1. CLINICAL STUDY REPORT

OPtimization of treatment for patients with chronic hepatitis C infected with HCV-genotype 2 or 3: 12 vs. 24 weeks of Treatment EXtension for patients without rapid virological response (OPTEX 2/3)

Investigational products: Pegylated interferon-α-2b
Ribavirin

Indication: Chronic hepatitis C virus infection genotype 2/3

Study design: German open label multi center randomized phase IV trial to assess the efficacy of 12 versus 24 weeks of extended treatment in HCV-G2/3 patients with an ongoing standard treatment with PEG-IFN alpha-2b and ribavirin.

Name of sponsor: HepNet funded by BMBF
HepNet Study-House
Hannover Medical School
Carl-Neuberg-Str. 1
D - 30625 Hannover
Responsible person: see principal investigator below

Protocol code: P05498

EudraCT no.: 2008-000706-36

ISRCTN:

Development phase of study: Phase IV

Trial start: July 1, 2008

First patient in: December 18, 2008

Last patient out: July 29, 2013

Study completion date: December 31, 2013

Principal investigator: Prof. Dr. med. Michael P. Manns
Clinic for Gastroenterology,
Hepatology, and Endocrinology
Hannover Medical School
Carl-Neuberg-Str. 1
D - 30625 Hannover

Scientific coordination: PD Dr. med. Markus Cornberg
Clinic for Gastroenterology,
Hepatology, and Endocrinology
Hannover Medical School
Carl-Neuberg-Str. 1
D - 30625 Hannover
Tel.:+49(0)511-532 6817
Fax:+49(0)511-532 6820
Email: cornberg.markus@mh-hannover.de

Study coordination and management:
Dr. rer.nat. Svenja Hardtke

Undine Jacobi (now Baum)
Hep-Net Study House, Hannover Medical School:
Carl-Neuberg-Str. 1
D - 30625 Hannover

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Date of report: July 23, 2014

Clinical Study Report Approval Signatures:

Prof. Dr. Michael Manns Principal Investigator	city, date
Dr. Marcus Cornberg Investigator and study coordinator	city, date
Prof. Dr. Armin Koch Supervising trial statistician	city, date

2. SYNOPSIS

Title of study: OPtimization of treatment for patients with chronic hepatitis C infected with HCV-genotype 2 or 3: 12 vs. 24 weeks of Treatment EXtension for patients without rapid virological response (OPTEX 2/3) Information about study protocol version(s): First submission: Vs. 21-APR-08, 21.04.2008 Subsequent substantial amendments: Vs. 02, 14.09.2010 Vs. 03, 30.11.2011
Investigator(s) and study centre(s): Name(s) and address(es) Prof. Dr. M. Manns (Coordinating Investigator), Medizinische Hochschule Hannover, Zentrum Innere Medizin, Carl-Neuberg-Str. 1, 30625 Hannover Prof. Dr. med. H. Wasmuth (Principal Investigator), Universitätsklinikum Aachen, Med. Klinik III, Pauwelsstr. 30, 52074 Aachen Prof. Dr. med. E. Schott (Principal Investigator), Charité Campus Virchow Klinikum, Med. Klinik Gastroenterologie / Hepatologie, Augustenburger Platz 1, 13353 Berlin Dr. med. C. John (Principal Investigator), Ärztehaus Leipzigerstr., Leipzigerstr. 43/44, 10117 Berlin Dr. med. U. Meyer (Principal Investigator), Praxis, Kaiserdamm 24, 14057 Berlin Dr. med. B. Möller (Principal Investigator), Hepatologische Schwerpunktpraxis im bng, Charlottenstr. 81, 10969 Berlin Prof. Dr. med .J. Ockenga (Principal Investigator), Klinikum Bremen-Mitte eGmbH, Zentrum für innere Medizin, Med. Klinik II, St. Jürgens Str. 1, 28205 Bremen Prof. Dr. med. M. Kraus (Principal Investigator), Kreiskliniken Burghausen/Altötting, Med.Klinik II, Krankenhausstr. 1, 84489 Burghausen/Altötting Dr. med. E. Zehnter (Principal Investigator), Hepatologische Schwerpunktpraxis, Am Oelpfad 12, 44263 Dortmund Dr. med. H.-J. Cordes (Principal Investigator), Vitanus GmbH, Stresemannallee 3, 60596 Frankfurt am Main Prof. Dr. med. M. Rössle (Principal Investigator), Praxis Zentrum Gastroenterologie und Endokrinologie, Bertoldstr. 48, 79089 Freiburg Dr. med. A. Stoehr (Principal Investigator), Institut für interdisziplinäre Infektiologie an der Asklepios Klink St.Georg, Haus K, Lohmühlenstr. 5, 20099 Hamburg

Prof. Dr. med. H. Lohse (Principal Investigator),
Universitätsklinikum Hamburg-Eppendorf, Klinik für Innere Medizin, Martinistr. 52, 20246 Hamburg

Prof. Dr. med. K. Böker (Principal Investigator),
Leberpraxis Dr.Böker, Rundestr. 10, 30161 Hannover

Dr. med. D. Hüppe (Principal Investigator),
Hepatologische Schwerpunktpraxis, Ärztehaus am Evangelischen Krankenhaus, Wiescherstr. 20, 44623 Herne

Prof. Dr. med. F .Lammert (Principal Investigator),
Universitätsklinikum des Saarlandes, Innere Medizin II / Gastroenterologie, Kirrbergerstr. 1, 66424 Homburg-Saar

Prof .Dr. med. A. Stallmach (Principal Investigator),
Klinik für Innere Medizin der FSU, Innere Medizin IV, Erlanger Allee 101, 07747 Jena

Dr. med .R. Günther (Principal Investigator),
UK S-H, Campus Kiel, Klinik für Allgemeine Innere Medizin, Schittenhelmstr. 12, 24105 Kiel

PD Dr. med. H. Hinrichsen (Principal Investigator),
Gastroenterologische Gemeinschaftspraxis 134 , Preetzer Chaussee, 24146 Kiel

Dr. med. Johannes Wiegand (Principal Investigator),
Universitätsklinikum Leipzig, Klinik und Poliklinik für Gastroenterologie, Liebigstr. 20, 04103 Leipzig

Dr. med. K.-G. Simon (Principal Investigator),
Gemeinschaftspraxis Dr. Simon, Franz-Kail-Str. 2, 51375 Leverkusen-Schlebusch

Dr. A. Grambihler (Principal Investigator),
Klinikum der Johannes Gutenberg Universität, Medizinische Klinik und Poliklinik, Langenbeckstr. 1, 55131 Mainz

Dr. med. C. Roggel (Principal Investigator),
Hepatologische Schwerpunktpraxis, Uferstr. 3, 32423 Minden

Dr. med. H. Busch (Principal Investigator),
Zentrum für innerdisziplinäre Medizin, Salzstr. 58, 48143 Münster

Dr. med. R. Link (Principal Investigator),
St.-Josefs-Klinik, Medizinische Klinik, Weingartenstr. 70, 77654 Offenburg

Dr. med. S. Schneider (Principal Investigator)
Uniklinikum Regensburg, Klinik und Poliklinik für innere Medizin I, Franz-Josef-Strauß-Allee 11, 93053 Regensburg

Dr. med. A. Trein (Principal Investigator),
Praxis, Schwabstr. 57/59, 70197 Stuttgart

Dr. med. Ch. Berg (Principal Investigator),
Universitätsklinikum Tübingen, Med. Klinik I, Ottfried-Müller-Str. 10, 70206 Tübingen

Dr. med. D. Klass (Principal Investigator),
PD Dr. med. N. Dikopoulos (Principal Investigator),

Universitätsklinikum Ulm, Abt .Innere Med, I, Albert-Einstein-Allee 23 , 89081 Ulm

Prof. Dr. med. H. Klinker (Principal Investigator),
Medizinische Klinik und Poliklinik II, Leber-/Infektonsambulanz , Haus A3, Oberdürrbacherstr. 6, 97080 Würzburg

Publication (reference):
OPtimization of treatment for patients with chronic hepatitis C infected with HCV-genotype 2 or 3: 12 vs. 24 weeks of Treatment EXtension for patients without rapid virological response (OPTEX). Poster AASLD 2013 Hepatology Volume 58, Issue S1, October 2013, Pages: 92A–207A.

Studied period (years): 4 years and 4 months (date of first enrolment): 18.12.2008 (date of last completed): 29.07.2013 Information about temporary halt(s) and premature termination of the trial: Premature termination: 05.08.2013	Phase of development: Phase IV

Objectives:
The objective of this study was to compare the efficacy of a treatment extension of 12 versus 24 weeks in patients with HCV-genotypes 2 and 3 who had been treated with 1.5 µg/kg PEG-IFN alpha-2b and 800-1400 mg ribavirin (standard dose) for 24 weeks (standard duration) and who were not HCV-RNA negative (< 15 IU/ml) after 4 weeks of standard treatment.

