalization of the NIS clinical study report (CSR) could not be achieved. Therefore, this CSR reflects only those data collected under the responsibility of Roche as a study initiator (i.e. period between 03 October 2011 and 15 July 2014). The final analysis was performed in 2021.

7.3 PATIENTS

The study population were men and women 18 years of age and older with chronic active HCV infection. Therapeutic decision was made at the sole discretion of the treating physician, irrespective of this NIS and prior to enrollment in this NIS.

Before documentation, the Investigator had to verify that the eligibility criteria were met and all other requirements of the study protocol had been fulfilled.

Eligibility criteria:

- Diagnosis of chronic hepatitis C
- ≥18 years of age
- Eligibility for treatment with Pegasys® (according to the current Summary of Product Characteristics, SmPC)
- Women of childbearing potential used adequate contraception

  - Two contraceptive methods at the same time during Pegasys® treatment and four months after treatment discontinuation.
- Signed Informed Consent

Patients were not enrolled, when they met any of the following exclusion criteria:

- Contraindications for the use of Peginterferon alfa-2a (Pegasys®) or combination therapy with Ribavirin (according to the current SmPC)
- Pregnant or breastfeeding women

During study participation, pregnancy tests should be performed monthly. Pregnancy was to be avoided for at least 7 months after treatment discontinuation in female sexual partners of male patients taking Ribavirin and up to 4 months after treatment discontinuation of Pegasys® in female patients. Both were required to use acceptable contraceptive methods.

7.4 VARIABLES

The primary objective of this NIS was to investigate effectiveness and safety of Pegasys® treatment in patients with chronic hepatitis C treated by gastroenterology specialists in a real-life setting.

The following parameters were to be collected throughout the study, if available, according to routine clinical care (Table 1).

Table 1: Study Variables

	Variables	**Parameters**
Primary Effectiveness Variable	HCV response by HCV polymerase chain reaction (PCR)	- Early virological response (EVR) - End of treatment-response (EoTR) - Sustained virological response (SVR)
Secondary Effectiveness Variables	Demographic data	Age, height, bodyweight, gender
	Anamnesis of hepatitis	Medical history, blood pressure, duration of infection, prior HCV therapy(-ies), liver ultrasound, biopsy, fibroscan (if available)
	Concomitant diseases / medications / alcohol or drug abuse	
	Current clinical symptoms	Predefined clinical symptoms in electronic case report form (eCRF)
	HCV laboratory diagnostics	HCV antibody, genotype and viral load, histology (if available)
	Reason(s)/ indication(s) for treatment of hepatitis C	
	Treatment modalities of Pegasys®	As monotherapy, in combination with Ribavirin or as triple therapy (including regime and dosage)

	Variables	Parameters
	Relevant laboratory parameters	- Autoantibodies - Albumin, bilirubin, creatinine, leucocytes, neutrophils, thrombocytes - Liver values: Aspartate aminotransferase (GOT/AST), Alanine aminotransferase (GPT/ALT), Gamma-glutamyltransferase (Gamma-GT)
	Therapy-related sick leave	Not analyzed in this final analysis
	Patients compliance and quality of life assessed with the questionnaire SF-36	Not analyzed in this final analysis
	Liver transplantation and pharmacoeconomics	Not analyzed in this final analysis
Primary Safety Variable	All adverse events (AEs) and serious adverse events (SAEs, SAEs) during treatment and follow-up period	
Secondary Safety Variables	All laboratory values	
	Vital signs	
	Pregnancy	

7.5 DATA SOURCE(S) AND MEASUREMENT

This NIS did not influence or intervene in the patient's individual course of treatment or medical decisions and procedures in any way. During routine treatment, patients were regularly seen by the Investigator either for the treatment itself or for monitoring disease activity post-treatment. Data on (serious) adverse events were collected starting from first dose of Pegasys® until end of study and were recorded in the electronic case report form eCRF including details like start- and stop date, seriousness, severity, causal relationship and corresponding therapy. Safety reporting occurred via spontaneous reporting within the eCRF for patients.

Therefore, the observational plan for the study did not specify mandatory visits or measurements. The documentation in the eCRF was as displayed in the flowchart in Table 2.

Table 2: Flowchart of Study Procedures

Parameter	**Screening**	**Baseline** Week 0	**Treatment Phase** Week 2, 4, 6, 8, 12, 16, 24, 36, 48, EoT	**Post-Treatment** 24 weeks
Eligibility	x	x		
Patient informed consent	x			
Demographic data	x	x		
Anamnesis	x	x	x[a]	x
Bodyweight/ blood pressure	x	x	x	x
HCV antibodies	x			
Genotyping of HCV	x			x
Prior HCV therapy(-ies), therapeutic indication	x			
HCV laboratory diagnostics	x	x	x[b]	x
Liver values	x	x	x[c]	x
Comorbidities	x		x	x
Pregnancy test[#]		x	x	x
Autoantibodies		x	x[d]	
Laboratory parameters		x	x[e]	x
Anti-HCV therapy		x	x	
Concomitant medication		x	x	x
Current clinical symptoms		x	x	x
SF-36 / social demographics		x	x[f]	x
Therapy-related sick leave			x[g]	x
AEs/ SAEs		x	x	x
Compliance			x[h]	

AE,Adverse Event; EoT,End of Treatment; HCV, Hepatitis C Virus; SAE, Serious Adverse Event; SF-36, 36-Item Short Form Survey.
[#] Pregnancy test in female patients and confirmation of female partner of male patient monthly
[a] From week 12 onwards until end of study
[b] Week 2, 4 and 6, and thereafter every 4 weeks where available
[c] Continuously at every documented visit
[d] At week 24
[e] At weeks 12, 24, 36, 48 and EoT, an additional, different set of laboratory values at weeks 2-8 and at week 16
[f] At weeks 12 and EoT
[g] From week 2 and thereafter continuously
[h] At weeks 12 and 24, and continuously thereafter

Additional modules of the eCRF were completed for opioid-substituted patients, Human Immunodeficiency Virus (HIV) co-infected patients and patients with liver transplants.

7.6 BIAS

An inherent limitation of all observational studies is that patients are not randomized to treatment. Thus, a selection bias cannot be excluded. However, since no comparative evaluation was planned, a possible selection bias is acceptable. Additionally, the observational plan for a NIS does not prescribe mandatory visits, introducing the possibility of attrition bias. The use of an eCRF, however, reduced the risk of missing data and ensured that data were collected in a systematic and verifiable manner. Generally, because the study was non-interventional, assessments were not mandatory. Nevertheless, data reporting/collection was carried out in a uniform manner to avoid bias in the data collection process (information bias).

The full range of hepatitis C specialists experienced in Interferon therapy, whether operating as private practice or hospital-based, could participate in this study. The study recruited 9822 patients at 510 centers, which in terms of number, type and geographic distribution provided a representative sample. To avoid concentration of patients at particular centers, each center documented about 10 - 15 patients on average and 300 patients (corresponding to 4% of planned number of evaluable patients) at a maximum.

7.7 DATA TRANSFORMATION

Derivations and transformation of variables were as follows:

Duration of treatment: (Date EoT - Date Start of Treatment) + 1 day

Body mass index (BMI): Weight (kg)/height (m)²

Histology

All histological data were presented according to Desmet/Scheuer. Where findings were assessed using other staging or grading systems, these were recoded according to the transformations specified in the statistical analysis plan (SAP). Histological results were presented only for baseline.

Blood pressure

Blood pressure (systolic blood pressure, diastolic blood pressure, and total blood pressure) was to be analyzed using the following categories.

Table 3: Categories of Systolic and Diastolic Blood Pressure (in mm Hg)

Categories of Systolic Blood Pressure	
Optimal	<120
Normal	120-129
Normal high	130-139
Slightly elevated	140-159
Moderatly elevated	160-179
Severely elevated	≥180
Categories of Diastolic Blood Pressure	
Optimal	<80
Normal	80-84
Normal high	85-89
Slightly elevated	90-99
Moderatly elevated	100-109
Severely elevated	≥110

Table 4: Definition and Classification of Blood Pressure in Total (in mmHg according to guidelines of the Deutsche Hochdruckliga of 06/2008)

Category	**Systolic**	**Diastolic**
Optimal	<120	<80
Normal	120-129	80-84
Normal high	130-139	85-89
Grade 1 hypertension (mild)	140-159	90-99
Grade 2 hypertension (moderate)	160-179	100-109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90

Safety laboratory

For the safety laboratory, descriptive statistics were generated for the parameters (hemoglobin, neutrophils, leukocytes, platelets, glutamate pyruvate transaminase (GPT), glutamic oxaloacetic transaminase (GOT), gamma-glutamyltransferase (GGT), creatinine, albumin, and bilirubin) over time for all patients. No center-specific laboratory cutoff values were recorded in this NIS. All laboratory value changes, classifications, and units described below were agreed upon prior to start of analyses. For this analysis, patients were stratified according to their HCV genotype and respective treatment.

Table 5 Conversion Factors of Laboratory Units

Parameter	Unit	Conversion factor	Evaluated unit
Hemoglobin	mmol/l	x 1.61	g/dl
Thrombocytes	x 10^9/l	x 1000	/µl
Leucocytes	/µl	/ 1000	10^9/l
Total Bilirubin	µmol/l	/ 17.104	mg/dl
GPT (ALT)	µkat/l	x 60	U/l
GOT (AST)	µkat/l	x 60	U/l
Gamma-GT	µkat/l	x 60	U/l
Creatinine	µmol/l	/ 88.41733	mg/dl
Triglyceride	mmol/l	/ 0.0114	mg/dl
HCV-Viral load	copies/ml	/ 2.5	IU/ml

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; Gamma-GT, Gamma-glutamyltransferase; GPT, glutamate pyruvate transaminase; GOT, glutamic oxaloacetic transaminase.

7.7.1 Safety Analyses

Safety Analysis in this final analysis comprised only the analysis population (AP). Safety data on non-analysis population were summarized in Listings (Annex 1).

Free text fields on adverse events (AEs) and serious adverse events (SAEs) were coded according to Medical Dictionary for Regulatory Activities (MedDRA, version 15.0). The analysis was performed using the coded variable (preferred term (PT), primary system organ class (SOC)).

For the tolerability analysis, AEs, SAEs, adverse drug reactions and serious adverse drug reactions were summarized separately by frequency using the respective PTs, sorted by SOCs. These summary tables were additionally stratified by causal relationship to Pegasys® and/or Ribavirin where such data were available.

All AEs that led to study discontinuation and all AEs that resulted in death were tabulated.

7.7.2 Effectiveness Analyses

For the effectiveness analyses, response rates were defined as follows:

Early virological response (EVR): HCV PCR qualitative result negative and/or viral load decrease by ≥2 log levels and/or viral load ≤50 IU/ml after 12 weeks of treatment. Treatment weeks: range for valid EVR: 74-94 days after start of therapy

Only valid (in the specified range) EVR were displayed.

End of treatment-response (EoTR): HCV PCR below detection limit or ≤50 IU/ml and/or result qualitatively negative at end of treatment.

Sustained virological response (SVR): HCV PCR qualitative result negative and/or viral loasmquantitatively below detection limit or ≤50 IU/ml at follow-up 24 weeks after end of therapy or discontinuation of therapy.

Range for valid SVR: 12 weeks to any valid measured value >24 weeks after end of therapy.

7.7.3 Other Analyses

Concomitant medications and interventions during the study were not subject to coding and presented as Listing only.

Clinical symptom data were presented as incidences only (each symptom across all visits - not per visit, but occurred at least once).

7.7.4 Interim and Final Analysis and Timing of Analyses

Database extracts were produced twice a year from study start and various analyses were performed for submissions to congresses and for publications. Separate statistical analysis plans were prepared for these analyses in consultation with the authors.

Deviating from the observational plan, the observation period was shortened by 29.5 months. Only patient data collected up to 15 July 2014 were included in this final analysis. The study was transferred to the German liver foundation (deutsche Leberstiftung) to broaden the study into a kind of registry. Due to various reasons, in particular in the context of handover to German liver foundation and the immanent change in type of NIS (Roche-managed into Roche-funded) a timely finalization of the NIS-CSR could not be achieved. The final analysis was performed in 2021, after the data was fully transferred to *AMS* Advanced Medical Services GmbH. Database lock was performed on 29 June 2021 after the safety reconciliation process was completed.

The final analysis consisted of all analyses described in the Statistical Analysis Plan (SAP; Final version 2.0, dated 04 June 2021) and additional procedures documented in the Data Analysis Meeting (DAM) minutes (11 October 2021).

7.8 STATISTICAL METHODS

7.8.1 Amendments to the Statistical Analysis Plan

SAP version 1.1 (14 January 2016) was amended prior to final analysis to SAP version 2.0 (04 June 2021). SAP v 2.0 comprised the following changes:

- Precise definition of the analysis population (AP)
  - Data from patients without release of data by the Investigator were to be excluded from the final analysis
  - Patients without Informed Consent (IC), withdrawn IC or date of IC after treatment start were to be excluded from final analysis
  - Patients treated off-label with Pegasys® were to be excluded from the final analysis as determined in the DAM

The following parameters **were not analyzed** according to SAP v 2.0 of 04 June 2021:

- Additional modules for opioid-substituted patients, HIV-co-infected patients and liver transplants
- Parameters on quality of HCV therapy
- Quality of life according to SF-36
- Parameters of pharmaceutical economics

Due to a calculation error, a shortened observation period of 27.5 months is reported in the SAP. However, the observation period was actually shortened by 29.5 months (study start date: 03 October 2011 and planned completion date: 31 December 2016, observation period terminated 15 July 2014).

7.8.2 Statistical Considerations and Planned Sample Size

The SAP for this study was finalized before data analysis. Below is a brief overview of applied statistical methods.

As specified in the observation plan, only descriptive analyses were performed. Categorical data were analyzed by frequency tables (absolute and relative frequencies). The percentage basis was by default the individual genotype or the total sample size (AP). If no analysis was performed according to individual genotypes, this was indicated in a footnote of the analysis table with a justification.