Methodology:

Overview of Study Design
This was a German open label multicenter randomized phase IV trial to assess the efficacy of 12 versus 24 weeks of extended treatment in HCV-G2/3 patients with an ongoing standard treatment with PEG-IFN alpha-2b and ribavirin.

Assignment to Treatment Groups
150 patients with chronic hepatitis C virus infection of genotypes 2 and 3 were to be enrolled. Patients were randomized 1:1 in group A (75 patients) and B (75 patients). Stratification factors were sex, age, genotype, cirrhosis, and the HCV RNA level > 600,000 IU/ml before the ongoing therapy.

Group A: PegIntron® 1.5 µg/kg once weekly (QW) subcutaneous (sc) plus Rebetol® 800-1400 mg per os divided in 2 daily doses for an additional 24 weeks beyond standard treatment with 24 weeks follow-up
Group B: PegIntron® 1.5 µg/kg QW sc plus Rebetol® 800-1400 mg per os divided in 2 daily doses for an additional 12 weeks beyond standard treatment with 24 weeks follow-up

Number of patients (planned and analysed):

Planned: in total 150 (Group A: 75, Group B: 75)
Analyzed: n=99

Diagnosis and main criteria for inclusion:

Diagnosis:
The target population was male and female adults with HCV-genotype 2 or 3 chronic hepatitis c virus infection.

Inclusion criteria
1. Male or female patients with HCV-genotype 2/3 chronic hepatitis C documented by detectable plasma HCV RNA (> 15 IU/mL) and positivity of anti-HCV antibodies.
2. Age ≥ 18 years
3. Compensated liver disease (Child-Pugh Grade A clinical classification)
4. Negative urine or blood pregnancy test (one of the two; for women of childbearing potential) documented within the 24-hour period prior to the first dose of study drug. Additionally, all fertile males and females must be using two forms of effective contraception during treatment and during the 7 months after treatment end. This includes using birth control pills (no interaction with investigational drugs), IUDs, condoms, diaphragms, or

implants, being surgically sterilized, or being in a postmenopausal state. At least one contraception method must be a barrier method
5. Ongoing treatment with 1.5 µg/kg Peg-Interferon alpha-2b (PegIntron®) and > 10.6 mg/kg ribavirin (Rebetol®)
6. No rapid virological response (HCV-RNA positive after week 4 of the ongoing therapy)
7. Willingness to give written informed consent and willingness to participate and to comply with the study protocol

Test product, dose and mode of administration, batch number:

Test product: PegIntron®
Dose: 1.5 µg/kg once weekly
Mode of administration: subcutaneous
Batch number: not available

Test product: Rebetol®
Dose: 800-1400 mg, divided in 2 daily doses
Mode of administration: oral
Batch number: not available

Duration of treatment:

Group A: 48 weeks
Group B: 36 weeks

Reference therapy, dose and mode of administration, batch number:
n/a

Criteria for evaluation:

Efficacy:
Primary endpoint: Reduction of relapse rate 24 weeks after the end of treatment and, thus, improved sustained virological response (SVR24) in the group with a prolongation of 24 weeks (group A) in comparison with SVR24 rates in patients without treatment prolongation (historical control group with SVR-rate 70%)

Secondary endpoints:
- Virological response rates at the end of treatment (EOT)
- Comparison of SVR rates between group A and group B at EOT and at the end of follow up
- Biochemical responses as determined by ALT and AST levels at the EOT and at the end of follow up
- Analysis of quality of life (with questionnaire SF-36)

Safety:
- Severity and frequency of adverse events (AE)

Statistical methods:
For the primary analysis SVR24-rate of group A was calculated with 95% Wald confidence intervals (CI). The study was considered successful if the lower bound of the 95% Wald CI of the SVR24-rate of group A was above 70%. As key secondary analysis the SVR24-rate of group B (12 week prolongation) was carried out in line with the primary analysis. Another key secondary objective was to compare group A with group B. For this comparison the analysis Mantel-Haenszel risk difference was used to adjust for stratification variables.

Summary - Conclusions

Efficacy Results: The primary efficacy analysis was conducted on the ITT population. The primary aim of this study was to show improved SVR24 with a treatment prolongation of an additional 24 weeks compared to standard duration. SVR24-rate was compared to a reference level of 70% (historical control group). The SVR24-rate in group A was 68.00% [95% Wald-CI: 55.07%;80.93%]. The Wald-CI clearly shows that the primary aim was not achieved in this study. Group B showed a similar result with a SVR24-rate of 57.14% [95% Wald-CI: 43.29%;71.00%].

Safety Results:

Patients with treatment prolongation of 24 weeks had more AEs than those with 12 weeks extentions. They also had more SAEs compared to shorter treatment extention except for the timepoint 12 weeks. Furthermore, more often the AEs which were ongoing or leading to concomitant medication. Treatment prolongation of 24 weeks compared to 12 weeks seems to be, as expected, increasingly physically demanding.

Conclusion: Longer treatment duration of >24 weeks with PEG-IFN and ribavirin of patients with genotypes 2/3 and non-RVR seems to have no additional major benefit and cannot be recommended. Genotype 2/3 patients with non-RVR should be treated with new direct acting antiviral agents such as sofosbuvir.

3. TABLE OF CONTENTS

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse events
AFP	Alpha fetoprotein
ALT (GPT)	Alanine transaminase
AMA	Antimitochondriale antibody
AMG	Arzneimittelgesetz
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
AST (GOT)	Aspartate transaminase
Asymp.	Asymptomatic
BMBF	Bundesministerium für Bildung und Forschung
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence intervall
CMV	Cytomegaly virus
CRF	Case report form
ECG	Electrocardiogram
EMEA	European Medicines Agency
EOT	End of treatment
EVR	Early virological response
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good clinical practice
GT	Glutamyltransferase
HAV	Hepatitis A virus
Hb	Hemoglobin
HCV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin

INR	International normalized ratio
ITT	Intent to treat
IU	International unit
LKP	Leiter der klinischen Prüfung (coordinating investigator)
MEDRA	Medical Dictionary for Regulatory Activities Terminology
MH	Mantel-Haenezel
MIP	Macrophage inflammatory protein
mITT	modified-ITT
NYHA	New York Heart Association
OR	Overall regression
os	Oral
PCR	Polymerase chain reaction
PEG	pegylated
QoL	Quality of life
QW	Once weekly
RBC	Red blood cell
RBV	Ribavirin
RD	Risk difference
RNA	Ribonucleic acid
RVR	Rapid virological response
SAE	Serious adverse events
Sc	Subcutaneous
SD	Standard deviation
SMA	Smooth muscle antibody
SmPC	Summary of Product Characteristics
SNP	Single nucleotide polymorphism
SpSVR	Spontaneous sustained virological response
SOC	System organ class
SOP	Standard operating procedure
SVR	Sustained virological response
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell

WK	Week

5. ETHICS

This study was conducted according to the Declaration of Helsinki 1996 and local rules and regulations of Germany. The study was approved by the ethics committee of the Hannover Medical School (Sept. 30, 2008) (see Appendix 16.1.4).

Patients gave informed consent at the screening visit. The written patient information and the consent form are provided in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Study sponsor: HepNet c/o Hannover Medical School

Principal investigator: Prof. Dr. med. Michael P. Manns, Clinic for Gastroenterology, Hepatology, and Endocrinology, Hannover, Germany

Scientific coordinator : PD Dr. med. Markus Cornberg

Study coordination and management: Dr. rer.nat. Svenja Hardtke
U. Jacobi (now Baum)
Hep-Net Study House, Hannover Medical School

The clinical laboratory tests were done by:

Biochemistry and hematology: Local labs at each site

Virology: Central lab, Dept. of Gastroenterology, Hannover Medical School

Technicians involved: Birgit Bremer, Hepatitis Serology, Dept. of Gastroenterology, Hannover Medical School

The statistical analysis was performed by:

Prof. Dr. rer.nat. Armin Koch and Andrea Gonnermann; Dept. of Biometry, Hannover Medical School, Carl-Neuberg Str. 1, 30625 Hannover; Germany

CRO: Hannover Clinical Trial Center, Carl-Neuberg Str. 1, 30625 Hannover; Germany

A list of investigators with their affiliations is provided in the synopsis.

7. INTRODUCTION

More than 120 million people worldwide are chronically infected with the hepatitis C virus (HCV; Shepard et al. 2005), an RNA virus belonging to the family flaviviridae which was discovered in 1989 (Choo et al. 1989). HCV is transmitted primarily through exposure to blood products and intravenous drug use. 50-90% of patients with acute HCV infection develop a persistent infection. Heterogeneity is high, there are 6 HCV-genotypes and more than 90 subtypes. The chronic sequelae of chronic

HCV infection are liver fibrosis, cirrhosis, and hepatocellular carcinoma (Hoofnagle 2002, Lauer and Walker 2001). In addition to liver disease, HCV infection has been associated with a wide variety of extrahepatic manifestations such as mixed cryoglobulinaemia, membranoproliferative glomerulonephritis, and porphyria cutanea tarda (Hoofnagle 1997, Manns et al. 2006).