For continuous data, sample statistics (N, missing N, mean, standard deviation, median, Q1 and Q3, minimum and maximum) were calculated.

For continuous variables collected multiple times over time, statistics with absolute differences between end of observation and baseline were calculated, if appropriate. For mean, standard deviation, median, Q1 and Q3, one additional decimal was given compared to minimum and maximum.

Missing values were not be replaced.

7.8.3 Analysis Population

The SAP defined only one analysis population, named 'Analysekollektiv', which is referred to as the analysis population (AP) in the following. This analysis population consisted of:

- All eligible patients included in the study with chronic hepatitis C
- Patients treated with Pegasys® in accordance with the current SmPC as monotherapy, in combination with Ribavirin or in combination with Ribavirin and Boceprevir / Telaprevir
- Patients who gave their IC prior to enrolment into the NIS and were observed between 03 October 2011 and 15 July 2014 and whose data was released by the site.

Data from this AP were employed to assess effectiveness and tolerability.

Subgroup analysis

Stratification according to anti-HCV treatment and HCV genotype is displayed in Table 6.

Table 6: Subgroups by anti-HCV Treatment and HCV Genotype

Treatment	Subgroups	
Monotherapy	-	-
Dual therapy/combination therapy (Pegasys® and Ribavirin)	Group 1: Genotype 1, 4, 5, 6	Group 2: Genotype 2, 3
Triple therapy	Group 1: Genotype 1 with Boceprevir	Group 2: Genotype 1 with Telaprevir

Subgroup analysis was performed for the following parameters:

- Virological response rates: EVR, EoTR and SVR
- Laboratory parameters: Hemoglobin, neutrophils, leukocytes, platelets, GPT, GOT, GGT, creatinine, albumin, bilirubin

Safety Listings were repeated for patients outside of the AP, treated with Pegasys® or Ribavirin, with IC and observed between 03 October 2011 and 15 July 2014 and whose data was released by the site.

7.8.4 Sample Size Justification

Overall, documentation of at least 7500 patients in specialized practices and outpatient clinics experienced in treating patients with HCV infection was planned over a duration of five years with a planned recruitment period of at least 3 years.

A response rate of 80%, i.e., approximately 6000 patients over 3 years or 2000 patients per year, was anticipated to be available for evaluation of effectiveness and tolerability. With approximately 80% active centers (480 centers; data from the previous ML21645

study), this resulted in an average patient number of n = 10-15 patients per center. To avoid oversized influences of single large centers on the main target variables, the maximum number of patients was limited to 300 patients per center (corresponding to 4% of the total number of evaluable patients). Physicians familiar with Interferon therapy throughout Germany who routinely used PegINFs in HCV-infected patients were eligible to participate.

7.9 QUALITY CONTROL

At the time this NIS was performed, quality control (QC) of non-interventional studies was operated on a less extensive level than today. Therefore, only random samples of QC checks were performed by the mandated clinical research organization (CRO); however, not following a strict monitoring plan or detailed information on outcomes.

8. RESULTS

8.1 PATIENT DISPOSITION

The study population, defined as analysis population (AP), comprised all eligible patients with chronic hepatitis C, treated with Pegasys® either as monotherapy, combination therapy with Ribavirin or triple therapy with additional Boceprevir or Telaprevir, who signed IC before enrollment in the study and whose data was approved and released for processing by the respective study site.

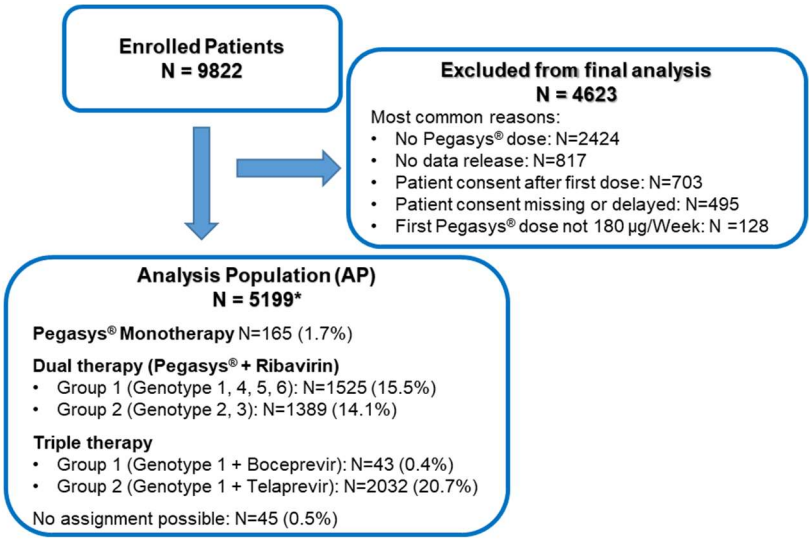
A total of 9822 patients were enrolled in this NIS, of whom 4623 patients (47.1%) were excluded from the final analysis. The most common reason for exclusion was that patients did not receive Pegasys® (2424 patients; 24.7%). Further reasons for exclusion are detailed in **Fehler! Verweisquelle konnte nicht gefunden werden.** and Source Table 14.1.2.1.2 (Annex 1).

All patients of the AP, except of two, fulfilled the selection criteria. These two patients failed to disclose information regarding pregnancy, breastfeeding or contraception status (Table 14.1.2.1.2, Annex 1). Patients in the AP were also part of additional eCRF modules, namely a drug module (826 patients; 15.9%), an HIV module (368 patients; 7.1%), a liver transplantation module (4 patients; 0.1%) and two modules of pharmacoeconomics (I: 5199 patients; 100% and II: 3483 patients; 67.0%) (Table 14.1.2.2, Annex 1). However, these additional modules were not included in this final analysis.

Patients of the AP were stratified according to their HCV genotype and respective treatment scheme. Most of the patients were in triple therapy Group 2 (Genotype 1 with Telaprevir; 39.1%) and dual therapy in Group 1 (Genotype 1, 4, 5, 6; 29.3%).

The patient disposition is displayed in Figure 1.

Figure 1: Patient Disposition



*2 patients with missing information on pregnancy/breastfeeding/contraception were included in the AP.
Source: Table 14.1.2.1.2 (Annex 1)
Percentages refer to all enrolled patients.

8.2 DESCRIPTIVE DATA

8.2.1 Baseline Characteristics

Baseline characteristics are displayed in Table 7.

About two-thirds of the patients in the AP were male (67.0%). The median age was 45.0 years (range 18.0 – 79.0) and about half of the patients were overweight (BMI >25 kg/m²: 2817 patients; 54.2%).

Data on systolic blood pressure at baseline was available of 60.8% of the patients of whom most had a normal or normal high systolic blood pressure (normal: 19.6% and normal high: 14.5%).

At study start, the majority of patients did not consume alcohol (84.0%). Data on the duration of alcohol consumption was only available in a fraction of the AP (292/5199 patients). About half of the AP were either current smokers (44.3%) or non-smokers (50.2%). Only 8.8% of the patients reported consumption of cannabis with a mean duration of 14 (±8.9) years.

Table 7: Baseline Characteristics - Analysis Population

Parameter	Statistics/Categories	Total (N=5199)
Gender		
Male	n (%)	3482 (67.0%)
Female	n (%)	1717 (33.0%)
Age [years]	n (missing)	5199 (0)
	Mean (SD)	45.0 (11.5)
	Median	45.0
	Min - Max	18 - 79
Height [cm]	n (missing)	5198 (1)
	Mean (SD)	173.7 (9.2)
	Median	174.0
	Min - Max	100 - 205
BMI [kg/m²]		
Patients with BMI >25	n (%)	2817 (54.2%)
Patients with BMI <25	n (%)	2354 (45.3%)
missing	n (%)	28 (0.5%)
Ethnicity	Caucasian	5031 (96.8%)
	Asian	73 (1.4%)
	African	69 (1.3%)
	Hispanic	25 (0.5%)
	Unknown	1 (0.0%)

Parameter	Statistics/Categories	Total (N=5199)
Systolic blood pressure [mmHg]	Optimal <120	609 (11.7%)
	Normal 120-129	1018 (19.6%)
	Normal high 130-139	756 (14.5%)
	Slightly elevated 140-159	635 (12.2%)
	Moderately elevated 160-179	121 (2.3%)
	Severely elevated ≥180	23 (0.4%)
	missing	2037 (39.2%)
Alcohol consumption	yes	806 (15.5%)
	no	4365 (84.0%)
	missing	28 (0.5%)
Duration of alcohol consumption [years]	n (missing)	292 (4907)
	Mean (SD)	14.7 (9.0)
	Median	13.0
	Min - Max	1 - 40
Tobacco consumption n (%)	Non-smoker	2610 (50.2%)
	Current smoker	2301 (44.3%)
	Ex-smoker	281 (5.4%)
	Missing	7 (0.1%)
Tobacco consumption [cigarettes/month]	n (missing)	2300 (2899)
	Mean (SD)	483.9 (252.4)
	Median	450.0
	Min - Max	1 - 3000
Cannabis consumption	yes	459 (8.8%)
	no	4712 (90.6%)
	missing	28 (0.5%)
Duration of Cannabis consumption [years]	n (missing)	455 (4744)
	Mean (SD)	14.0 (8.9)
	Median	13.0
	Min - Max	1 - 43

BMI, body mass index; SD, standard deviation.

Source: Tables 14.1.5,14.1.6, 14.1.7, 14.1.8, 14.3.1 and 14.3.2 (Annex 1)

Co-infection with hepatitis B was assessed at baseline, but only about half of the patients (47.5%) had data on hepatitis B laboratory diagnostics collected less than 12 months ago. For most of the parameters, data of a large proportion of patients was missing. Out of those patients with data, most patients were tested negative on hepatitis B surface antigen (HBsAg, 52.5%) and on antibodies against hepatitis B core antigen (anti-HBc, 39.5%) (Table 8).

Table 8: Hepatitis B Laboratory Diagnostics at Baseline - Analysis Population

Parameter		Frequency, n (%) Total (N=5199)
Data collection	<12 months ago	2467 (47.5%)
	>12 months ago	351 (6.8%)
	No laboratory diagnostic performed	2354 (45.3%)
	missing	27 (0.5%)
HBsAg	negative	2732 (52.5%)
	positive	86 (1.7%)
	missing	2381 (45.8%)
Anti-HBc	negative	2056 (39.5%)
	positive	762 (14.7%)
	missing	2381 (45.8%)
HBV DNA / PCR test performed	Yes, result below detection limit	196 (3.8%)
	Yes, with quantitative results	42 (0.8%)
	No	2706 (52.0%)
	missing	2255 (43.4%)

Anti-HBc, antibody against hepatitis B core antigen; DNA, desoxyribonucleic acid; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; PCR, polymerase chain reaction.

Source: Table 14.1.12 (Annex 1)

Safety laboratory parameters as well as liver values were collected at different time points throughout the study. These results are displayed in Tables 14.3.4 and 14.3.5 (Appendix 1).

Baseline results of safety laboratory parameters (albumin, bilirubin, hemoglobin and creatinine) and liver value (AST, ALT and gamma-GT) are presented in Table 9.

Table 9: Safety Laboratory Diagnostics and Liver Values at Baseline - Analysis Population

Parameter	Statistics	Total (N=5199)
Albumin [g/l]	n (missing)	1532 (3667)
	Mean (SD)	43.35 (8.88)
	Median	44.00
	Min - Max	2.8 - 75.0
Total bilirubin [mg/dl]	n (missing)	4008 (1191)
	Mean (SD)	0.65 (0.48)
	Median	0.53
	Min - Max	0.0 - 8.9
Hemoglobin [g/dl]	n (missing)	4683 (516)
	Mean (SD)	14.77 (1.44)
	Median	14.80
	Min - Max	7.2 - 20.0
Creatinine [mg/dl]	n (missing)	4116 (1083)
	Mean (SD)	0.84 (0.27)
	Median	0.81
	Min - Max	0.1 - 8.4
AST / GOT [U/l]	n (missing)	4470 (729)
	Mean (SD)	76.37 (112.03)
	Median	54.00
	Min - Max	0.4 - 5520.0
ALT / GPT [U/l]	n (missing)	4706 (493)
	Mean (SD)	108.05 (110.54)
	Median	75.00
	Min - Max	0.5 - 2104.0
Gamma-GT [U/l]	n (missing)	4637 (562)
	Mean (SD)	119.79 (982.58)
	Median	63.00
	Min - Max	0.5 - 66349.1

ALT / GPT, alanine aminotransferase / glutamate pyruvate transaminase; AST / GOT, aspartate aminotransferase / glutamic oxaloacetic transaminase; Gamma-GT, gamma-glutamyltransferase.

Source: Tables 14.3.4 and 14.3.5 (Annex 1)

8.2.2 Anamnesis of HCV infection

The median estimated duration of HCV infection was 11 years (range 1 - 60) and 62.0% of patients were positive for HCV antibodies. The most frequent route of transmission of hepatitis C was drugs (37.4%). Two-thirds of patients (66.4%) were not previously treated for HCV, while one-third of the patients (33.6%) were previously treated (Table 10).

Table 10: History of HCV - Analysis Population

Parameter	Statistics/Categories	Total (N=5199)
Estimated duration of infection [years]	n (missing)	5199 (0)
	Mean (SD)	13.9 (10.3)
	Median	11.0
	Min - Max	1 - 60
Route of HCV transmission	Drugs	1942 (37.4%)
	Unknown	1900 (36.5%)
	Blood products	545 (10.5%)
	Sexual transmission	365 (7.0%)
	Surgical or medical measures	284 (5.5%)
	Others	163 (3.1%)
Anamnesis of HCV	Non-pretreated patients	3453 (66.4%)
	Pretreated patients	1746 (33.6%)
HCV antibody	positive	3223 (62.0%)
	missing	1829 (35.2%)
	negative	147 (2.8%)

HCV, hepatitis C virus; SD, standard deviation.Virus;
Source: Table 14.1.10 (Annex 1)

Out of the 1746 patients, who received prior HCV treatment, the majority of patients had a previous PegIFN-monotherapy (75.2%) or an IFN - Ribavirin combination therapy (18.8%). About half of the patients with prior HCV treatment experienced a relapse (50.5%) or no virological response (37.8%) (Table 11).

Table 11: Prior HCV Therapies - Analysis Population

Prior HCV therapy		Frequency, n (%) Total (N=1746)
Last previous therapy	Pretreated patients	1746 (100.0%)
	IFN-Monotherapy	67 (3.8%)
	IFN-Ribavirin-combi therapy	329 (18.8%)
	PegIFN-Monotherapy	1313 (75.2%)
	PegIFN-Ribavirin-combi therapy	37 (2.1%)
Result of previous therapy	Relapse	882 (50.5%)
	Non-response: Partial Responder	206 (11.8%)
	Non-response: No details	340 (19.5%)
	Non-response: Null responder	114 (6.5%)
	Sustained virological Response (SVR)	67 (3.8%)
	SVR + Reinfection	52 (3.0%)
	Termination due to intolerance	60 (3.4%)
	Termination due to personal reasons	115 (6.6%)

HCV, hepatitis C virus; IFN, interferon; PegIFN, pegylated interferon; SVR, sustained virological response.

Source: Table 14.1.11 (Annex 1)

Genotype 1 was the predominant HCV genotype, followed by Genotype 3 (68.5% and 24.1%, respectively). Genotype 2 and Genotype 4 were represented in less than 5% of the patients. Both Genotypes 5 and 6 were the most underrepresented (both 0.1% of the patients).

Data on autoantibodies was not collect in about half of the patients (48.0%). Overall, 15.3% of the patients had at least one positive autoantibody test result, whereas 36.7% of the patients had no autoantibodies. Among patients with at least one positive result of autoantibodies, the most common were antinuclear antibodies (ANAs) in 11.0% of all patients (Table 12).

Table 12: HCV Genotype and Autoantibodies - Analysis Population

Parameter		Frequency, n (%) Total (N=5199)
HCV genotype	Genotype 1	3561 (68.5%)
	Genotype 2	221 (4.3%)
	Genotype 3	1252 (24.1%)
	Genotype 4	155 (3.0%)

Parameter		Frequency, n (%) Total (N=5199)
	Genotype 5	3 (0.1%)
	Genotype 6	7 (0.1%)
Autoantibodies	Patients without autoantibodies	1907 (36.7%)
	Patients with autoantibodies	796 (15.3%)
	Patients without data collection	2496 (48.0%)
ANA		574 (11.0%)
LKM		26 (0.5%)
SMA		149 (2.9%)
AMA		52 (1.0%)
SLA		25 (0.5%)
Trak		17 (0.3%)
MAK		60 (1.2%)
Rheumatoid factors		112 (2.2%)
Others		9 (0.2%)

AMA, antimitochondrial antibody; ANA, antinuclear antibody; HCV, hepatitis C virus; LKM, anti–liver-kidney microsomal antibody, MAK, microsomal antibody; SLA, soluble liver antigen antibody; SMA, smooth muscle antibody; Trak, TSH-receptor antibody.

Source: Tables 14.1.13.1 and 14.1.17.1 (Annex 1)

Ultrasound diagnostic results of the liver were ‘normal’ in about half of the patients (48.8%), and revealed an image of chronic liver disease in 11.7% of the patients, and fatty liver in 10.2% of the patients.

Histology data on fibrosis was missing in the majority of patients (91.5%). In patients with histological fibrosis, most results showed minimal or mild fibrosis (2.9% and 2.2%, respectively). Histology data regarding necrosis was also missing in the majority of patients (93.2%), but patients with data on necrosis mostly had mild or minimal necrosis (3.3% and 1.8%, respectively) (Table 13).

Table 13: Ultrasound / Histology Results at Baseline - Analysis Population

Parameter		Frequency, n (%) Total (N=5199)
Ultrasound liver	Normal results	2535 (48.8%)
	Splenomegaly	353 (6.8%)
	Image of a chron. liver disease	606 (11.7%)
	Fatty liver	531 (10.2%)
	Ultrasound signs of liver cirrhosis	328 (6.3%)

Parameter		Frequency, n (%) Total (N=5199)
Ultrasound liver (continued)	No result available*	15 (0.3%)
	No information on result	1 (<0.1%)
	Not performed	1141 (21.9%)
	No information on the conduct	5 (0.1%)
Histology – Fibrosis staging (Desmet/Scheuer)	0 / no fibrosis	59 (1.1%)
	1 / mild fibrosis	151 (2.9%)
	2 / moderate fibrosis	112 (2.2%)
	3 / severe fibrosis	70 (1.3%)
	4 / cirrhosis	49 (0.9%)
	missing	4758 (91.5%)
Histology – Necrosis staging (Desmet/Scheuer)	(0) none	20 (0.4%)
	(1) minimal	93 (1.8%)
	(2) mild	174 (3.3%)
	(3) moderate	54 (1.0%)
	(4) severe	13 (0.3%)
	missing	4845 (93.2%)

*Conducted by the pre-treating physician

Source: Table 14.1.15 (Annex 1)

8.2.3 Hepatitis Therapy

The median duration of hepatitis treatment was 172.0 days (range 1 - 706). The mean minimal to maximal doses administered for Pegasys® ranged from 174.3 (±18.9) to 180.0 (±0.0) µg/week, while the mean minimal to maximal dose for Ribavirin ranged from 942.9 (±292.0) to 1048.2 (±244.7) mg/day (Table 14).

Table 14: HCV Treatment -Analysis Population

Parameter	Statistics	Total (N=5199)
Duration of hepatitis therapy [days]	n (missing)	4935 (264)
	Mean (SD)	202.3 (102.6)
	Median	172.0
	Min-Max	1 - 706

Parameter	Statistics	Total (N=5199)
Pegasys®: minimal dose [µg/week]*	n (missing)	5199 (0)
	Mean (SD)	174.3 (18.9)
	Median	180.0
	Min-Max	45 - 180
Pegasys®: maximal dose [µg/week]*	n (missing)	5199 (0)
	Mean (SD)	180.0 (0.0)
	Median	180.0
	Min-Max	180 - 180
Ribavirin: minimal dose [mg/day]*	n (missing)	5183 (16)
	Mean (SD)	942.9 (292.0)
	Median	1000.0
	Min-Max	30 - 2000
Ribavirin: maximal dose [mg/day]*	n (missing)	5183 (16)
	Mean (SD)	1048.2 (244.7)
	Median	1200.0
	Min-Max	30 - 3600

*Minimal and maximal dose were calculated on per patient basis.

Boceprevir (2400 mg/d) and Telaprevir (2250 mg/d) were not displayed as dosing was set.

Source: Table 14.1.4 (Annex 1)

Approximately one-quarter of the patients (25.5%) discontinued Pegasys® therapy prematurely. The most common reasons for treatment discontinuation were lack of virological response (lack of effectiveness; 8.7%) and patients' wishes (5.7%). Death and SAEs were the reason for premature discontinuation of therapy in less than 1% of the patients (0.2% and 0.8%, respectively) (Table 15).

Listing 16.2.1 (Appendix 1) indicates the dates for discontinuation/ completion and the reason for discontinuation including free text explanations.

Table 15: Reasons for Pegasys® Therapy Discontinuation - Analysis Population

Reason for treatment discontinuation	Frequency, n (%) (N=5199)
Patients with premature termination	1327 (25.5%)
Patients with multiple answers	261 (5.0%)
Lack of virological response / lack of effectiveness	454 (8.7%)
Patient's wish	296 (5.7%)
Patient lost to follow-up	218 (4.2%)
Lack of tolerance to Pegasys®	177 (3.4%)
Lack of compliance (treatment incomplete or irregular)	123 (2.4%)
Lack of tolerance to Ribavirin	75 (1.4%)
Lack of tolerance to Telaprevir	57 (1.1%)
Unplanned event (e.g. detention, detoxification)	49 (0.9%)
Patient relocation	43 (0.8%)
Change of treating physician	38 (0.7%)
Lack of tolerance Boceprevir	28 (0.5%)
Death	12 (0.2%)
Lack of tolerance (drug without specification)"	6 (0.1%)
Other reasons	91 (1.8%)
AE	47 (0.9%)
SAE	40 (0.8%)

AE, adverse event; SAE, serious adverse event.

Source: Table 14.1.3 (Annex 1)

8.2.4 Comorbidities

In the AP, 66.2% of the patients had concomitant diseases. The three most common terms in medical history were 'drug substitution' (15.8%), 'state after drug abuse' (15.5%) and 'depression' (13.5%) (Table 16).

Table 16: Medical History by predefined categories in ≥ 5% of Patients - Analysis Population

Category Subcategory	Frequency, n (%) (N=5199)
Patients with concomitant diseases	3441 (66.2%)
Drug abuse	1418 (27.3%)
Drug substitution	824 (15.8%)

Category Subcategory	Frequency, n (%) (N=5199)
State after drug abuse	806 (15.5%)
Others	956 (18.4%)
Psychiatric disorder	800 (15.4%)
Depression	703 (13.5%)
State after suicide attempt	24 (0.5%)
Cardiovascular disease	695 (13.4%)
Arterial hypertension	667 (12.8%)
Acquired immunodeficiency (AIDS/HIV): anti-HIV IgM	382 (7.3%)
Patient was documented in the HIV module	364 (7.0%)
Thyroid dysfunction	314 (6.0%)
Diabetes mellitus	286 (5.5%)

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; IgM, immunoglobulin M; PT, preferred term; SOC, system organ class.

Source: Table 14.1.18 (Annex 1)

8.3 OUTCOME DATA

Data collected in this study originate from routine visits recorded via eCRF documentation (section 7.5). Effectiveness and safety data relate to the 5199 patients who constitute the 'analysis population' (AP). The outcome data on virological response as well as laboratory analysis were displayed in total and per subgroup. Patients were stratified according to their HCV genotype and HCV treatment.

8.4 MAIN RESULTS

8.4.1 Virological Response

Table 17 presents the following virological response rates: early virological response (EVR), end of treatment-response (EoTR) and sustained virological response (SVR) in the AP. Virological response rates are defined in section 7.7.2.

The proportion of responders was the highest in triple therapy Group 2 (Genotype 1 mutation + Boceprevir: EVR: 56.3%; EoTR: 60.0% and SVR: 34.0%) and the smallest in triple therapy Group 1 (EVR: 44.2%, SVR: 14.0%) or Pegasys® monotherapy group (EoTR: 44.2%).

In the AP, HCV PCR data was available for the assessment of virological response rates in 87.7% of the patients for EVR, 69.3% for EoTR and only 32.7% for SVR.

Table 17: Virological Response - Analysis Population and per Subgroup

	Frequency, n (%)					
Virological Response	**Total (N=5199)**	**Mono Therapy (N=165)**	**Dual Therapy Group 1 (N=1525)**	**Dual Therapy Group 2 (N=1389)**	**Triple Therapy Group 1 (N=43)**	**Triple Therapy Group 2 (N=2032)**
Early virological Response (EVR)	2623 (50.5%)	80 (48.5%)	716 (47.0%)	662 (47.7%)	19 (44.2%)	1145 (56.3%)
Patients with measurement 74-94 days after start of treatment	4561 (87.7%)	139 (84.2%)	1314 (86.2%)	1213 (87.3%)	37 (86.0%)	1814 (89.3%)
End of Treatment-Response (EoTR)	3161 (60.8%)	73 (44.2%)	836 (54.8%)	863 (62.1%)	21 (48.8%)	1342 (66.0%)
Patients with measurement at/after End of Treatment	3603 (69.3%)	87 (52.7%)	985 (64.6%)	934 (67.2%)	27 (62.8%)	1538 (75.7%)
Sustained virological Response (SVR)	1414 (27.2%)	28 (17.0%)	338 (22.2%)	342 (24.6%)	6 (14.0%)	690 (34.0%)
Patients with measurement >168 days after End of Treatment	1699 (32.7%)	37 (22.4%)	423 (27.7%)	404 (29.1%)	8 (18.6%)	817 (40.2%)

EoTR, End of Treatment-Response; EVR, Early virological Response; SVR, Sustained virological Response.

Source: Tables 14.2.1, 14.2.2 and 14.2.3 (Annex 1)

8.5 OTHER ANALYSES

Patients were continuously monitored on pre-specified clinical symptoms. Overall, 84.8% of the patients had clinical symptoms that were documented in the eCRF capturing certain clinical symptoms. The three most common clinical symptoms were ‘fatigue’ (55.4%), ‘skin alterations’ (27.8%) and ‘elevated GPT’ (26.9%). Current clinical symptoms that occurred in ≥5% of the AP are displayed in Table 18.

Table 18: Current Clinical Symptoms in ≥ 5% of the Patients - Analysis Population

Parameter	**Frequency, n (%) (N=5199)**
Patients without data	789 (15.2%)
Patients with clinical symptoms	4410 (84.8%)
Fatigue	2878 (55.4%)
Others	2142 (41.2%)

Parameter	Frequency, n (%) (N=5199)
Skin alterations	1446 (27.8%)
Elevated GPT	1401 (26.9%)
Nausea	999 (19.2%)
Headache	966 (18.6%)
Pruritus	863 (16.6%)
Insomnia	821 (15.8%)
Joint pain	810 (15.6%)
Depressive mood	780 (15.0%)
Anemia	739 (14.2%)
Muscle pain	586 (11.3%)
Fever	572 (11.0%)
Abdominal discomfort	555 (10.7%)
Irritability	525 (10.1%)
Weight loss	504 (9.7%)
Depression	454 (8.7%)
Hair loss	424 (8.2%)
Taste sensation disorder	344 (6.6%)
Restlessness	301 (5.8%)
Lack of concentration	275 (5.3%)

GPT, glutamate pyruvate transaminase.
Source: Table 14.3.3.1 (Annex 1)

The Investigators assessed pre-specified clinical symptoms regarding causal relationship to treatment, either to Pegasys®, or to Ribavirin or to both (Table 19).