Measures to prevent HCV infection such as blood screening programs led to a decline in HCV incidence in the developed world. However, despite prevention measures, we still anticipate an increasing number of patients with sequelae of HCV infection in the following 10-20 years (Davis et al. 2003, Hoofnagle 2002).

During the last 15 years there has been an enormous achievement in the diagnosis, management, and therapy of hepatitis C. Analysis of HCV-genotypes, quantification of HCV-RNA viral load, and calculation of viral kinetics allow better management of patients with chronic hepatitis C. Treatment of HCV with pegylated interferon alpha (PEG-IFN) and ribavirin has been optimized and the first direct antiviral drugs are in development and may lead to a cure of chronic hepatitis C in the majority of cases (Cornberg et al. 2006, Manns et al. 2006).

At the start of the study, standard treatment of chronic hepatitis C was a combination of PEG-IFN alpha-2b with ribavirin adjusted according to body weight. PEG-IFN is given as a subcutaneous injection (1.5 µg/kg once weekly) and ribavirin is taken orally (> 10.6 mg/kg daily). The main discussion within the scientific community was to optimize the current standard treatment of chronic hepatitis C (CHC) to improve the response rates, in particular the treatment duration. There are two different concepts to optimize the latter. While some patients may be treated for a shorter period of time to reduce costs and side-effects, others may need longer treatment to improve the response rates.

Many studies have investigated treatment duration reductions to 16, 14, or even 12 weeks for HCV-genotypes 2 and 3. The first reported results are promising, but it turns out that individual factors need to be considered when treating patients for less than 24 weeks. The rapid virological response (RVR) after 4 weeks of therapy (HCV-RNA negative in the serum at treatment week (TW) 4) is one of the critical factors that are associated with the success of a shorter therapy. Only patients who showed RVR at week 4 had high SVR rates after 16 weeks (von Wagner et al. 2005), 14 weeks (Dalgard et al. 2004, Dalgard et al. 2008), or even after 12 weeks of therapy (Mangia et al. 2005), whereas those without RVR had lower response rates, even

with the 24-week schedule. In addition to RVR, other factors are associated with the response in patients with HCV-genotypes 2 and 3. These are the baseline viral load (Dalgard et al. 2004, Shiffman et al. 2007, von Wagner et al. 2005) and the presence of liver cirrhosis (Aghemo et al. 2006). In conclusion, patients with HCV-genotype 2 and 3 and low viral load who have a RVR after 4 weeks of therapy can be treated for less than 24 weeks and patients without RVR (especially HCV-genotype 3 and high viral load) may be treated for even more than 24 weeks. However to date, the optimal treatment duration for patients without RVR is not known.

In this study we treated patients with chronic hepatitis C of genotype 2 or 3 who had characteristics associated with poor treatment response for an additional 12 or 24 weeks beyond the standard treatment of PEG-IFN alpha-2b plus ribavirin.

8. STUDY OBJECTIVE

The objective of this study was to compare the efficacy of a treatment extension of 12 versus 24 weeks in patients with HCV-genotypes 2 and 3 who were treated with 1.5 µg/kg PEG-IFN alpha-2b and 800-1400 mg ribavirin (standard dose) for 24 weeks (standard duration) and who were not HCV-RNA negative (< 15 IU/ml) after 4 weeks of standard treatment.

Endpoints

Primary endpoints:

- Reduction of relapse rate (HCV-RNA positive in serum by a standard HCV-PCR with a detection limit of at least 15 IU/ml) 24 weeks after the end of treatment und, thus, improvement of sustained virological response rates (SVR)

Secondary endpoints:

- Virological response rates (HCV-RNA negative in serum by a standard HCV-PCR with a detection limit of at least 15 IU/ml) at the end of therapy
- Comparison of SVR rates between group A and group B at EOT and at the end of follow up
- Biochemical responses as determined by ALT and AST levels at the end of treatment and at the end of follow up.
- Analysis of quality of life (with questionnaire SF-36)
- Severity and frequency of adverse events (AE)

9. INVESTIGATIONAL PLAN

This was a German open label multicenter randomized phase IV trial to assess the efficacy of 12 versus 24 weeks of extended treatment in HCV-G2/3 patients with an ongoing standard treatment with PEG-IFN alpha-2b and ribavirin. Patients with HCV-genotype 2 and 3 were

eligible if they were non-rapid virological responders (HCV-RNA positive after 4 weeks of treatment).

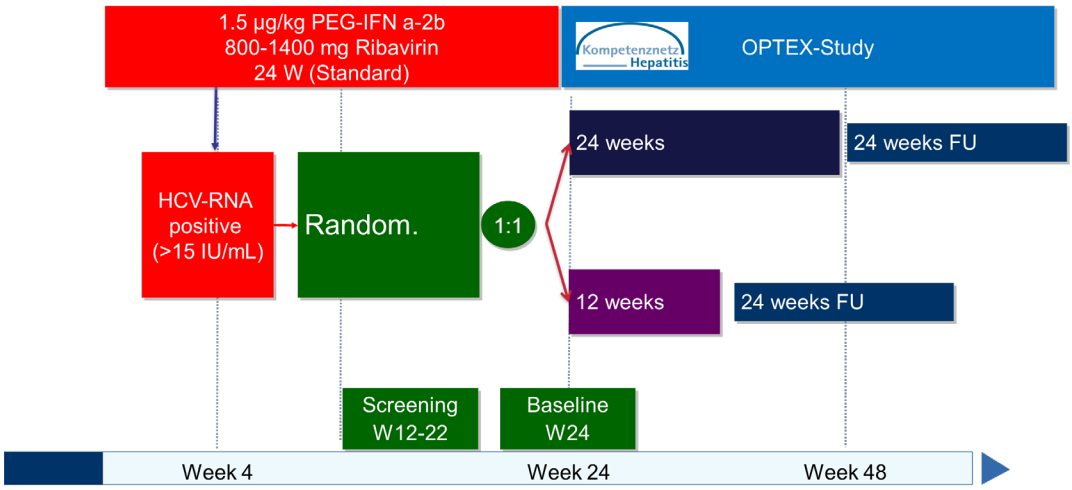


Figure 1: Study design

Randomization was performed using a telematic-platform of Hep-Net (Randoulette Version 3.1, Munich, Germany). Access to the web-based randomization service was restricted to the experts in the coordination center in Hannover. They assigned patients to one of the treatment arms. Stratification was done according to sex, age, genotype, cirrhosis, and the HCV RNA level > 600,000 IU/ml before the ongoing therapy.

9.1 Discussion of design and choice of control groups

An open label randomized study design was chosen to compare 12 and 24 week extended treatment with PEG-IFN alpha-2b and ribavirin in patients with HCV-genotype 2 and 3 who were non-rapid virological responders, because patients may benefit from prolonged treatment. A historical group with SVR-rate 70% was chosen as a control. We did not include a control group treated for 24 weeks, because the expected number of patients which could be included was too low for an additional treatment arm. Dalgard et al. (2008) published data with a similar treatment regimen (Peg-IFN alpha-2b plus weight based ribavirin) in patients with genotypes 2/3 from Northern Europe (Sweden and Norway). 70% SVR in patients with non-RVR but EVR were taken from this cohort of 126 patients.

9.2 Selection of study population

The target population consisted of males and females age ≥ 18 years with HCV-genotype 2 or 3 chronic hepatitis C virus infection who were non-rapid virological responders.
Adults with chronic HCV infection documented by detectable plasma HCV RNA (> 15 IU/mL) and positivity of anti-HCV antibodies were enrolled.

To ensure uniform standards at the different sites, enrollment and treatment criteria were strictly controlled by the Hep-Net study house. Before a patient was enrolled, each local investigator had to contact the central study unit in Hannover where the inclusion/exclusion criteria were checked.

Study centers

In the first years of the study, 46 centers were recruited within the Hep-Net and initiated by the CRO, HCTC. Finally, 30 centers included at least one patient into the study.