More than half of the patients had clinical symptoms with causal relationship to treatment (to Pegasys® 67.8%; to Ribavirin 60.8% or to both 54.0%). The most common treatment related clinical symptoms with causal relationship were similar. The three most common clinical symptoms were ‘fatigue’ (Pegasys® 43.9%; Ribavirin 39.6%, both 35.8%), ‘skin alterations’ (Pegasys® 19.2%, Ribavirin 15.0%, both 12.4%) and ‘headache (Pegasys® 16.2%, Ribavirin 11.0%, both 10.5%). In Table 19 current clinical symptoms with causal relationship to treatment are presented, if they occurred in ≥5% of the patients with causal relationship to Pegasys®.

Table 19: Current Clinical Symptoms with Causal Relationship to Treatment Occurring in ≥ 5% of the Patients - Analysis Population

Causal relationship to:			
Parameter	**Pegasys® Frequency, n (%) (N=5199)**	**Ribavirin Frequency, n (%) (N=5199)**	**Pegasys® & Ribavirin Frequency, n (%) (N=5199)**
Patients without data	789 (15.2%)	789 (15.2%)	789 (15.2%)
Patients with clinical symptoms	4410 (84.8%)	4410 (84.8%)	4410 (84.8%)
Patients with clinical symptoms in causal relationship to Pegasys®/ Ribavirin	3525 (67.8%)	3159 (60.8%)	2808 (54.0%)
Fatigue	2281 (43.9%)	2058 (39.6%)	1859 (35.8%)
Others	1575 (30.3%)	1377 (26.5%)	1249 (24.0%)
Skin alterations	999 (19.2%)	782 (15.0%)	647 (12.4%)
Headache	841 (16.2%)	573 (11.0%)	544 (10.5%)
Insomnia	687 (13.2%)	443 (8.5%)	423 (8.1%)
Nausea	633 (12.2%)	730 (14.0%)	546 (10.5%)
Joint pain	641 (12.3%)	443 (8.5%)	333 (6.4%)
Pruritus	619 (11.9%)	523 (10.1%)	434 (8.3%)
Depressive mood	605 (11.6%)	350 (6.7%)	325 (6.3%)
Muscle pain	471 (9.1%)	255 (4.9%)	241 (4.6%)
Fever	501 (9.6%)	216 (4.2%)	208 (4.0%)
Irritability	424 (8.2%)	236 (4.5%)	225 (4.3%)
Weight loss	413 (7.9%)	341 (6.6%)	313 (6.0%)
Anemia	376 (7.2%)	694 (13.3%)	348 (6.7%)
Hair loss	367 (7.1%)	235 (4.5%)	217 (4.2%)
Depression	293 (5.6%)	181 (3.5%)	176 (3.4%)

Source: Tables 14.3.3.2, 14.3.3.3 and 14.3.3.4

8.6 ADVERSE EVENTS AND ADVERSE REACTIONS

The following sections refer to the safety analyses of the AP.

Safety data of the non-analysis population is displayed in Listing 16.2.25.2 for AEs, Listing 16.2.26.2 for AEs with causal relationship, Listing 16.2.27.2 for SAEs and Listing 16.2.25.4for deaths (Annex 3). The non-analysis population did not reveal any new safety signals.

8.6.1 Summary of Adverse Events

In the AP, 4161 patients (80.0%) experienced 22626 adverse events (AEs) during the course of the study. Of these, 3715 patients (71.5%) experienced 16291 AEs related to Pegasys® (Table 20).

A total of 420 (8.1%) patients experience 667 serious adverse events (SAEs). About 4% of the patients had SAEs related to either Pegasys® (4.1%) or Ribavirin (3.8%) and in 2.9% of the patients SAEs were related to both.

AEs leading to death were analyzed of 15 patients (Table 20).

Table 20: Summary of Adverse Events - Analysis Population

	Total (N= 5199) **Patients, n (%) – Events, n**
AEs	4161 (80.0%) - 22626
AEs related to Pegasys®	3715 (71.5%) - 16291
AEs related to Ribavirin	3271 (62.9%) - 12847
AEs related to Pegasys® and Ribavirin	2846 (54.7%) - 10748
Serious AEs (SAEs)	420 (8.1%) - 667
SAEs related to Pegasys®	215 (4.1%) - 310
SAEs related to Ribavirin	196 (3.8%) - 275
SAEs related to Pegasys® and Ribavirin	152 (2.9%) - 207
AEs leading to death	15 (0.3%) - 28

AE, adverse event; SAE,serious adverse event.

Source: Table 14.3.1.1

8.6.2 Incidence of Adverse Events

The majority of reported AEs were mild to moderate in severity (mild: 12810/22626 events, moderate: 8894/22626 events, severe: 785/22626 events) (Table 21).

The most common SOCs with AEs were general disorders and administration site conditions (57.9%), skin and subcutaneous tissue disorders (43.0%), gastrointestinal disorders (33.6%), and psychiatric disorders (31.3%).

The most common AE by PT was fatigue (50.8%). Most commonly fatigue was mild (29.8% of patients; 1650/2870 events) or moderate (21.2% of patients; 1154/2870 events). The second and third most common AEs by PT were skin disorder (25.0%) and anemia (19.2%) (Table 21).

Table 21: Adverse Events Occurring in ≥ 3% of Patients by SOC and PT – Analysis Population

	Total (N=5199) Patients, n (%) / Events, n			
System Organ Class (SOC) Preferred Term (PT)	**Mild**	**Moderate**	**Severe**	**Total**
AEs (%) / Number AEs	3403 (65.5%) /12810	2827 (54.4%) / 8894	518 (10.0%) / 785	4161 (80.0%) /22626
General disorders and administration site conditions	2006 (38.6%) / 2758	1361 (26.2%) / 1726	96 (1.8%) / 112	3008 (57.9%) / 4608
Fatigue	1549 (29.8%) / 1650	1100 (21.2%) / 1154	60 (1.2%) / 62	2642 (50.8%) / 2870
Pyrexia	400 (7.7%) / 412	180 (3.5%) / 185	13 (0.3%) / 13	585 (11.3%) / 612
Irritability	294 (5.7%) / 299	164 (3.2%) / 166	9 (0.2%) / 9	467 (9.0%) / 475
Influenza like illness	151 (2.9%) / 159	68 (1.3%) / 71	3 (0.1%) / 3	219 (4.2%) / 233
Skin and subcutaneous tissue disorders	1579 (30.4%) / 2225	893 (17.2%) / 1186	101 (1.9%) / 122	2238 (43.0%) / 3543
Skin disorder	892 (17.2%) / 932	392 (7.5%) / 402	31 (0.6%) / 33	1298 (25.0%) / 1371
Pruritus	607 (11.7%) / 622	367 (7.1%) / 373	25 (0.5%) / 25	983 (18.9%) / 1022
Alopecia	294 (5.7%) / 299	140 (2.7%) / 141	8 (0.2%) / 9	441 (8.5%) / 450
Rash	121 (2.3%) / 131	116 (2.2%) / 122	36 (0.7%) / 36	263 (5.1%) / 291
Gastrointestinal disorders	1156 (22.2%) / 1642	798 (15.3%) / 1098	68 (1.3%) / 84	1749 (33.6%) / 2838
Nausea	615 (11.8%) / 628	370 (7.1%) / 376	24 (0.5%) / 26	995 (19.1%) / 1034
Diarrhea	184 (3.5%) / 192	115 (2.2%) / 122	12 (0.2%) / 12	304 (5.8%) / 328
Abdominal discomfort	139 (2.7%) / 144	86 (1.7%) / 88	6 (0.1%) / 6	229 (4.4%) / 239
Gastrointestinal pain	87 (1.7%) / 87	69 (1.3%) / 69	3 (0.1%) / 3	160 (3.1%) / 160
Psychiatric disorders	1003 (19.3%) / 1331	804 (15.5%) / 1054	77 (1.5%) / 87	1629 (31.3%) / 2488
Insomnia	397 (7.6%) / 405	328 (6.3%) / 332	9 (0.2%) / 9	730 (14.0%) / 746
Depressed mood	400 (7.7%) / 405	268 (5.2%) / 270	11 (0.2%) / 11	677 (13.0%) / 688
Depression	178 (3.4%) / 180	182 (3.5%) / 185	17 (0.3%) / 18	374 (7.2%) / 386
Restlessness	152 (2.9%) / 152	97 (1.9%) / 97	5 (0.1%) / 5	254 (4.9%) / 255
Nervous system disorders	1009 (19.4%) / 1268	590 (11.3%) / 696	41 (0.8%) / 44	1477 (28.4%) / 2012
Headache	590 (11.3%) / 605	360 (6.9%) / 370	12 (0.2%) / 12	950 (18.3%) / 989

	Total (N=5199) Patients, n (%) / Events, n			
System Organ Class (SOC) Preferred Term (PT)	**Mild**	**Moderate**	**Severe**	**Total**
Dysgeusia	247 (4.8%) / 254	107 (2.1%) / 108	3 (0.1%) / 3	355 (6.8%) / 366
Disturbance in attention	156 (3.0%) / 158	83 (1.6%) / 85	4 (0.1%) / 4	241 (4.6%) / 247
Dizziness	159 (3.1%) / 163	66 (1.3%) / 67	5 (0.1%) / 5	226 (4.3%) / 235
Blood and lymphatic system disorders	585 (11.3%) / 777	778 (15.0%) / 1001	110 (2.1%) / 128	1294 (24.9%) / 1920
Anemia	416 (8.0%) / 426	524 (10.1%) / 544	80 (1.5%) / 84	998 (19.2%) / 1064
Leukopenia	145 (2.8%) / 146	207 (4.0%) / 209	9 (0.2%) / 10	357 (6.9%) / 365
Thrombocytopenia	148 (2.8%) / 151	192 (3.7%) / 195	18 (0.3%) / 19	354 (6.8%) / 367
Musculoskeletal and connective tissue disorders	678 (13.0%) / 891	480 (9.2%) / 613	30 (0.6%) / 37	1109 (21.3%) / 1547
Arthralgia	429 (8.3%) / 445	291 (5.6%) / 301	18 (0.3%) / 18	734 (14.1%) / 769
Myalgia	312 (6.0%) / 318	200 (3.8%) / 200	8 (0.2%) / 8	517 (9.9%) / 526
Respiratory, thoracic and mediastinal disorders	446 (8.6%) / 531	281 (5.4%) / 323	26 (0.5%) / 29	692 (13.3%) / 890
Cough	151 (2.9%) / 152	94 (1.8%) / 97	9 (0.2%) / 9	248 (4.8%) / 260
Dyspnea exertional	110 (2.1%) / 115	55 (1.1%) / 55	3 (0.1%) / 3	165 (3.2%) / 173
Investigations	398 (7.7%) / 446	324 (6.2%) / 357	23 (0.4%) / 26	717 (13.8%) / 836
Weight decreased	288 (5.5%) / 297	201 (3.9%) / 203	11 (0.2%) / 11	498 (9.6%) / 513
Infections and infestations	229 (4.4%) / 277	247 (4.8%) / 313	41 (0.8%) / 47	475 (9.1%) / 655
Metabolism and nutrition disorders	196 (3.8%) / 201	141 (2.7%) / 150	10 (0.2%) / 10	337 (6.5%) / 363
Decreased appetite	161 (3.1%) / 166	105 (2.0%) / 108	4 (0.1%) / 4	266 (5.1%) / 278
Eye disorders	128 (2.5%) / 137	65 (1.3%) / 70	2 (<0.1%) / 3	188 (3.6%) / 210

AE, adverse event; PT, preferred term; Adverse Event; SOC, system organ class.

Source: Table 14.3.1.2

8.6.3 Treatment-Related Adverse Events

8.6.3.1 Pegasys®-Related Adverse Events

A total of 71.5% patients experienced AEs related to Pegasys®. The majority of these Pegasys®-related AEs were mild to moderate in severity (mild: 9306/16291 events, moderate: 6495/16291 events, severe: 479/16291 events) (Table 22).

The most common SOC with Pegasys®-related AEs were general disorders and administration site conditions (51.5%), skin and subcutaneous tissue disorders (31.7%) and psychiatric disorders (28.0%).

The most common Pegasys®-related AE by PT was fatigue (44.2%) which was mild in severity in 25.5% of the patients (1398/2468 events), moderate in 18.7% of the patients 1019/2468 events) and severe in 0.9% of the patients (51/2468 events).

The second and third most common Pegasys®-related AEs by PT were headaches, (16.4%) and skin disorder (16.4%) (Table 22).

Table 22: Pegasys®-Related Adverse Events by SOC and PT in ≥ 3% of Patients – Analysis Population

	Total (N=5199) Patients, n (%) / Events, n			
System Organ Class (SOC) Preferred Term (PT)	**Mild**	**Moderate**	**Severe**	**Total**
Patients with AEs	2935 (56.5%) / 9306	2353 (45.3%) / 6495	330 (6.3%) / 479	3715 (71.5%) / 16291
General disorders and administration site conditions	1772 (34.1%) / 2376	1192 (22.9%) / 1492	78 (1.5%) / 91	2679 (51.5%) / 3959
Fatigue	1328 (25.5%) / 1398	973 (18.7%) / 1019	49 (0.9%) / 51	2297 (44.2%) / 2468
Pyrexia	358 (6.9%) / 368	151 (2.9%) / 155	10 (0.2%) / 10	512 (9.8%) / 533
Irritability	276 (5.3%) / 280	156 (3.0%) / 157	8 (0.2%) / 8	439 (8.4%) / 445
Influenza like illness	135 (2.6%) / 141	53 (1.0%) / 55	2 (<0.1%) / 2	188 (3.6%) / 198
Skin and subcutaneous tissue disorders	1150 (22.1%) / 1523	643 (12.4%) / 840	51 (1.0%) / 64	1649 (31.7%) / 2428
Skin disorder	590 (11.3%) / 612	253 (4.9%) / 258	19 (0.4%) / 21	851 (16.4%) / 892
Pruritus	409 (7.9%) / 417	282 (5.4%) / 286	16 (0.3%) / 16	693 (13.3%) / 719
Alopecia	275 (5.3%) / 279	125 (2.4%) / 126	5 (0.1%) / 5	404 (7.8%) / 410
Psychiatric disorders	889 (17.1%) / 1161	710 (13.7%) / 913	55 (1.1%) / 62	1458 (28.0%) / 2138
Insomnia	352 (6.8%) / 360	301 (5.8%) / 303	7 (0.1%) / 7	656 (12.6%) / 670
Depressed mood	362 (7.0%) / 366	244 (4.7%) / 246	9 (0.2%) / 9	611 (11.8%) / 621
Depression	152 (2.9%) / 154	158 (3.0%) / 161	17 (0.3%) / 18	323 (6.2%) / 333
Restlessness	132 (2.5%) / 132	88 (1.7%) / 88	5 (0.1%) / 5	224 (4.3%) / 225
Nervous system disorders	801 (15.4%) / 966	479 (9.2%) / 552	29 (0.6%) / 31	1211 (23.3%) / 1549
Headache	522 (10.0%) / 529	332 (6.4%) / 339	11 (0.2%) / 11	853 (16.4%) / 879
Disturbance in attention	136 (2.6%) / 138	78 (1.5%) / 80	3 (0.1%) / 3	215 (4.1%) / 221
Dizziness	127 (2.4%) / 130	57 (1.1%) / 58	4 (0.1%) / 4	184 (3.5%) / 192
Gastrointestinal disorders	677 (13.0%) / 887	452 (8.7%) / 585	30 (0.6%) / 39	1049 (20.2%) / 1513
Nausea	396 (7.6%) / 399	230 (4.4%) / 232	10 (0.2%) / 12	627 (12.1%) / 643
Diarrhea	88 (1.7%) / 92	64 (1.2%) / 67	7 (0.1%) / 7	158 (3.0%) / 167

	Total (N=5199) Patients, n (%) / Events, n			
System Organ Class (SOC) Preferred Term (PT)	**Mild**	**Moderate**	**Severe**	**Total**
Musculoskeletal and connective tissue disorders	577 (11.1%) / 748	409 (7.9%) / 522	18 (0.3%) / 24	945 (18.2%) / 1294
Arthralgia	391 (7.5%) / 402	260 (5.0%) / 269	14 (0.3%) / 14	659 (12.7%) / 685
Myalgia	281 (5.4%) / 285	186 (3.6%) / 186	8 (0.2%) / 8	472 (9.1%) / 479
Blood and lymphatic system disorders	362 (7.0%) / 453	517 (9.9%) / 668	66 (1.3%) / 79	848 (16.3%) / 1203
Anemia	159 (3.1%) / 162	257 (4.9%) / 264	40 (0.8%) / 43	450 (8.7%) / 471
Thrombocytopenia	130 (2.5%) / 133	175 (3.4%) / 178	16 (0.3%) / 17	316 (6.1%) / 328
Leukopenia	125 (2.4%) / 125	184 (3.5%) / 185	8 (0.2%) / 9	314 (6.0%) / 319
Investigations	312 (6.0%) / 334	250 (4.8%) / 270	14 (0.3%) / 16	562 (10.8%) / 620
Weight decreased	246 (4.7%) / 253	180 (3.5%) / 182	10 (0.2%) / 10	433 (8.3%) / 445
Respiratory, thoracic and mediastinal disorders	297 (5.7%) / 345	189 (3.6%) / 211	14 (0.3%) / 15	467 (9.0%) / 571
Cough	100 (1.9%) / 101	62 (1.2%) / 64	7 (0.1%) / 7	163 (3.1%) / 172
Metabolism and nutrition disorders	156 (3.0%) / 159	110 (2.1%) / 115	9 (0.2%) / 9	269 (5.2%) / 283
Decreased appetite	135 (2.6%) / 138	90 (1.7%) / 92	4 (0.1%) / 4	227 (4.4%) / 234
Infections and infestations	78 (1.5%) / 89	88 (1.7%) / 100	20 (0.4%) / 24	174 (3.3%) / 214

AE, adverse event; PT, preferred term; SOC, system organ class.

Source: Table 14.3.1.3

8.6.3.2 Ribavirin-Related Adverse Events

A total of 62.9% patients experienced AEs related to Ribavirin. The majority of these Ribavirin-related AEs were mild to moderate in severity (mild: 7138/12847 events, moderate: 5270/12847 events, severe: 430/12847 events) (Table 23).

The most common SOCs with Ribavirin-related AEs were general disorders and administration site conditions (41.4%); skin and subcutaneous tissue disorders (24.3%); and gastrointestinal disorders (21.5%).

The most common Ribavirin-related AE by PT was fatigue (37.8%) which was mild in severity in 21.5% of the patients (1167/2096 events), moderate in 16.2% of the patients (881/2096 events) and severe in 0.9% of the patients (48/2096 events).

The second and third most common Ribavirin-related AEs by PT were anemia (17.9%) and nausea (13.9%) (Table 23).

Table 23: Ribavirin-Related Adverse Events by SOC and PT in ≥ 3% of Patients – Analysis Population

	Total (N=5199) Patients, n (%) / Events, n			
System Organ Class (SOC) Preferred Term (PT)	**Mild**	**Moderate**	**Severe**	**Total**
Patients with AEs	2457 (47.3%) / 7138	2056 (39.5%) / 5270	307 (5.9%) / 430	3271 (62.9%) / 12847
General disorders and administration site conditions	1314 (25.3%) / 1617	969 (18.6%) / 1149	65 (1.3%) / 74	2153 (41.4%) / 2840
Fatigue	1116 (21.5%) / 1167	843 (16.2%) / 881	48 (0.9%) / 48	1966 (37.8%) / 2096
Irritability	129 (2.5%) / 131	90 (1.7%) / 90	4 (0.1%) / 4	222 (4.3%) / 225
Pyrexia	141 (2.7%) / 144	68 (1.3%) / 70	4 (0.1%) / 4	208 (4.0%) / 218
Skin and subcutaneous tissue disorders	840 (16.2%) / 1128	521 (10.0%) / 671	46 (0.9%) / 60	1265 (24.3%) / 1861
Skin disorder	446 (8.6%) / 461	195 (3.8%) / 199	13 (0.3%) / 14	644 (12.4%) / 675
Pruritus	319 (6.1%) / 325	234 (4.5%) / 238	13 (0.3%) / 13	555 (10.7%) / 576
Alopecia	152 (2.9%) / 154	86 (1.7%) / 86	7 (0.1%) / 8	245 (4.7%) / 248
Gastrointestinal disorders	728 (14.0%) / 990	484 (9.3%) / 645	29 (0.6%) / 36	1120 (21.5%) / 1673
Nausea	464 (8.9%) / 471	254 (4.9%) / 258	10 (0.2%) / 11	721 (13.9%) / 741
Diarrhea	103 (2.0%) / 107	67 (1.3%) / 68	5 (0.1%) / 5	172 (3.3%) / 180
Blood and lymphatic system disorders	511 (9.8%) / 633	637 (12.3%) / 787	96 (1.8%) / 108	1135 (21.8%) / 1532
Anemia	395 (7.6%) / 403	487 (9.4%) / 503	75 (1.4%) / 77	933 (17.9%) / 987
Thrombocytopenia	108 (2.1%) / 111	132 (2.5%) / 132	8 (0.2%) / 9	245 (4.7%) / 252
Leukopenia	89 (1.7%) / 89	123 (2.4%) / 125	8 (0.2%) / 9	217 (4.2%) / 223
Psychiatric disorders	511 (9.8%) / 628	421 (8.1%) / 534	39 (0.8%) / 41	878 (16.9%) / 1203
Insomnia	205 (3.9%) / 206	188 (3.6%) / 191	5 (0.1%) / 5	398 (7.7%) / 402
Depressed mood	175 (3.4%) / 177	129 (2.5%) / 131	7 (0.1%) / 7	310 (6.0%) / 315
Depression	89 (1.7%) / 89	82 (1.6%) / 84	10 (0.2%) / 10	178 (3.4%) / 183
Nervous system disorders	567 (10.9%) / 681	358 (6.9%) / 409	20 (0.4%) / 23	884 (17.0%) / 1113
Headache	313 (6.0%) / 320	230 (4.4%) / 234	8 (0.2%) / 8	545 (10.5%) / 562

	Total (N=5199) Patients, n (%) / Events, n			
System Organ Class (SOC) Preferred Term (PT)	**Mild**	**Moderate**	**Severe**	**Total**
Dizziness	111 (2.1%) / 114	57 (1.1%) / 58	3 (0.1%) / 3	168 (3.2%) / 175
Musculoskeletal and connective tissue disorders	304 (5.8%) / 392	216 (4.2) / 260	9 (0.2%) / 12	499 (9.6%) / 664
Arthralgia	200 (3.8%) / 205	130 (2.5%) / 131	8 (0.2%) / 8	334 (6.4%) / 344
Myalgia	141 (2.7%) / 142	90 (1.7%) / 90	3 (0.1%) / 3	234 (4.5%) / 235
Respiratory, thoracic and mediastinal disorders	321 (6.2%) / 371	211 (4.1%) / 236	17 (0.3%) / 19	513 (9.9%) / 626
Cough	91 (1.8%) / 92	76 (1.5%) / 77	7 (0.1%) / 7	168 (3.2%) / 176
Investigations	265 (5.1%) / 286	212 (4.1%) / 227	16 (0.3%) / 18	476 (9.2%) / 531
Weight decreased	199 (3.8%) / 203	137 (2.6%) / 138	10 (0.2%) / 10	343 (6.6%) / 351
Metabolism and nutrition disorders	138 (2.7%) / 142	105 (2.0%) / 110	7 (0.1%) / 7	243 (4.7%) / 259
Decreased appetite	120 (2.3%) / 124	88 (1.7%) / 90	3 (0.1%) / 3	209 (4.0%) / 217

AE, adverse event; PT, preferred term; SOC, system organ class.

Source: Table 14.3.1.4

8.6.3.3 Adverse Events Related to both Pegasys® and Ribavirin

The proportion of patients with AEs related to both Pegasys® and Ribavirin was smaller for treatment related AEs to either Pegasys® or Ribavirin (related to both: 54.7%, Pegasys®-related: 71.5%, Ribavirin-related: 62.9%).

The majority of AEs experienced by patients related to both Pegasys® and Ribavirin were mild to moderate in severity (mild: 5903/10748 events, moderate: 4502/10748 events, severe: 340/10748 events).

The most common SOC with treatment related AEs was general disorders and administration site conditions (37.1%), similar to the high frequency in this SOC for AEs related to either Pegasys® or Ribavirin. The other SOCs with the most treatment related AEs were skin and subcutaneous tissue disorders (20.4%) and gastrointestinal disorders (16.3%).

The most common treatment related AE by PT was fatigue with (33.5%), which was mild in severity in 18.9% of the patients (1021/1854 events), moderate in 14.6% of the patients (793/1854 events) and severe in 0.8% of the patients (40/1854 events).

The second and third most common treatment related AEs by PT were skin disorder (10.1%) and nausea (10.0%) (Table 24).

Table 24: Adverse Events Related to Pegasys® and Ribavirin by SOC and PT in ≥ 3% of Patients- Analysis Population

	Total (N=5199) Patients, n (%) / Events, n			
System Organ Class (SOC) Preferred Term (PT)	**Mild**	**Moderate**	**Severe**	**Total**
Patients with AEs	2099 (40.4%) / 5903	1754 (33.7%) / 4502	245 (4.7%) / 340	2846 (54.7%) / 10748
General disorders and administration site conditions	1178 (22.7%) / 1456	878 (16.9%) / 1046	57 (1.1%) / 65	1930 (37.1%) / 2567
Fatigue	981 (18.9%) / 1021	758 (14.6%) / 793	40 (0.8%) / 40	1743 (33.5%) / 1854
Irritability	127 (2.4%) / 129	88 (1.7%) / 88	4 (0.1%) / 4	218 (4.2%) / 221
Pyrexia	140 (2.7%) / 143	65 (1.3%) / 67	4 (0.1%) / 4	204 (3.9%) / 214
Skin and subcutaneous tissue disorders	674 (13.0%) / 882	461 (8.9%) / 596	37 (0.7%) / 48	1058 (20.4%) / 1527
Skin disorder	347 (6.7%) / 360	173 (3.3%) / 176	12 (0.2%) / 13	524 (10.1%) / 550
Pruritus	243 (4.7%) / 248	208 (4.0%) / 212	12 (0.2%) / 12	452 (8.7%) / 472
Alopecia	141 (2.7%) / 143	80 (1.5%) / 80	4 (0.1%) / 4	225 (4.3%) / 227
Gastrointestinal disorders	535 (10.3%) / 718	376 (7.2%) / 489	22 (0.4%) / 28	847 (16.3%) / 1235
Nausea	321 (6.2%) / 324	196 (3.8%) / 197	7 (0.1%) / 8	519 (10.0%) / 529
Psychiatric disorders	480 (9.2%) / 594	410 (7.9%) / 519	36 (0.7%) / 38	835 (16.1%) / 1151
Insomnia	194 (3.7%) / 195	185 (3.6%) / 187	4 (0.1%) / 4	383 (7.4%) / 386
Depressed mood	164 (3.2%) / 166	123 (2.4%) / 125	6 (0.1%) / 6	292 (5.6%) / 297
Depression	85 (1.6%) / 85	80 (1.5%) / 82	10 (0.2%) / 10	172 (3.3%) / 177
Nervous system disorders	519 (10.0%) / 621	341 (6.6%) / 389	20 (0.4%) / 22	825 (15.9%) / 1032
Headache	290 (5.6%) / 294	225 (4.3%) / 229	8 (0.2%) / 8	517 (9.9%) / 531
Dizziness	103 (2.0%) / 106	53 (1.0%) / 54	3 (0.1%) / 3	156 (3.0%) / 163
Blood and lymphatic system disorders	278 (5.3%) / 344	388 (7.5%) / 498	52 (1.0%) / 62	670 (12.9%) / 905
Anemia	148 (2.8%) / 150	242 (4.7%) / 248	36 (0.7%) / 37	420 (8.1%) / 436
Thrombocytopenia	95 (1.8%) / 98	122 (2.3%) / 122	6 (0.1%) / 7	221 (4.3%) / 227
Leukopenia	74 (1.4%) / 74	105 (2.0%) / 106	7 (0.1%) / 8	184 (3.5%) / 188