	Total number of patients	Number of patients per arm	
		Arm A	Arm B
Berlin Möller	12	5	7
Würzburg Klinker	11	4	7
Hannover Manns	9	6	3
Berlin Meyer	5	2	3
Freiburg Rössle	5	3	2
Burghausen Kraus	5	3	2
Frankfurt Cordes	5	3	2
Stuttgart Trein	4	1	3
Minden Roggel	4	1	3
Hannover Böker	4	2	2
Mainz-UK	4	2	2
Hamburg Stoehr	4	2	2
Hamburg UK	3	2	1
Offenburg Link	3	0	3
Berlin Charite	3	3	0
Kiel Hinrichsen	3	2	1
Jena Stallmach	2	1	1
Dortmund- Zehnter	2	2	0
Tübingen Gregor	2	2	0
Leipzig Wiegand	1	1	0
Berlin-Leipziger St	1	1	0
Kiel-UK	1	0	1
Bremen Ockenga	1	1	0
Herne	1	1	0
Münster CIM	1	0	1
Aachen Wasmuth	1	0	1
Homburg Lammert	1	0	1
Ulm-Uk	1	0	1
Regensburg Wiest	1	1	0
Leverkusen	1	1	0
Total	**101**	**52**	**49**

9.2.1 Inclusion criteria

Patients fulfilling the following documented criteria were included:

1. Male or female patients with HCV-genotype 2/3 chronic hepatitis C documented by detectable plasma HCV RNA (> 15 IU/mL) and positivity of anti-HCV antibodies
2. Age ≥ 18 years
3. Compensated liver disease (Child-Pugh Grade A clinical classification)
4. Negative urine or blood pregnancy test for women of child bearing potential) documented within the 24-hour period prior to the first dose of study drug. Additionally, all fertile males and females must be using two forms of effective contraception during treatment and during the 7 months after treatment end. This includes using birth control pills (no interaction with investigational drugs), IUDs, condoms, diaphragms, or implants, being surgically sterilized, or being in a postmenopausal state. At least one contraception method must be a barrier method.
5. Ongoing treatment with 1.5 µg/kg Peg-Interferon alpha-2b (PegIntronR) and > 10.6 mg/kg ribavirin (RebetolR)
6. No rapid virological response (HCV-RNA positive after week 4 of the ongoing therapy)
7. Willingness to give written informed consent and willingness to participate and to comply with the study protocol

9.2.2 Exclusion criteria

Patients with any of the following were excluded:

1. Women with ongoing pregnancy or breast feeding
2. Male partners of women who are pregnant
3. Positive tests at screening for anti-HAV IgM Ab, HBsAg, anti-HBc IgM Ab, HBeAg, anti-HIV, HIV-RNA
4. History or other evidence of a medical condition associated with chronic liver disease other than HCV associated (e.g., hemochromatosis, autoimmune hepatitis, alcoholic liver disease, toxin exposures)
5. History or other evidence of bleeding from esophageal varices or other conditions consistent with decompensated liver disease
6. Patients with liver cirrhosis with a lesion suspicious for hepatic malignancy on the screening
7. Absolute neutrophil count (ANC) <750 cells/mm3 at screening
8. Platelet count <50,000 cells/mm3 at screening
9. Hb <10 g/dl at screening
10. Dose modification of Peg-Interferon alpha-2b (PegIntron®) or ribavirin (Rebetol®) during the first 4 weeks of the ongoing therapy

11. Interferon alpha or ribavirin therapy at any time point before the actual ongoing treatment
12. Less than 80% adherence to treatment of the ongoing treatment until randomizaion (week 20-22 of ongoing treatment)
13. Serum creatinine level >1.5 times the upper limit of normal at screening
14. History of severe psychiatric disease, especially depression (ICD 10 codes F30–F33). Severe psychiatric disease is defined as treatment with an antidepressant medication or a major tranquilizer at therapeutic doses for major depression or psychosis, respectively, for at least 3 months at any previous time. Patients are excluded if any history of suicidal attempts is evident. If hospitalization for psychiatric disease, or a period of disability due to a psychiatric disease are documented, psychiatric consultation is mandatory. Patients with a mild or moderate psychiatric disease (ICD 10 codes F32.0, F32.1, F33.0, F33.1) are only allowed to be included into the trial if a regular monitoring by a psychiatrist is performed during the trial
15. History of a severe seizure disorder or current anticonvulsant use
16. History of immunologically mediated disease (e.g. inflammatory bowel disease, idiopathic thrombocytopenic purpura, lupus erythematosus, autoimmune hemolytic anemia, scleroderma, severe psoriasis, rheumatoid arthritis)
17. History or any other evidence of autoimmune diseases
18. History or other evidence of chronic pulmonary disease associated with functional limitation
19. History of significant cardiac disease that could be worsened by acute anemia (e.g. NYHA Functional Class III or IV, myocardial infarction within 6 months prior to treatment with Peg-Interferon/ribavirin therapy, ventricular tachyarrhythmias requiring ongoing treatment, unstable angina)
20. Evidence of thyroid disease that is poorly controlled on prescribed medications
21. Evidence of severe retinopathy (e.g. CMV retinitis, macular degeneration)
22. History of major organ transplantation with an existing functional graft
23. History or other evidence of severe illness, malignancy, or any other conditions which would make the patient, in the opinion of the investigator, unsuitable for the study
24. History of any systemic anti-neoplastic or immunomodulatory treatment (including supraphysiologic doses of steroids and radiation) 6 months prior to the first dose of study drug or the expectation that such treatment will be needed at any time during the study
25. Patients with evidence for tuberculosis
26. Drug abuse within 6 months prior to the first dose of study drug and excessive alcohol

consumption. Patients on methadone/polamidone/buprenorphine programs were not excluded

27. Any investigational drug and/or participation in another clinical study prior 6 months to the actual ongoing antiviral treatment
28. Limited contractual capability

9.3 Treatments

Patients included in the study were treated at the corresponding study center. All laboratory testing was done locally at each site. Each investigator submitted appropriate laboratory certificates and all ranges of normal values to the Hep-Net study coordinator. HCV-RNA was analyzed centrally at Hannover Medical School, Clinic for Gastroenterology, Hepatology, and Endocrinology, Prof. Manns, Dr. H. Wedemeyer, Carl-Neubergstr.1, 30625 Hannover; Tel: 0511-532-6814.

9.3.1 Treatments administered

Both groups received PegIntron® 1.5 µg/kg once weekly (QW) subcutaneous (sc) plus Rebetol® 800-1400 mg per os divided in 2 daily doses for 24 weeks (standard treatment). Group A received the treatment for an additional 24 weeks and group B for an additional 12 weeks beyond standard treatment. A 24 week follow-up was done for both groups.

Group A: PEG-Intron® 1.5 µg/kg QW sc plus Rebetol® 800-1400 mg divided in 2 daily doses for additional 24 weeks with 24 weeks follow-up

Group B: PEG-Intron® 1.5 µg/kg QW sc plus Rebetol® 800-1400 mg divided in 2 daily doses for additional 12 weeks with 24 weeks follow-up

9.3.2 Identity of investigational products

PEG-IFNα-2b (PegIntron®, SCH 54031, Merck, Sharp & Dohme),

Ribavirin (REBETOL®, SCH 18908, Merck, Sharp & Dohme)

Detailed information is given in the Summary of Product Characteristics (SmPC; "Fachinformation").

9.3.3 Method of assigning patients to treatment groups

At the beginning of the study, it was planned to enroll 150 patients with chronic hepatitis C virus infection of the genotypes 2 and 3. Due to slow recruitment and the changing therapies in the last year, it was decided to terminate the study early. Recruitment of the study was finished at the end of September 2012. Last patient on treatment was finished on April 5th, 2013, and the study was signed out at the Bundesoberbehörde and the ethic commission on August 5th, 2013.

Patients with chronic HCV infection G2/3 were recruited to a HepNet patient registry. Patients were monitored during standard care. RVR patients were excluded first (see figure 2). Non-RVR patients were monitored until end of SOC and then included in the study.

Patients were randomized 1:1 to group A (52 patients) and B (49 patients). Stratification factors were sex, age, genotype, cirrhosis, and the HCV RNA level > 600,000 IU/ml before the ongoing therapy.

Figure 2 shows the number of patients who were recruited to the registry to include 99 patients into the study.

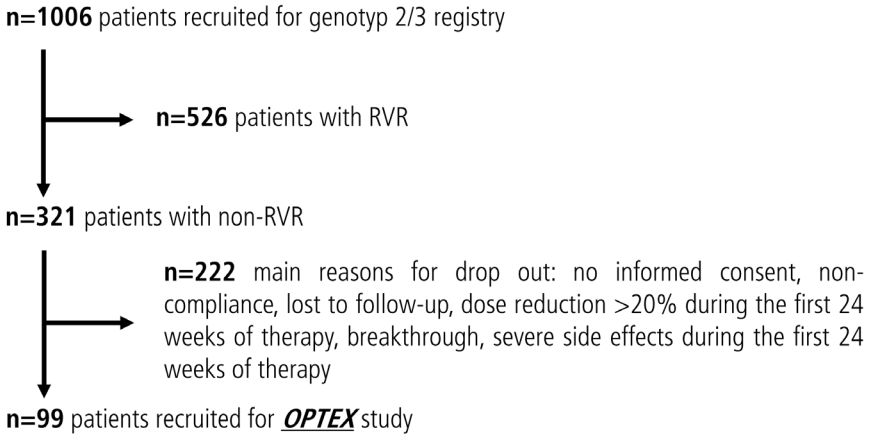


Figure 2: Recruitment

9.3.4 Selection of doses

PEG-Interferon alpha-2b dosages

PEG-Interferon alpha-2b (PegIntron®) was given as a subcutaneous injection once weekly weight adjusted as follows[#]:

Body Weight	Dose	Pen Size (µg)	Injection Volume (ml)
40-43 kg	60 µg	100 µg	0,3
44-50 kg	70 µg	100 µg	0,35
51-56 kg	80 µg	100 µg	0,4
57-63 kg	90 µg	100 µg	0,45
64-68 kg	100 µg	100 µg	0.5
69-75 kg	105 µg	150 µg	0.35
76-85 kg	120 µg	150 µg	0.4
86-95 kg	135 µg	150 µg	0.45
≥ 96 kg	150 µg	150 µg	0,5

[#] the body weight before the ongoing standard therapy defined the dosing

Ribavirin doses

Ribavirin (Rebetol®) was given as capsules weight adjusted daily as follows[#]:

Body weight	Dose	Capsules/ daily intake
< 64 kg	800 mg	2-0-2
65-75 kg	1000 mg	2-0-3
76-85 kg	1000 mg	2-0-3
>85 kg	1200 mg	3-0-3
>105 kg	1400 mg	3-0-4

[#] the body weight before the ongoing standard therapy defined the dosing

Dose modifications

If necessary, the ribavirin and IFNα-2b doses were modified as shown in Table 1.