	Total (N=5199) Patients, n (%) / Events, n			
System Organ Class (SOC) Preferred Term (PT)	**Mild**	**Moderate**	**Severe**	**Total**
Musculoskeletal and connective tissue disorders	286 (5.5%) / 370	211 (4.1%) / 255	9 (0.2%) / 12	477 (9.2%) / 637
Arthralgia	191 (3.7%) / 195	128 (2.5%) / 129	8 (0.2%) / 8	323 (6.2%) / 332
Myalgia	132 (2.5%) / 132	87 (1.7%) / 87	3 (0.1%) / 3	222 (4.3%) / 222
Respiratory, thoracic and mediastinal disorders	248 (4.8%) / 288	171 (3.3%) / 189	11 (0.2%) / 11	404 (7.8%) / 488
Investigations	236 (4.5%) / 251	183 (3.5%) / 197	13 (0.3%) / 15	422 (8.1%) / 463
Weight decreased	183 (3.5%) / 187	129 (2.5%) / 130	9 (0.2%) / 9	318 (6.1%) / 326
Metabolism and nutrition disorders	125 (2.4%) / 127	97 (1.9%) / 102	7 (0.1%) / 7	224 (4.3%) / 236
Decreased appetite	107 (2.1%) / 109	81 (1.6%) / 83	3 (0.1%) / 3	190 (3.7%) / 195

AE, adverse event; PT, preferred term; SOC, system organ class.

Source: Table 14.3.1.5

8.6.4 Overview of Serious Adverse Events

In total, 8.1% of the patients experienced 667 SAEs. There were more severe SAEs documented, than those of a mild to moderate severity (severe: 277/667 events, mild: 63/667 events, moderate: 242/667 events).

The most common SAEs belong to the SOCs: blood and lymphatic system disorders (2.3%), infections and infestations (1.3%), and psychiatric disorders (1.0%). The most common SAE by PT was anemia (1.5%).

An overview of the SAEs documented during the study is summarized in Table 25 for SAEs occurring in ≥ 1% of patients of the AP.

Table 25: Overview of Serious Adverse Events in ≥ 1% of Patients – Analysis Population

	Total (N=5199) Patients, n (%) / Events, n			
System Organ Class (SOC) Preferred Term (PT)	**Mild**	**Moderate**	**Severe**	**Total**
Patients with SAEs	52 (1.0%) / 63	182 (3.5%) / 242	216 (4.2%) / 277	420 (8.1%) / 667
Blood and lymphatic system disorders	19 (0.4%) / 20	53 (1.0%) / 54	48 (0.9%) / 50	122 (2.3%) / 135
Anemia	7 (0.1%) / 8	32 (0.6%) / 32	34 (0.7%) / 36	79 (1.5%) / 84
Infections and infestations	8 (0.2%) / 8	22 (0.4%) / 22	30 (0.6%) / 35	65 (1.3%) / 79
Psychiatric disorders	4 (0.1%) / 4	23 (0.4%) / 30	27 (0.5%) / 32	52 (1.0%) / 70
Gastrointestinal disorders	1 (<0.1%) / 1	22 (0.4%) / 24	21 (0.4%) / 25	50 (1.0%) / 60

PT, preferred term; SAE, serious adverse event; SOC, system organ class.

Source: Table 14.3.1.6

8.6.4.1 Serious Adverse Events Related to Pegasys® or Ribavirin

The proportion of patients with SAEs related to either Pegasys® or Ribavirin were similar (Pegasys®-related: 4.1%, Ribavirin-related: 3.8%).

There were more severe treatment related SAEs documented than mild or moderate events (severe SAEs: Pegasys®-related 146/310 events, Ribavirin-related 130/275 events). The most common treatment related SAEs belong to SOC blood and lymphatic system disorders (Pegasys®-related: 1.5% of the patients; Ribavirin-related: 1.9% of the patients). A summary of treatment related SAEs ≥ 1% of patients is presented in Table 26.

Table 26: Serious Adverse Events Related to Pegasys® or Ribavirin in ≥ 1% of Patients – Analysis Population

	Total (N=5199) Patients, n (%) / Events, n			
System Organ Class (SOC) Preferred Term (PT)	**Mild**	**Moderate**	**Severe**	**Total**
	Pegasys®			
Patients with SAEs	26 (0.5%) / 31	90 (1.7%) / 122	111 (2.1%) / 146	215 (4.1%) / 310
Blood and lymphatic system disorders	11 (0.2%) / 11	37 (0.7%) / 38	29 (0.6%) / 31	76 (1.5%) / 83
	Ribavirin			
Patients with SAEs	23 (0.4%) / 25	80 (1.5%) / 111	105 (2.0%) / 130	196 (3.8%) / 275
Blood and lymphatic system disorders	14 (0.3%) / 15	42 (0.8%) / 43	44 (0.8%) / 44	98 (1.9%) / 106
Anemia	6 (0.1%) / 7	27 (0.5%) / 27	32 (0.6%) / 32	67 (1.3%) / 70

PT, preferred term; SAE, serious adverse event; SOC, system organ class.

Source: Tables 14.3.1.7, 14.3.1.8

8.6.4.2 Serious Adverse Events Related to Both Pegasys® and Ribavirin

In total, 2.9% patients experienced 207 SAEs related to both Pegasys® and Ribavirin. There were more patients with severe SAEs related to both Pegasys® and Ribavirin than moderate or mild treatment related SAEs (severe: 99/207 events, moderate: 88/207 events, mild: 17/207 events) (Table 27). The most common SOC associated with SAEs related to both Pegasys® and Ribavirin was blood and lymphatic system disorders, as also observed for SAEs related to either Pegasys® or Ribavirin.

Table 27: Serious Adverse Events Related to Both Pegasys® and Ribavirin in ≥ 1% of Patients – Analysis Population

	Total (N=5199) Patients, n (%) / Events, n			
System Organ Class (SOC) Preferred Term (PT)	**Mild**	**Moderate**	**Severe**	**Total**
Patients with SAEs	16 (0.3%) / 17	63 (1.2%) / 88	82 (1.6%) / 99	152 (2.9%) / 207
Blood and lymphatic system disorders	9 (0.2%) / 9	30 (0.6%) / 31	26 (0.5%) / 26	63 (1.2%) / 67

PT, preferred term;SAE, serious adverse event; SOC, system organ class.

Source Table: 14.3.1.9

8.6.4.3 AEs Leading to Death

AEs leading to death are presented in Table 28 and Table 29.

A total of 17 patients of AP died during NIS participation (Table 29). There were 15 deaths analyzed according to SOC and PT in this study (Source Table 14.3.1.11). The 28 events of these 15 patients were recorded as AEs leading to death within the eCRF.

For one patient death was recorded without corresponding AE (Patient ID 8270, Listing 16.2.1) and for the other patient a PT 'fever' and date of death was documented, but the AE was not recorded as leading to death (Patient ID 7720, Listing 16.2.25.3). Therefore, these 2 patients were not analyzed in the Source Tables 14.3.1.1 and 14.3.1.11 (Annex 1).

Three deaths each were associated with the following SOCs: general disorders and administration site conditions, infections and infestations, and hepatobiliary disorders. The three most common PTs associated with fatal AEs were death, sepsis and hepatorenal syndrome (Table 28).

Table 28: Adverse Events Leading to Death by SOC and PT – Analysis Population

System Organ Class (SOC) Preferred Term (PT)	Total (N=5199) Patients, n (%) / Events, n
Patients with AEs leading to death	15 (0.3%) / 28
General disorders and administration site conditions	3 (0.1%) / 5
Death	3 (0.1%) / 3
Fatigue	1 (<0.1%) / 2
Infections and infestations	3 (0.1%) / 5
Sepsis	2 (<0.1%) / 2
Urinary tract infection	1 (<0.1%) / 1
Febrile infection	1 (<0.1%) / 1
Endocarditis	1 (<0.1%) / 1
Gastrointestinal disorders	2 (<0.1%) / 4
Abdominal compartment syndrome	1 (<0.1%) / 1
Nausea	1 (<0.1%) / 1
Abdominal pain	1 (<0.1%) / 1
Abdominal discomfort	1 (<0.1%) / 1
Hepatobiliary disorders	3 (0.1%) / 3
Hepatorenal syndrome	2 (<0.1%) / 2
Jaundice	1 (<0.1%) / 1
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (<0.1%) / 2
Hepatic neoplasm malignant	1 (<0.1%) / 1
Brain neoplasm	1 (<0.1%) / 1
Nervous system disorders	1 (<0.1%) / 2

System Organ Class (SOC) Preferred Term (PT)	Total (N=5199) Patients, n (%) / Events, n
Headache	1 (<0.1%) / 1
Disturbance in attention	1 (<0.1%) / 1
Psychiatric disorders	2 (<0.1%) / 2
Depressed mood	1 (<0.1%) / 1
Completed suicide	1 (<0.1%) / 1
Blood and lymphatic system disorders	1 (<0.1%) / 1
Anemia	1 (<0.1%) / 1
Cardiac disorders	1 (<0.1%) / 1
Cardiac failure acute	1 (<0.1%) / 1
Investigations	1 (<0.1%) / 1
Alanine aminotransferase increased	1 (<0.1%) / 1
Musculoskeletal and connective tissue disorders	1 (<0.1%) / 1
Arthralgia	1 (<0.1%) / 1
Respiratory, thoracic and mediastinal disorders	1 (<0.1%) / 1
Pulmonary fibrosis	1 (<0.1%) / 1

AE, adverse event; PT, preferred term; SOC, system organ class.

Source Table: 14.3.1.11

A Listing of the deaths documented in the study, the AEs and relationship to Pegasys® treatment (i.e. yes, no or causality is missing) are presented in Table 29.

Table 29: Listing of Deaths

Patient ID	AE by PT	Related to Pegasys® treatment
550	Death	not reported
972	Sepsis	yes
	Hepatorenal Syndrome	yes
1294	Hepatorenal Syndrome	no
1699	Jaundice	no
1982	Endocarditis	not reported
2132	Abdominal Compartment Syndrome	yes
2256	Urinary Tract Infection	yes
	Febrile Infection	yes
	Sepsis	yes
2356	Anaemia	yes
2588	Cardiac Failure Acute	yes
3590	Hepatic Neoplasm Malignant	no
4245	Pulmonary Fibrosis	not reported
5115	Depressive Mood	yes
	Abdominal Discomfort	no
	Abdominal Pain	no
	Arthralgia	yes

Patient ID	AE by PT	Related to Pegasys® treatment
	Disturbance In Attention	yes
	Headache	no
	Fatigue	yes
	Alanine Aminotransferase Increased	yes
	Nausea	no
	Death	not reported
5737	Brain Neoplasm	no
7220	Pyrexia	no
7479	Death	no
8270	No Adverse Event Documented	not reported
9046	Completed Suicide	yes

AE, adverse event; ID, identification; PT, preferred term.
Source: Listing 16.2.25.3

It was noticed, that for one patient (Pat. ID 2356) the SAE 'Anemia' was reported with fatal outcome in the clinical database (CDB), but in the safety database (SDB) the SAE leading to death was 'Liver failure', this information was based on a telephone contact report from Roche Safety with the site.

For another patient (Pat.ID 7220) the SAE 'Fever' was reported with fatal outcome in the CDB, but in the SDB the SAE leading to death was 'Multi-organ failure', based on follow-up information sent directly to Roche by the Investigator.

Both discrepancies were noticed by Roche Safety during review of the statistical output of this final analysis regarding 'death' (Listing 16.2.25.3 and Tables 14.3.1.1 and 14.3.1.11), but were not assessed during safety reconciliation and therefore not listed in the discrepancy report.

8.6.5 Pregnancies

As per study protocol, pregnancies were reported directly to Roche by the participating physicians within one working day and were processed within the Roche drug safety database. The occurrence of pregnancies was to be documented up to 7 months after end of therapy for female partner of male patients and up to 4 months for female patients as mandated by the respective SmPC and the study protocol.

In total, four pregnancy cases were reported during the observational period 03 October 2011 until 14 July 2014 (QTT062578, Annex 1).

The relevant details for each pregnancy case are summarized in the following:

Maternal exposure (Pat. ID 3858)

The female patient received triple therapy (Pegasys®, Ribavirin, and Telaprevir). In the patient medical history, nicotine and drug abuse was mentioned. During pregnancy, the patient received a methadone substitution therapy. It was reported that the infant

had intrauterine growth retardation and was born with neonatal abstinence syndrome. The treating physician assessed the causality for neonatal abstinence syndrome and intrauterine growth retardation as not related to Peginterferon alfa-2a but as related to Levomethadone hydrochloride substitution therapy and nicotine abuse.

Paternal exposure (Pat. ID 843)

The case concerned a male patient who received dual therapy (Pegasys® with Ribavirin). He impregnated his female partner. The pregnancy was terminated by therapeutic abortion. No causality assessment was provided by the treating physician.

Paternal exposure (Pat. ID 6633)

The patient's partner became pregnant while the patient received therapy with Peginterferon alfa-2a and Ribavirin. Concomitant diseases included methadone dependence. Further case details are not available due to lost to follow-up.

Paternal exposure (Pat. ID 4078)

During triple therapy, the male patient exposed his female partner in the 2nd, 3rd pregnancy trimester to Pegasys®, Ribavirin and Telaprevir. A condom was used as a contraception method. Pregnancy outcome was live birth with a normal healthy baby.

8.6.6 Discrepancies Between Safety and Clinical Database

For all enrolled patients (N=9822), AEs have been reconciled between the CDB and the SDB. After AE reconciliation, a total number of 11,946 discrepancies between the CDB and the SDB have been identified regarding seriousness, causal relationship, PT coding and SOC allocation of PTs (Annex 2).

9. DISCUSSION

9.1 KEY RESULTS

The following sections summarize the key results of this final analysis with reference to the study objectives.

9.1.1 Key Results Regarding Baseline Characteristics

Two-thirds of the AP were male (67.0%), had a median age of 45.0 years and about half of the patients were overweight (BMI >25 kg/m^2: 54.2%). Data on systolic blood pressure at baseline was available of 60.8% of the patients, of whom most had a normal or normal high blood pressure (normal: 19.6% and normal high: 14.5%).

At study start, the majority of patients did not consume alcohol (84.0%) and were either current smokers (44.3%) or non-smokers (50.2%).

Co-infection with hepatitis B was assessed at baseline, but only about half of the patients (47.5%) had data on hepatitis B laboratory diagnostics collected less than 12 months ago. Out of those patients with data, most patients were tested negative on HBsAg (52.5%) and negative on anti-HBc (39.5%).

9.1.2 Key Results Regarding HCV Anamnesis and HCV Therapy

HCV anamnesis

In the AP, the median estimated duration of HCV infection was 11 years and 62.0% of patients were positive for HCV antibodies. The most frequent route of transmission of hepatitis C was drugs (37.4%).

Only one-third of the patients (33.6%) received previous antiviral therapy. Out of these 1746 patients, the majority received PegIFN-monotherapy (75.2%). About half of the patients with prior HCV treatment experienced a relapse (50.5%) or no virological response (37.8%).

Regarding HCV genotyping, Genotype 1 was the predominant group followed by Genotype 3 (68.5% and 24.1%, respectively). Ultrasound diagnostic results of the liver were ‘normal’ in about half of the patients (48.8%). and revealed an image of chronic liver disease in 11.7% of the patients, and fatty liver in 10.2% of the patients.

Key results regarding HCV anamnesis are depicted in Table 30.

Table 30: Key Results Regarding HCV Anamnesis

Parameter	Statistics	Total (N = 5199)
Estimated duration of HCV infection [years]	Median (range)	11.0 (1 – 60)
HCV antibody	positive	3223 (62.0%)
Route of HCV transmission	Drugs	1942 (37.4%)
Anamnesis of HCV	Pretreated patients	1746 (33.6%)
Last previous therapy	Pretreated patients	1746 (100.0%)
	PegIFN-Monotherapy	1313/1746 (75.2%)
Result of previous therapy	Relapse	882/1746 (50.5%)
	Non-response: added up	660/1746 (37.8%)

Parameter	Statistics	Total (N = 5199)
HCV genotype	Genotype 1	3561 (68.5%)
	Genotype 3	1252 (24.1%)
Ultrasound liver	Normal results	2535 (48.8%)
	Image of a chron. liver disease	606 (11.7%)
	Fatty liver	531 (10.2%)

HCV therapy during the NIS

The median duration of hepatitis treatment was 172.0 days. The mean minimal to maximal doses administered for Pegasys® ranged from 174.3 - 180.0 µg/week, while the mean minimal to maximal dose for Ribavirin ranged from 942.9 - 1048.2 mg/day.

Approximately one-quarter of the patients (25.5%) discontinued Pegasys® therapy prematurely. The most common reasons for treatment discontinuation were lack of virological response (lack of effectiveness; 8.7%) and patients' wishes (5.7%). Death and SAEs were the reason for premature discontinuation of therapy in less than 1% of the patients (0.2% and 0.8%, respectively).

Key results regarding HCV therapy are presented in Table 31.

Table 31: Key Results Regarding HCV Therapy

Parameter	Statistics	Total (N = 5199)
Duration of hepatitis therapy [days]	Median (range)	172.0 (1-706)
Pegasys®:		
minimal dose [µg/week]*	Mean (SD)	174.3 (18.9)
maximal dose [µg/week]*	Mean (SD)	180.0 (0.0)
Ribavirin:		
minimal dose [mg/day]*	Mean (SD)	942.9 (292.0)
maximal dose [mg/day]*	Mean (SD)	1048.2 (244.7)
Patients with premature treatment termination		1327 (25.5%)
Reasons thereof:		
Lack of virological response / lack of effectiveness		454 (8.7%)
Patient's wish		296 (5.7%)
Death		12 (0.2%)
SAE		40 (0.8%)

9.1.3 Key Results of Comorbities and Clinical Symptoms

Comorbidities

In the AP, 66.2% of the patients had concomitant diseases. The three most common terms in medical history were 'drug substitution' (15.8%), 'state after drug abuse' (15.5%) and 'depression' (13.5%).

Clinical Symptoms

Patients were continuously monitored on pre-specified clinical symptoms. Overall, 84.8% of the patients had certain clinical symptoms that were documented in the eCRF capturing certain clinical symptoms. More than half of the patients had clinical

symptoms with causal relationship to treatment (to Pegasys® 67.8%; to Ribavirin 60.8% or to both 54.0%). The three most common treatment related clinical symptoms were 'fatigue' (Pegasys® 43.9%; Ribavirin 39.6%, both 35.8%), 'skin alterations' (Pegasys® 19.2%, Ribavirin 15.0%, both 12.4%) and 'headache (Pegasys® 16.2%, Ribavirin 11.0%, both 10.5%).

9.1.4 Key Results Regarding Effectiveness Objective

The proportion of responders was the highest in triple therapy Group 2 (Genotype 1 mutation + Boceprevir: EVR: 56.3%; EoTR: 66.0 and SVR: 34.0%) and the smallest in triple therapy Group 1 (EVR: 44.2%, SVR: 14.0%) or monotherapy group (EoTR: 44.2%).

In the AP, HCV PCR data was available for the assessment of virological response rates in 87.7% of the patients for EVR, 69.3% for EoTR and only 32.7% for SVR.

The key results regarding virological responses EVR, EoTR and SVR are presented in Table 32.

Table 32: Key Effectiveness Results – Analysis Population

Virological Response	Frequency, n (%) (N=5199)
Early virological Response (EVR)	**2623 (50.5%)**
Patients with measurement 74-94 days after start of treatment	4561 (87.7%)
End of Treatment-Response (EoTR)	**3161 (60.8%)**
Patients with measurement at/after End of Treatment	3603 (69.3%)
Sustained virological Response (SVR)	**1414 (27.2%)**
Patients with measurement >168 days after End of Treatment	1699 (32.7%)

9.1.5 Key Results Regarding Safety Objective

In the AP, 4161 patients (80.0%) experienced 22626 AEs during the course of the study. Of these, 71.5% experienced AEs related to Pegasys®, 62.9% experienced AEs related to Ribavirin, and 54.7% experienced AEs related to both Pegasys® and Ribavirin.

The majority of reported AEs were mild to moderate in severity (mild: 12810/22626 events, moderate: 8894/22626 events, severe: 785/22626 events). The most common SOC with AEs was general disorders and administration site conditions (57.9%), and the most common AE by PT was fatigue 50.8%.

The most common SOC with all treatment related AEs was general disorders and administration site conditions (Pegasys®-related AE: 51.5% of the patients, Ribavirin-related AEs: 41.4% of the patients, and AEs related to both 37.1% of the patients). The most common treatment related AE by PT was fatigue (Pegasys®-related: 44.2% of the patients, Ribavirin-related AEs 37.8% of the patients, and AEs related to both: 33.5% of the patients).

In total, 8.1% of the patients experienced SAEs. There were more severe SAEs documented, than those of a mild to moderate severity (severe: 277/667 events, mild: 53/667 events, moderate: 242/667 events). The proportion of patients with SAEs related to either Pegasys® or Ribavirin were similar (Pegasys®-related: 4.1%, Ribavirin-related: 3.8%).

The most common treatment related SAEs belong to SOC blood and lymphatic system disorders (Pegasys®-related: 1.5% of the patients; Ribavirin-related: 1.9% of the patients; both: 1.2% of the patients) and PT anemia (Pegasys®-related: 0.8% of the patients; Ribavirin-related: 1.3% of the patients; both: 0.7% of the patients).

There were 15 deaths analyzed according to SOC and PT in this study, but 17 patients died during NIS participation. For one patient death was recorded without corresponding AE (Patient ID 8270, Listing 16.2.1) and for the other patient an AE, namely PT 'fever', and date of death were documented, but the AE was not recorded as leading to death (Patient ID 7720, Listing 16.2.25.3).

Table 33: Key Safety Results- Analysis Population

AEs **System Organ Class (SOC)** **Preferred Term (PT)**	**Total (N= 5199)** **Patients, n (%) – Events, n**
AEs	**4161 (80.0%) - 22626**
General disorders and administration site conditions	3008 (57.9%) - 4608
Fatigue	2642 (50.8%) - 2870
AEs related to Pegasys®	**3715 (71.5%) - 16291**
AEs related to Ribavirin	**3271 (62.9%) - 12847**
AEs related to Pegasys® and Ribavirin	**2846 (54.7%) - 10748**
SAEs	**420 (8.1%) - 667**
Blood and lymphatic system disorders	122 (2.3%) - 135
Anemia	79 (1.5%) - 84
SAEs related to Pegasys®	**215 (4.1%)- 310**
Blood and lymphatic system disorders	76 (1.5%) - 83
SAEs related to Ribavirin	**196 (3.8%)- 275**
Blood and lymphatic system disorders	98 (1.9%) - 106
Anemia	67 (1.3%) - 70
SAEs related to Pegasys® and Ribavirin	**152 (2.9%) - 207**
Blood and lymphatic system disorders	63 (1.2%) - 67
AEs leading to death	**15 (0.3%) - 28**
Death	3 (0.1%) - 3
Sepsis	2 (<0.1%) - 2
Hepatorenal syndrome	2 (<0.1%) - 2

In total, four pregnancy cases were reported during the observational period, 3 cases with paternal exposures and 1 case with maternal exposure.

A total of 11,946 discrepancies regarding seriousness, causal relationship and/or preferred terms of AEs between the clinical database (CDB) and the safety database (SDB) have been identified (Annex 2).

9.2 LIMITATIONS

As this was a NIS, assessments were not mandatory; the type, frequency and method were solely based on routine medical care. Nevertheless, data reporting/collection was conducted in a consistent way to avoid bias in the data collection process (information bias).

In this final analysis of PAN only about half of the enrolled patients (N=9822) were included in the AP (N=5199). The most common reason for exclusion of 4623 patients (47.1%) from the final analysis was that patients did not receive Pegasys® (2424 patients; 24.7%).

The nature of a non-interventional observational study and the limited degree of monitoring and data cleaning may affect the quality of the data and may lead to data discrepancies, which cannot be ruled out completely. There was a large amount of missing data for several parameters. Therefore, it is difficult to draw conclusions for the effectiveness endpoint of virological response, especially for SVR, for which data were available from only one-third of patients.

Incomplete patient data sets, especially missing follow-up data due to the sponsor change, may affect the quality and interpretation of the results. This CSR reflects only those data collected under the responsibility of Roche as a study initiator (i.e. period between 03 October 2011 to 14 July 2014). The final analysis was performed in 2021.

9.3 INTERPRETATION

Until 2011, the existing standard chronic hepatitis C therapy consisted of PegINF (Pegasys®) in combination with Ribavirin and serine protease inhibitors (Boceprevir or Telaprevir) in patients with HCV Genotype 1. With the launch of direct-acting antivirals (DAA) in 2014 / 2015, the first IFN-free treatments became available.

Nowadays, INF-based therapy regimes are no longer indicated in HCV treatment (Sarrazin et al. 2018 and 2020). However, combination therapies of DAAs, Ribavirin, and early Peginterferon alfa continue to be approved for the treatment of HCV infection.

9.4 GENERALIZABILITY

Not applicable, because Pegasys® is no longer standard of care for HCV therapy.

10. OTHER INFORMATION

None

11. CONCLUSION

Virological response was the effectiveness endpoint. Virological response in terms of EVR, EoTR and SVR was achieved by 50.5%, 60.8% and 27.2 of the patients, respectively, in the AP. It is not possible to draw conclusions about SVR, because HCV PCR data were available in only one-third of patients (32.7%) during the given timeframe.

There seems to be a small advantage in terms of virological response in patients in triple therapy Group 2 (with Boceprevir) compared with the other subgroups.

At study start the median estimated duration of HCV infection was 11 years (range 1 - 60) and only one-third of the patients (33.6%) received previous antiviral therapy. The predominant HCV genotypes were Genotype 1 and Genotype 3 (68.5% and 24.1%, respectively).

The median duration of HCV therapy in this study was 172.0 days (range 1 - 706). Approximately one-quarter of the patients (25.5%) discontinued Pegasys® therapy prematurely. The most common reasons for treatment discontinuation were lack of virological response (8.7%) and patients' wishes (5.7%).

The safety profile of Pegasys® and Ribavirin in PAN corresponds to the known safety profile; no new safety signals were detected.

Data of PAN were collected at a time Pegasys® was standard of care therapy for patients with chronic HCV infection. Because therapeutic approaches changed, data of PAN should not be compared to any published data.