Table 1: Rules for dose reductions of PegIntron and Rebetol

	Dose reduction	Permanent discontinuation of treatment
Hemoglobin	< 10 g/dl (Rebetol®)	< 8.5 g/dl (Rebetol®)
White blood cells (WBC)	< 1.5 X 109/l (PegIntron®)	< 1.0 X 109/l (PegIntron®)
Granulocytes	< 0.75 X 109/l (PegIntron®)	< 0.5 X 109/l (PegIntron®)
Platelets	< 50 X 109/l (PegIntron®)	< 30 X 109/l (PegIntron®)
Creatinine	n/a	> 3.0 mg/dl
ALT/AST	n/a	2 x baseline and >10 x ULN
Bilirubin-indirect	> 5 mg/dl (or > 85.5 µmol/l)* (Rebetol®)	> 4mg/dl (or >68.4 umol/l) (for > 4 weeks)
Bilirubin-direct		> 2.5 x ULN

* Discontinued ribavirin alone for at least 1 week and no more than 2 weeks. Also a blood sample was taken to determine clotting. If indirect bilirubin fell to < 2.5 mg/dl after ribavirin treatment was interrupted, ribavirin treatment could be restarted at the nearest reduced daily dose stated in the protocol. If bilirubin remained stable at values below 2.5 mg/dl for a period of 4 weeks, ribavirin treatment could be resumed at the full (100%) protocol dose.
The daily dose was reduced if indirect bilirubin rose again above 4 mg/dl. This dose was then maintained. Treatment could be continued only if indirect bilirubin remained below 2.5 mg/dl. If indirect bilirubin remained high (> 4 mg/dl for more than 4 weeks), PEG-interferon alfa-2b and ribavirin was permanently discontinued.

If an adverse laboratory event persisted that was not severe enough to mandate permanent discontinuation of the drugs, the reduced dose of PEG-interferon alfa-2b or ribavirin (whichever was reduced) could be maintained. If the ribavirin dose was reduced following a decline in hemoglobin to below 10 g/dl, the dose reduction was continued for at least 4 weeks.

The reduced doses could also be maintained if the hemoglobin value was ≥ 12 g/dl for women and ≥ 13 g/dl for men. If the adverse laboratory event recurred, a reduced, previously tolerated dose could be administered and maintained or the subject could be taken off the treatment optimization study at the physician's discretion.

The dose reduction was done by lowering the PEG-interferon alfa-2b injection volume and number of ribavirin capsules as described in the tables above. Subjects who developed life-threatening adverse events discontinued PEG-interferon alfa-2b and ribavirin.

To ensure that daily dosing was maintained, the dose was reduced, not the frequency of use.

9.3.5 Blinding

This is not applicable, because this was an open label study.

9.3.6 Prior or concomitant therapy

Patients who initiated treatment with other approved or investigational anti-HCV therapies were discontinued from this study. Systemic antiviral, anti-neoplastic, and immunomodulatory treatments (including steroids and radiation) were not allowed during the entire study period. Steroids given as physiologic replacement were permitted. Other investigational drugs and herbal and other remedies taken by the patient for possible or perceived effects against HCV were not acceptable. The total daily dose of acetaminophen (paracetamol) was not allowed to exceed 4 g per day.

Alcohol consumption was strongly discouraged. During the study patients did not consume more than an average of 20 g of alcohol daily.

9.3.7 Treatment compliance

Compliance to therapy was assessed before and at the end of the study separately for Ribavirin and Peginterferon. Also, the doses were assessed before and at the end of the study as well as change of dose during the study. The results are summarized in section 12.1 Extent of Exposure.

9.4 Efficacy and safety variables

9.4.1 Efficacy and safety measurements assessed

The schedule of efficacy and safety assessments during the study is shown in Table 2.

Table 2: Schedule of assessments and procedures

Assessment	Screening	Study treatment week (TW) 0	Study treatment week (TW) 4,8,12,16*,20*,24* (*only group A)	Follow-up (FU) 4,12,24
Informed consent	X			
Medical & medication history	X			
Physical examination	X			
Vital signs	X	X	X	X
Adverse events	X	X	X	X
Weight	X	X	X	X

ECG	X			
HCV-RNA	X	X	Only end of treatment	X
Hematology	X	X	X	X
Chemistry	X	X	X	X
TSH	X		Only TW 12, 24	Only FU24
Pregnancy test (females)	X	X	X	X
Questionnaire SF-36		X	Only TW 12, 24	Only FU12, 24

Vital Signs: Blood pressure, heart rate

Hematology: hemoglobin, RBC, WBC, platelets, coagulation (INR)

Chemistry: creatinine, ALT, AST, Bilirubin, glucose

A total of approximately 15 ml of blood was taken at each visit.

Screening assessments

A screening examination was done between week 12 and 22 of ongoing treatment before randomization and at study entry (week -12 and week -2 of study). A form documenting the patient's fulfillment of the entry criteria for all patients considered for the study and subsequently included or excluded was completed by the investigator.

Patients with concomitant hypertension or diabetes mellitus had to have an ophthalmologic examination at screening.

Screening Assessments:

Medical history and physical examination	Included body weight, vital signs
Clinical chemistry	ALT, AST, total bilirubin, alkaline phosphatase, total protein, albumin, BUN, creatinine, glucose, sodium, chloride, potassium.
Hematology	Complete blood count (hematocrit, WBC, platelets), prothrombin time.
Virology	Quantitative HCV RNA measured by real time PCR (e.g. COBAS TaqMan HCV test)
Thyroid function tests	TSH, T3, or T4
Chest x-ray	If indicated by the investigator
Electrocardiogram	If indicated by the investigator
HCG pregnancy test	For women of childbearing potential, a negative urine (or serum) HCG test was documented within 24 hours prior to the first dose.

Note:.(+) Ceruloplasmin and alfa1-antitrypsin screening values were not obtained if historical values were available that were inconsistent with a diagnosis of Wilson's disease or alfa1-antitrypsin deficiency, respectively.

Additional blood samples were collected and stored in a serum bank in the event that some tests had to be repeated or additional testing was warranted.

Efficacy assessment

Biochemistry

Biochemical response was defined as normal ALT ≤ 1 x ULN and was determined according to standard procedures.

HCV RNA

HCV RNA was measured in serum using a commercially available real-time PCR-based assay (e.g. Cobas TaqMan HCV test; lower limit of detection was 15 IU/ml, with ≥95% probability, using 1 ml of serum (Germer et al. 2005) according to the manufacturer's instructions). Tests were done locally and in the hepatitis serology lab in Hannover. If the local test was positive (>15 IU/ml), but the one done in Hannover negative, HCV RNA was considered positive.

Safety assessment

Safety was assessed according to the AEs (defined in the study protocol) reported spontaneously by participants, and following specific questioning by the investigators throughout the treatment and follow-up periods. In addition, plasma samples were analyzed for routine assessment of hematological variables (leukocytes and platelet counts).

Measures of safety were:

- Clinical adverse events (AEs)
- Vital signs consisting of systolic and diastolic blood pressure and pulse rate
- Clinical chemistry including ALT, AST, total bilirubin, alkaline phosphatase, total protein, albumin, BUN, creatinine, glucose, sodium, chloride, and potassium
- Hematology including complete blood count (hemoglobin, hematocrit, WBC, platelets) and absolute neutrophil count.
- Thyroid function tests including TSH, T3, or T4.
- Women of child-bearing potential had a serum pregnancy test (a) within 24 hours before the first dose of study drug and (b) at any time a secondary amenorrhea of more than one week occurred. Counseling about contraception was repeated on a regular basis
- Ophthalmologic examination: Patients with pre-existing ophthalmologic disorders (e.g. diabetic or hypertensive retinopathy) received periodic ophthalmologic exams during therapy by an ophthalmologist. PEG-IFNα-2b treatment was discontinued in patients who developed new or worsening ophthalmologic disorders. Any patient complaining of decrease or loss of vision had to have an eye examination by an ophthalmologist
- Documentation of dose adjustments and premature withdrawals for safety reasons or intolerance

Clinically significant laboratory abnormalities prompted repeat measures no less than every 4 weeks or in shorter intervals as clinically indicated, with appropriate clinical management until values returned to normal or baseline levels.

9.4.2 Appropriateness of measurements

The variables recorded are standard parameters for HCV detection and have been used in several previous trials in HCV infection.

9.4.3 Primary efficacy variables

The primary measures of efficacy were normalization of ALT levels and negativation of HCV-RNA at the end of therapy.

9.5 Quality assurance

Quality assurance was performed centrally according to the Hep-Net SOPs.

9.6 Statistical methods planned and determination of sample size

9.6.1 Efficacy analysis

The primary endpoint was the reduction of relapse rate 24 weeks after the end of treatment and, thus, improved sustained virological response (SVR24) in the group with a treatment prolongation of 24 weeks (group A) in comparison with SVR24 rates in patients without treatment prolongation (historical control group with SVR24-rate 70%). For the primary analysis, SVR24 rate of group A was calculated with 95% Wald confidence intervals (CI). The study was considered successful if the lower bound of the 95% Wald CI of the SVR24-rate of group A was above 70%. As key secondary analysis the SVR24-rate of group B (12 week prolongation) was compared to the SVR24-rate of the historical control group. The analysis was carried out in line with the primary analysis. Another key secondary objective was to compare group A with group B. For this comparison the analysis was adjusted for the stratification variables and, therefore, Mantel-Haenszel risk differences were used for the comparison of these two groups. Due to too many stratification variables and the reduced sample size, empty cells were explored in the subgroups. Therefore, stratification variables had to be removed for the analysis. According to the prespecified order, the last stratification variable was excluded until calculation was possible.

The primary analysis was conducted according to the intention-to-treat (ITT) principle in all randomized patients. Patients were asked to participate in the study during the standard therapy between weeks 12 and 22. Some patients dropped out before they had started the study. Sensitivity analysis was conducted on all patients that had a baseline visit and, therefore, started study therapy. Additionally, a data set with only compliant patients was created. This was defined as completer analyses (further details in section 11.1 Data sets analyzed). All statistical analyses were conducted using SAS (Version 9.3).

Two strategies to replace missing values on HCV RNA (qualitative) were used: For those patients that had missing values on HCV RNA during the course of the study, but had negative HCV RNA at the previous and the next visit, HCV RNA was considered to be negative and missing values were replaced with negative. All other missing values were replaced as positive, following a conservative strategy for the primary analysis (ITT-principle;

further details in section 11.1 Data sets analyzed). Missing values in key secondary laboratory variables were replaced with last observation carried forward (LOCF). Missing values for quantitative HCV RNA were not replaced as this was not a prespecified key secondary variable and LOCF methods may lead to an anti-conservative estimation if patients had a relapse.

Quantitative variables are given as mean, median, min, max, and standard deviation (SD). Group A and group B were compared exploratoraly with t-tests for independent groups. For categorical variables absolute (and relative) frequencies are presented and compared using Chi²-test and Fisher exact test, respectively.

9.6.2 Safety analysis

All subjects who entered the study were included in the safety analysis. Demographic data, vital signs, local/systemic tolerability, and laboratory data were listed, tabulated, and assessed by means of descriptive statistical analysis. Adverse events were listed, summarized, and commented by the investigator.

9.6.3 Determination of sample size

Sample size was chosen such that not only the primary statistical analysis but also the main secondary statistical analysis has a high power and that a comparison of both treatment groups which was done as further secondary statistical analysis still has a power above 50%.

9.7 Changes in the conduct of the study

The study was terminated due to changes in the treatment of hepatitis C in 2012. A new therapy had been licensed and, therefore, the recruitment of new patients stagnated and it was decided to stop the recruitment (on 22nd October 2012). The last study visit of the last enrolled patient was on 29th July 2013.

Furthermore, in January 2011, special procedures were taken, because the alcohol swabs supplied with PegIntron® Redipen were potentially contaminated (see 16.1.5).

In addition, there was a temporary recruitment halt in October 2010 due to a recall of PegIntron (see 16.1.5 for details).

10. STUDY PATIENTS

10.1 Changes to original data

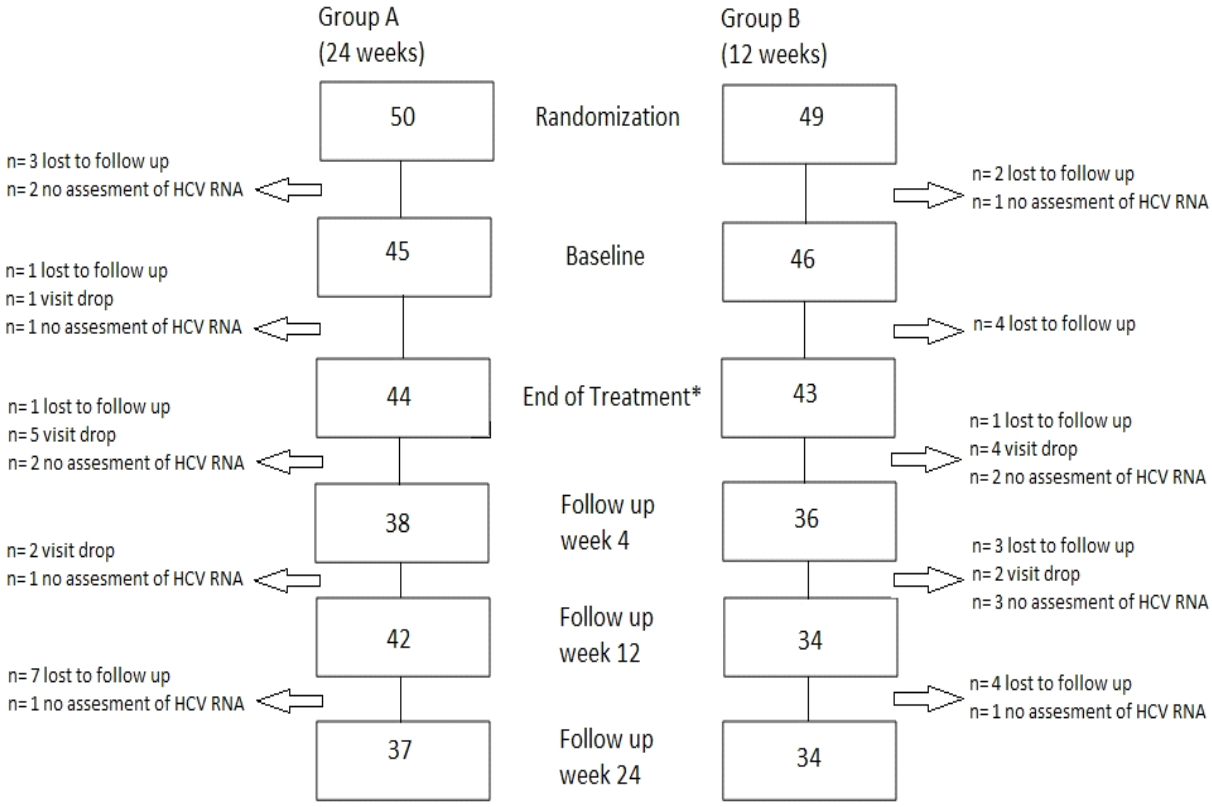
After data base closing, a few implausible data were explored during the analysis regarding laboratory data and adverse events. Changes that were applied before analysis are documented as note to files and can be found in the appendix (16.2.2).

10.2 Disposition of patients and deviation from the protocol

HCV RNA positive patients under treatment were screened for eligibility for the OPTEX study between weeks 12 and 22 of treatment. Baseline visit was 24 weeks after standard treatment. 104 patients were screened for the study and 5 patients did not fulfil the in- or

exclusion criteria (1 patient withdrew informed consent before start of study, 4 did not fulfil the in- or exclusion criteria). 99 patients were randomized to group A (50 patients) and group B (49 patients). During the course of the study, visits were planned every 4 weeks. After treatment, patients were followed-up for 24 weeks at weeks 4, 12, and 24 after end of treatment. Patients were already randomized during the screening phase (standard treatment week 12-22) and 5 patients dropped out before the start of study therapy but after randomization. They were included in the analysis.

The primary endpoint variable HCV RNA (positive or negative) was assessed at baseline, treatment week 12, treatment week 24, and at every follow-up visit. Not all patients attended all visits and some had no HCV RNA assessment at the specified visits (see figure 1).



*In group A after 24 in group B after 12 weeks

Figure 3: Patients with evaluable HCV RNA per visit

28 missing values for HCV RNA had to be replaced as positive. During the course of the study patients dropped out for various reasons. They are summarized in Table 3 below. In group A 39 patients and in group B 35 patients were recorded as having completed the study according to protocol. According to the HCV RNA measurement (compare figure 3), 12 patients in group A and 14 patients in group B dropped out before the end of study. The reason for the difference was that 1 patient in group A did not have a follow-up visit at week 24, but is marked as completion of study according to the protocol. Until the end of study, 26 patients dropped out.