12. REFERENCES

Sarrazin C.; Zimmermann,T., Berg T., Neumann U. P., Schirmacher P., Schmidt H. et al. (2018) Prophylaxis, diagnosis and therapy of hepatitis-C-virus (HCV) infection: the German S3-guidelines on the management of HCV infection, AMWF-Register-No.: 021/012, Z Gastroenterol; 56(07): 756-838, DOI: 10.1055/a-0599-1320

Sarrazin C.; Zimmermann T., Berg T., Hinrichsen H., Mauss S, Wedemeyer H, et al (2020) Prophylaxe, Diagnostik und Therapie der Hepatitis-C-Virus (HCV)-Infektion, Z Gastroenterol 2020; 58(11): 1110-1131, DOI: 10.1055/a-1226-0241

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Date	Title
1	28 February 2013	Observational plan ML25724 final v. 2.0 incl. amendment 1
2	28 February 2013	Amendment to observational plan v. 1.0
3	04 June 2021	Statistical analysis plan v. 2.0
4	28 October 2021	Data analysis meeting minutes final
5	14 February 2022	ML25724 final Listings 1-24, 25-27, 28-31
6	16 February 2022	ML25724 final Tables
7	03 May 2022	Pregnancy Listing QTT062578_S01_FU00_Pregnancy_Listing
8	16 May 2022	ML25724_PAN_Discrepancies_Overview Listing of Discrepancies between Clinical and Safety Database

ANNEX 2. DIFFERENCE BETWEEN THE CLINICAL DATABASE AND THE SAFETY DABASE

Discrepancies between Safety Database Roche (SDB) and Clinical Database CRO (CDB) identified during final safety reconciliation

The study PAN was a multicenter, observational, cohort, prospective non-interventional study (NIS), aimed to assess the effectiveness and the safety of Pegasys® (Peginterferon alfa-2a) in dual therapy with Ribavarin or triple therapy with Ribavarin and protease inhibitor in patients with chronic hepatitis C.

For a NIS, it is an integral part of Roche´s Safety and Data Quality Management to review all safety data, collected in the respective study. This includes the re-evaluation of seriousness assessments of AEs - in terms of need of seriousness upgrade – and review of all causality assessments provided by Investigators through single-case reviews by experienced drug safety experts.

Depending on respective assessment outcomes, discrepancies may occur between the seriousness of AEs as reported by the Investigator versus the seriousness as assessed by Roche, followed by a Roche (company) upgrade (i.e. from non-serious to serious) of the respective events. Additionally, episodes of events and the seriousness for each event are captured in the narrative as per Roche Safety Coding Convention, where seriousness is captured as the most serious one in the SDB.Therefore, differences may occur between the CDB and the company's SDB in terms of SAE counts. There are also differences in the assessments of causality, Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) coding, System Organ Class (SOC) allocation of PTs and in other categories listed and described in Table 34. If there was a mismatch between the data in any of the described categories between the two databases (SDB and CDB), discrepancies were included in reconciliation files (QTT_SAERT), and were reviewed and commented upon. From that step, all the discrepancies have been reviewed and listed in a data reconciliation master document "ML25724_PAN_Discrepancies_Overview" in Annex 1.

Some identified discrepancies could not be queried and solved in the CDB, e.g. splitting of adverse event terms, double or missing entries, because the discrepancies where identified after the obligation to retain the documents already had passed.

In this NIS, the combination of two drugs (PEGInterferon alfa 2a / Ribavirin) was observed. A total of 11,946 discrepancies were identified. All of these discrepancies were classified as either accepted or justifiable for both, the patients included in the Analysis Population and the patients, which were excluded of the Analysis Population. When sorted by SOC, 12,016 discrepancies were identified, since event terms containing several medical conditions were split in the SDB and the corresponding discrepancies were allocated to all SOCs provided in the SDB. As a consequence, the number of discrepancies sorted by SOC exceeds the number of discrepancies sorted by discrepancy categories.

Overall, 6403 discrepancies resulted from overreporting (categories 'Overreporting 1-3'). The majority of these discrepancies (n=6383) resulted from non-serious events, in which according to the source from the Interactive Response System (IRT) these events were documented after 02 July 2012 and therefore had to be processed in the SDB, while according to the CDB these events were reported before 02 July 2012 and therefore, no processing in the SDB would have been required. As a consequence,

these cases do not appear in the CDB data dump for the reconciliation ('Overreporting 1'). Additionally, 16 overreporting discrepancies were identified resulting from events, where on the source documents "other clinical symptoms" was reported. Queries were raised to clarify the event term. However, no answers were received. A resolution of these discrepancies was impossible ('Overreporting 2'). Four overreporting discrepancies were identified resulting from events, where the CDB entry was missing as the events were not related to both Roche study drugs ('Overreporting 3').

One aspect of safety reconciliation is related to PT coding and SOC allocation of PTs. Here, the same event must be present in both databases and the reported term must be identical or medically equivalent in both databases, whereas the PT must be identical in the SDB and CDB. Identical PTs should result in identical SOC allocation in CDB and SDB. Overall, 2612 discrepancies were identified resulting from MedDRA coding issues, in which the event was coded to different PTs, which nevertheless represent the same medical condition ('MedDRA Coding 1'), systematic translation errors in SDB ('MedDRA Coding 2') or CDB ('MedDRA Coding 3'), e.g. "Schwindel" was translated to "vertigo" instead of "dizziness", or incorrect PTs in CDB, as well as different reported terms in CDB and SDB, due to Safety Coding Convention ('MedDRA Coding 4'). Consequently, some of these differences in PTs also resulted in different SOC allocations between CDB and SDB.

Additionally, 144 discrepancies were identified resulting from events, in which the adverse event reported term included several medical conditions and therefore was split into several events in the SDB, but remained documented as one event in the CDB.

Overall, 897 discrepancies were identified resulting from reported episodes, in which the event was not recorded as a distinct event in SDB, but as a not-timely but clinically related episode captured in the narrative of a previously occurring event with different onset date as per Roche Safety Coding Convention.

Overall, 787 discrepancies correspond to events with different relationship (categories 'Relationship 1-3'). In total, 443 discrepancies correspond to events, in which the causality assessments differed in terms of
1: changing 'causality, not reported' or 'causality, not related' to 'causality, unknown' or
2: changing 'not reported' to 'not related' or 'related as per company assessment' or
3: changing 'related' to 'not related as per company assessment' or
4: changing 'not related' to 'related as per company assessment' ('Relationship 1').
326 relationship discrepancies correspond to events, in which the discrepancy arose because, according to the source documentation received by the local safety unit (LSU), no study drugs were administered at time of the event, whereas according to CDB the study drugs were administered. In these cases, the relationship was recorded as "Not applicable" in the SDB as per Roche Safety Coding Convention and as "Not reported" or "Not related" in CDB ('Relationship 2'). Eighteen discrepancies correspond to special situation events, and the different relationship in these cases was the result of the Roche Safety Coding Convention ('Relationship 3'). Causality of special situation events was documented as "Not applicable" in the SDB as per Roche Safety Coding Convention.

A further 357 discrepancies corresponded to events with different seriousness assessments. 295 discrepancies correspond to events, in which the assessment of

seriousness was not the same between the databases or within SDB between company and reporter (category ‘Seriousness’). Sixty-two discrepancies corresponded to events, which were upgraded from non-serious to serious events according to Roche Safety Rules (category ‘Upgraded’).

Overall, 328 discrepancies corresponded to events, in which according to the source documentation received at LSU no study drug was administered, in contrast to the documentation in the CDB, where according to the documentation a study drug was administered (category ‘No drug administered’).

Less frequent discrepancies concerned double (n=48) or missing (n=22) events in the CDB as well as double (n=1) or missing (n=49) events in the SDB. Missing events in the CDB resulted e.g. from direct reporting to Roche, in which the eCRF was bypassed. Missing events in SDB resulted from invalid event terms, events, which were only recorded as symptoms in the narrative of other events, or divergent information regarding suspect products in the source document received by the LSU and the data reflected in the CDB. E.g. in the source document only Peginterferon alfa-2a was reported as suspect drug, whereas according to CDB Ribavirin also was reported as suspect drug.

A summary of the discrepancies sorted by SOC (n=12,016) is provided in Table 35 below. If SOC allocation of the PT was different in CDB and SDB, the SOC allocation from SDB was prioritized. If the SOC allocation was missing in the SDB, the SOC allocation from the CDB was considered. For event terms containing several medical conditions, which were split in the SDB, the discrepancies were allocated to all SOCs provided in the SDB. As a consequence, the number of discrepancies sorted by SOC exceeds the number of discrepancies sorted by discrepancy categories.

The most common SOCs with discrepancies were ‘General disorders and administration site conditions’ (n=2286), ‘Gastrointestinal disorders’ (n=1893) and ‘Skin and subcutaneous tissue disorders’ (n=1662).

Discrepancies between the CDB and the SDB, which could not be resolved, are summarized according to category of discrepancy and listed below (Table 34: Discrepancy categories sorted by number of discrepancies in each category, based on “ML25724_PAN_Discrepancies_Overview” in Annex 1 andTable 35: Number of discrepancies sorted by MedDRA System Organ Class (SOC) in descending order of discrepancies). A Listing (ML25724_PAN_Discrepancies_Overview) of the discrepancies of the safety databases (CDB and SDB) for the PAN is provided as separate Table in Annex 1, List of stand-alone documents.

Table 34: Discrepancy categories sorted by number of discrepancies in each category, based on "ML25724_PAN_Discrepancies_Overview" in Annex 1

Discrepancy category	Explanation	Type	Count (Total=11946)
Overreporting 1	*Non-serious event, CDB eCRF documentation date before 02 Jul 2012, therefore the event is not included in CDB data dump for the reconciliation*	justifiable	**6383**
MedDRA coding 1	*Different Preferred Terms, but representing the same medical condition*	accepted	**1310**
Episode	*Event is not recorded as a distinct event, but as a not-timely but clinically related episode captured in the narrative of a previously occurring event with different onset date as per Roche Safety Coding Convention*	justifiable	**897**
MedDRA coding 3	*Different Preferred Terms with different medical condition or error in CDB /translation error*	justifiable	**883**
Relationship 1	*Reporter relationship is different in CDB and SDB*	justifiable	**443**
MedDRA coding 2	*Systematic translation error in SDB*	justifiable	**417**
No drug administered	*According to source doc. received at LSU no drug administered, but in CDB drug administered*	justifiable	**328**
Relationship 2	*Relationship is different due to no drug administered according to received source doc*	justifiable	**326**
Seriousness	*Seriousness is different in CDB and SDB or within SDB between company and reporter*	justifiable	**295**
Different onset dates	*Different onset dates between CDB and SDB: not reconciled in this NIS*	justifiable	**288**
Split	*Term containing several medical conditions split in SDB, but not in CDB*	justifiable	**144**
Upgraded	*Difference in seriousness is due to the upgrading of the cases based on Safety Coding Convention*	accepted	**62**
CDB double entry	*Similar events reported in CDB with same onset date*	justifiable	**48**

SDB missing 3	*Invalid event term, not entered as an event in SDB*	justifiable	**30**
Relationship 3	*Relationship is different for Special Situations due to Safety Coding Convention*	justifiable	**18**
Overreporting 2	*On source doc "other clinical symptoms" was reported. Query was raised to clarify the event term; but no answer was received; resolution of discrepancy impossible*	justifiable	**16**
CDB missing 2	*Missing in CDB; reported via company representative (eCRF bypassed, direct reporting to Roche)*	justifiable	**14**
Patient ID missing	*Patient ID is missing in SDB*	justifiable	**10**
SDB missing 2	*Event is not recorded in SDB, only captured in the narrative*	justifiable	**10**
CDB missing 1	*Event not recorded in the CDB (event not related and not serious / Event reported via Adverse Event Form / no drug administered)*	justifiable	**8**
SDB missing 1	*Event not recorded in the SDB*	justifiable	**7**
Overreporting 3	*Overreporting (CDB missing here) as not related to both Roche study drugs*	justifiable	**4**
MedDRA coding 4	*Verbatim is different due to Safety Coding Convention*	justifiable	**2**
SDB deleted	*Event available in CDB, but deleted in SDB (described in narrative event is an Medical History)*	justifiable	**2**
SDB duplicated	*Event is duplicated in the SDB (one event in CDB, duplicated in SDB)*	justifiable	**1**

Table 35: Number of discrepancies sorted by MedDRA System Organ Class (SOC) in descending order of discrepancies

MedDRA System Organ Class	Number of discrepancies (N=12016)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**2286**
GASTROINTESTINAL DISORDERS	**1893**
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**1662**
PSYCHIATRIC DISORDERS	**1338**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**916**
NERVOUS SYSTEM DISORDERS	**867**
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**746**
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**500**
EAR AND LABYRINTH DISORDERS	**478**
INVESTIGATIONS	**387**
INFECTIONS AND INFESTATIONS	**313**
METABOLISM AND NUTRITION DISORDERS	**205**
CARDIAC DISORDERS	**107**
EYE DISORDERS	**97**
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**43**
VASCULAR DISORDERS	**43**
RENAL AND URINARY DISORDERS	**30**
ENDOCRINE DISORDERS	**26**
OTHER SOCs*	**26**
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**20**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**19**
HEPATOBILIARY DISORDERS	**14**

*SOCs with less than 10 discrepancies, were summarized under “Other SOCs”

A Listing (ML25724_PAN_Discrepancies_Overview) of the discrepancies for the PAN NIS is provided as separate Table in Annex 1, List of stand-alone documents.

ANNEX 3. ADDITIONAL INFORMATION

Safety Listings of the non-analysis population:

Listing 16.2.25.2 Adverse Events (AEs). Patients excluded from analysis population, treated with Pegasys® or Ribavirin.

Listing 16.2.26.2 AEs with causal relationship to Pegasys® and/or Ribavirin. Patients excluded from analysis population treated with Pegasys® or Ribavirin.

Listing 16.2.27.2 Serious Adverse Events (SAEs). Patients excluded from analysis population, treated with Pegasys® or Ribavirin.

Listing 16.2.25.4 Adverse Events (AEs) leading to death. Patients excluded from analysis population, treated with Pegasys® or Ribavirin.