Table 3: Number of patients with completion of study according to the protocol and reasons for withdrawal

	Therapy arm		
	Group A (24 wk) N=50	Group B (12 wk) N=49	Total N=99
Status at end of study			
Study completed according to protocol	39 (78.0%)	35 (71.4%)	74 (74.7%)
Early study termination	11 (22.0%)	14 (28.6%)	25 (25.3%)
p-VALUE (Chi^2)			0.4518
Reason for study withdrawal			
MISSING	39	35	74
Death / Serious Adverse Event	1 (9.1%)	0 (0.0%)	1 (4.0%)
Patient who withdrew consent	3 (27.3%)	3 (21.4%)	6 (24.0%)
Lost-to-follow-up	3 (27.3%)	6 (42.9%)	9 (36.0%)
Therapy failure	1 (9.1%)	3 (21.4%)	4 (16.0%)
Other	3 (27.3%)	2 (14.3%)	5 (20.0%)
p-VALUE (FISHER)			0.624

11. EFFICACY EVALUATION

11.1 Data sets analyzed

The primary and key secondary endpoints were analyzed in 3 different data sets:

- ITT with replacement of missing values (n=99)
- modified-ITT (mITT) without those 5 patients that dropped out before baseline, and with replacement of missing values (n=94)
- Completer data set: only compliant patients without replacement of missing values (n is variable). Compliance was defined as all patients that completed the study according to the protocol and received at least 80% of the duration and dose of therapy.

Confirmatory conclusions are based on all randomized patients in the ITT-data set with replacement of missing values. Missing values on HCV RNA (qualitative) were replaced as

stated in section 9.6 under Efficacy analysis.

Randomization was stratified by sex, age, genotype, cirrhosis, and HCV RNA level >600,000IU/ml. The number of stratification variables with only 99 patients led to empty cells in some of the 32 subgroups. Stratification variables were removed in the prespecified ordering (age, gender, genotype, cirrhosis, HCV RNA level) for the adjusted analysis with Mantel-Haenszel risk differences (RD) to collapse empty strata. In the main analysis only age and gender remained in the analysis.

For sensitivity analyses subgroups with logistic regression were performed with 4 stratification variables (age: < 40 years female, < 40 years male, ≥ 40 years female, and ≥ 40 years male) as well as with all stratification variables.

11.2 Demographic and other baseline characteristics

Baseline information on medical and medication history, as well as results of physical examinations and vital signs are given in Appendix 16.2.1. Figure 2 on recruitment mentioned in section 9.3 demonstrates how many patients were recruited to the registry to include 99 patients into the study. Table 4 gives the baseline characteristics of patients in the genotype 2/3 registry (n = 1006) and the recruited OPTEX study participants (n = 99).

Table 4: Baseline characteristics

	2/3 Registry	OPTEX
Male [%]	63.7	65.7
Age [mean in years]	44.2	45.0
HCV GT 2/3	(17%)/ (83%)	(16%)/ (84%)
BMI [mean kg/m²]	25.5	25.4

11.3 Measurement of treatment compliance

Compliance to therapy was assessed before and at the end of the study separately for Ribavirin and Peg-interferon. Also, the doses were assessed before and at the end of the study as well as change of dose during the study.

11.4 Efficacy results and conclusions

11.4.1 Analysis of efficacy

The primary aim of this study was to show that a prolongation of treatment for 24 weeks (48 weeks in total) is superior to standard treatment duration of 24 weeks in HCV infected patients with genotype 2 or 3 who are still HCV-RNA positive after 4 weeks of therapy. The primary endpoint variable was SVR24 (sustained virological response 24 weeks after end of treatment assessed as being HCV RNA negative) and was compared to a historical control group. Key secondary endpoints were the comparison of SVR24 of group B with a treatment prolongation of 12 weeks (36 weeks in total) to the historical control group and the comparison of SVR24 between the two randomized groups. Further endpoint variables were the SVR-rates at end of treatment, biochemical responses as determined by ALT and AST levels at the EOT and at FU24, analysis of quality of life (with questionnaire SF-36), and severity and frequency of adverse events (AE).

HCV RNA was measured before study (before therapy and at weeks 4, 6, and 8 during standard therapy), at screening, at baseline, at end of treatment, and at follow-up weeks 4, 12, and 24. HCV RNA was quantitatively as well as qualitatively (positive and negative) measured. The primary outcome variable was qualitative HCV RNA. Results of HCV RNA negativity is described in this section; quantitative HCV RNA measures are illustrated in the biometry report (see Appendix 16.2.1). The distribution of HCV RNA quantitative is skewed, however, transformation of HCV RNA was mostly not helpful as patients often had zero counts. Results on non- and $\log_{10}$ transformed HCV RNA is provided in the biometry report (see Appendix 16.2.1). For descriptive analysis, quantiles are also displayed.

11.4.2 Statistical/analytical issues

For the primary analysis SVR24 of group A was compared to the SVR24 of the historical control group, which was considered to be 70%. The two-sided 95%-Wald confidence interval was calculated. A significant improvement in SVR24 was reached if the lower bound of the 95%Wald-CI was above 70%. No adjustment for stratification variables was performed at this stage as it is a comparison against a fixed value. For the key secondary endpoint SVR24 in group B, the analysis was performed in line with the primary analysis. Addtionally, SVR12 (12 weeks after end of treatment) was assessed. In the intention-to-treat (ITT) analysis all patients were analyzed as randomized and missing values were replaced. For sensitivity analysis patients not attending any study visit were excluded from the analysis. A

third data set was created with patients that completed the study and had sufficient duration and dose of treatment (see 4.1. Data sets analysed).

For the comparison between the two randomized groups, Mantel-Haenszel risk differences (MH-RD) were calculated. As there were too many stratification factors, some had to be deleted (see 11.1. Data sets analysed). The analysis was adjusted for age and sex only, whereas in a second sensitivity analysis it was adjusted for age, sex and HCV status. To calculate MH-RD, a macro by Senn et al. (2011) was used in SAS 9.3.

Efficacy results on SVR

Table 5: SVR-rates – ITT

	Time point	Frequency (%)	95%-CI	P-value[1]
Group A	**EOT**	45/50(90.00%)	[81.68%;98.32%]	<.0001
	FU12	39/50(78.00%)	[66.52%;89.48%]	0.0860
Primary endpoint	**FU24**	34/50(68.00%)	[55.07%;80.93%]	0.6191
Group B	**EOT**	41/49(83.67%)	[73.32%;94.02%]	0.0048
	FU12	31/49(63.27%)	[49.77%;76.76%]	0.8359
	FU24	28/49(57.14%)	[43.29%;71.00%]	0.9655

[1]These are one-sided p-values, which have to be compared to 0.025

The primary aim of the study was not reached as only a SVR24-rate of 68% (point estimate) was observed (Table 5). Only at EOT the SVR-rate was above 70%.

Table 6: Risk differences of SVR-rates – ITT

	Time point B/A	MH-RD	95%-CI	P-value
Group B-A (at equal visits)	**EOT/EOT**	-5,42%	[-18.55%;-7.72%]	0.4191
	FU12/FU12	-13.27%	[-30.57%;4.04%]	0.1329
	FU24/FU24	-9.55%	[-27.84%;8.73%]	0.3059
Group B-A (at equal time points)	**FU12/EOT**	-28.82%	[-41.46%;10.17%]	0.0012
	FU24/FU12	-19.78%	[-37.23%;-2.32%]	0.0264

Differences in SVR-rates between both groups were only observed when comparing the groups at equal time points, which was study week 24 and week 36 (Table 6). However, differences diminished at later time points. Younger female patients seem to benefit most from a 48 week therapy compared to 36 weeks of therapy (see Forest plots in the biometry report in Appendix 16.2.1).

The following table illustrates the SVR-rates in the mITT population.

Table 7: SVR-rates – mITT

	Time point	Frequency (%)	95%-CI	P-value[1]
Group A	**EOT**	45/47(95.74%)	[89.97%;100%]	<.0001
	FU12	39/47(82.98%)	[72.23%;93.72%]	0.0090
	FU24	34/47(72.34%)	[59.55%;85.13%]	0.3599
Group B	**EOT**	41/47(87.23%)	[77.69%;96.77%]	0.0002
	FU12	31/47(65.96%)	[52.41%;79.50%]	0.7207
	FU24	28/47(59.57%)	[45.54%;73.60%]	0.9274

[1]These are one-sided p-values, which have to be compared to 0.025

Sensitivity analysis on all patients participating at least once (mITT) in the study gives a slightly different picture compared to ITT: SVR-rates were also improved at FU12 in group A (Table 7 and 8).

Table 8: Risk differences of SVR-rates – mITT

	Time point B/A	MH-RD	95%-CI	P-value
Group B-A (at equal visits)	**EOT/EOT**	-7.80%	[-18.21%;2.61%]	0.1421
	FU12/FU12	-15.65%	[-32.28%;0.98%]	0.0651
	FU24/FU24	-11.58%	[-29.73%;6.37%]	0.2045
Group B-A (at equal time points)	**FU12/EOT**	-29.07%	[-43.19%;-14.95%]	<.0001
	FU24/FU12	-22.43%	[-29.28%;-5.59%]	0.0091

Table 9: SVR-rates – completer

	Time point	Frequency (%)	95%-CI	P-value[1]
Group A	**EOT**	37/38(97.37%)	[92.28%;100%]	<.0001
	FU12	31/36(86.11%)	[74.81%;97.41%]	0.0026
	FU24	32/35(91.43%)	[82.15%;100%]	<.0001
Group B	**EOT**	33/34(97.06%)	[91.38%;100%]	<.0001
	FU12	24/29(82.74%)	[69.01%;96.51%]	0.0345
	FU24	27/33(81.82%)	[68.66%;94.98%]	0.0392

[1]These are one-sided p-values, which have to be compared to 0.025

The analysis of SVR-rates in the completer data set shows improved SVR rates in group A at all time points, but SVR-rates are not improved in group B at FU12 or FU24 (Table 9). The results are overly optimistic as only compliant patients were analyzed and missing values were not replaced.

When comparing SVR-rates between both groups, differences diminished in the completer data set (Table 10).

Table 10: Risk differences of SVR-rates – completer

	Timepoint B/A	MH-RD	95%-CI	P-value
Group B-A (at equal visits)	**EOT/EOT**	-0.34%	[-8.17%;7.49%]	0.9318

	FU12/FU12	-5.74%	[-22.34%;10.86%]	0.4980
	FU24/FU24	-6.08%	[-23.48%;11.31&]	0.4932
Group B-A (at equal time points)	**FU12/EOT**	-16.68%	[-30.78%;-2.59%]	0.0204
	FU24/FU12	-8.82%	[-25.89;8.25%%]	0.3114

As with the sensitivity analysis, for the stratified analysis logistic regression was used with all (Table 11) and with only 4 strata (Table 12). The results shown are those for SVR24 in all three populations used.

The OR is above 1 for treatment group A compared to treatment group B, which means that more patients were HCV negative in group A compared to group B. 24 weeks after EOT female and cirrhosis negative patients seem to benefit most from a 24 week treatment prolongation compared to 12 week treatment prolongation. When regarding only 4 strata, the effect is even more pronounced in female patients. Similar results were obtained in the mITT analysis (Tables 13 and 14). However, when looking at the completer population, there is no effect of gender or cirrhosis (Tables 15 and 16). This may be caused by the imputation of missing values. In total 28 missing values had to be replaced as positive. In the male group 22 out of 65 male patients had missing values, in the cirrhosis group 6 out of 12 missing values had to be replaced.

Table 11: Risk differences of SVR24-rates – ITT (sensitivity analysis with all strata)

Odds Ratio Estimates				
Effect	**Point Estimate**	**95% Wald Confidence Limits**		**Pr > Chi²**
Group A (24 wk) vs Group B (12 wk)	1.563	0.641	0.3454	0.3257
<40 years vs ≥40 years	1.434	0.515	0.3257	0.4907
Male vs female	0.352	0.126	0.4907	0.0467
Genotype 2 vs genotype 3	2.104	0.552	0.0467	0.2760
Cirrhose negative vs positive	4.432	1.020	0.2760	0.0469
≥ HCV 600000 IU/ml vs < 600000 IU/ml	1.589	0.631	0.0469	0.3257

Table 12: Risk differences of SVR24-rates – ITT (sensitivity analysis with 4 strata)

Odds Ratio Estimates				
Effect	**Point Estimate**	**95% Wald Confidence Limits**		**Pr > Chi²**
Group A (24 wk) vs Group B (12 wk)	1.542	0.657	3.616	0.3194
<40 years vs ≥40 years	1.604	0.601	4.282	0.3455
Male vs female	0.308	0.116	0.815	0.0176

Table 13: Risk differences of SVR24-rates – mITT (sensitivity analysis with all strata)

Odds Ratio Estimates				
Effect	**Point Estimate**	**95% Wald Confidence Limits**		**Pr > Chi²**
Group A (24 wk) vs Group B (12 wk)	1.871	0.721	4.853	0.1976
<40 years vs ≥40 years	1.355	0.458	4.010	0.5826
Male vs female	0.356	0.120	1.060	0.0635
Genotype 2 vs genotype 3	2.638	0.591	11.775	0.2038
Cirrhose negative vs positive	5.079	1.098	23.495	0.0376
≥ HCV 600000 IU/ml vs < 600000 IU/ml	1.533	0.581	4.047	0.3880

Table 14: Risk differences of SVR24-rates – mITT (sensitivity analysis with 4 strata)

Odds Ratio Estimates				
Effect	**Point Estimate**	**95% Wald Confidence Limits**		**Pr > Chi²**
Group A (24 wk) vs Group B (12 wk)	1.736	0.706	4.265	0.2292
<40 years vs ≥40 years	1.514	0.539	4.258	0.4314
Male vs female	0.302	0.108	0.848	0.0230

Table 15: Risk differences of SVR24-rates – completer (sensitivity analysis with all strata)

Odds Ratio Estimates				
Effect	**Point Estimate**	**95% Wald Confidence Limits**		**Pr > Chi²**
Group A (24 wk) vs Group B (12 wk)	1.446	0.376	5.553	0.5915
<40 years vs ≥40 years	4.976	0.563	43.982	0.1489
Male vs female	0.264	0.049	1.426	0.1218
Genotype 2 vs genotype 3	5.553	0.512	60.172	0.1585
Cirrhose negative vs positive	3.761	0.508	27.823	0.1945
≥ HCV 600000 IU/ml vs < 600000 IU/ml	0.890	0.216	3.666	0.8713

Table 16: Risk differences of SVR24-rates – completer (sensitivity analysis with 4 strata)

Odds Ratio Estimates				
Effect	**Point Estimate**	**95% Wald Confidence Limits**		**Pr > Chi²**
Group A (24 wk) vs Group B (12 wk)	1.343	0.379	4.755	0.6473
<40 years vs ≥40 years	5.362	0.634	45.357	0.1232
Male vs female	0.258	0.051	1.302	0.1008

Relapse and breakthrough rates

Additional outcome variables were relapse and breakthrough rates. Patients who were HCV RNA negative at the EOT visit and positive afterwards were counted as relapses. Patients who were negative at baseline, but positive at EOT were counted as breakthroughs. The following tables summarize relapse and breakthrough rates per treatment group at different time points and in the three respective populations analyzed (Tables 17-19). The Fisher test was used to descriptively compare both groups.

Table 17: Relapses and breakthroughs (ITT)

Relapse and Breakthrough (ITT)	Therapy Arm		
	Group A (24 wk) N=50	Group B (12 wk) N=49	Total N=99
Relapse			
No relapse	39 (78.0%)	36 (73.5%)	75 (75.8%)
Relapse until FU12	6 (12.0%)	10 (20.4%)	16 (16.2%)
Relapse between FU12 and FU24	5 (10.0%)	3 (6.1%)	8 (8.1%)
p-VALUE (FISHER)			0.4698
Breakthrough			
No Breakthrough	49 (98.0%)	44 (89.8%)	93 (93.9%)
Breakthough	1 (2.0%)	5 (10.2%)	6 (6.1%)
p-VALUE (FISHER)			0.1117

Table 18: Relapses and breakthroughs (mITT)

Relapse and Breakthrough (mITT)	Therapy Arm		
	Group A (24 wk) N=47	Group B (12 wk) N=47	Total N=94
Relapse			
No relapse	36 (76.6%)	34 (72.3%)	70 (74.5%)
Relapse until FU12	6 (12.8%)	10 (21.3%)	16 (17.0%)
Relapse between FU12 and FU24	5 (10.6%)	3 (6.4%)	8 (8.5%)
p-VALUE (FISHER)			0.4971
Breakthrough			
No Breakthrough	46 (97.9%)	42 (89.4%)	88 (93.6%)
Breakthough	1 (2.1%)	5 (10.6%)	6 (6.4%)
p-VALUE (FISHER)			0.2035

Table 19: Relapses and breakthroughs (completer)

Relapse and Breakthrough (completer)	Therapy Arm		
	Group A (24 wk) N=38	Group B (12 wk) N=34	Total N=72
Relapse			
No relapse	33 (86.8%)	28 (82.4%)	61 (84.7%)
Relapse until FU12	4 (10.5%)	5 (14.7%)	9 (12.5%)
Relapse between FU12 and FU24	1 (2.6%)	1 (2.9%)	2 (2.8%)
p-VALUE (FISHER)			0.8614
Breakthrough			
No Breakthrough	37 (97.4%)	34 (100.0%)	71 (98.6%)
Breakthough	1 (2.6%)	0 (0.0%)	1 (1.4%)
p-VALUE (FISHER)			1

Efficacy results on biochemical responses

A key secondary endpoint was biochemical response as determined by ALT and AST levels at the EOT and at the end of follow up (FU24). Response was defined as normalization of ALT (=GPT) and AST (=GOT) if the value was below or equal to 1.5 times the upper limit of normal. The following tables illustrate the response rates for the respective data sets analyzed (Tables 20-22). For the ITT and mITT missing values were replaced with last observation carried forward (LOCF). One patient (Scr. No. 033-005) did not have any measurements on AST and is therefore marked as missing as LOCF could not be applied. The Chi^2-test was used to descriptively compare both groups.

Table 20: Response rates determined by ALT and AST (ITT)

Response as determined by ALT and AST (ITT)	Therapy arm		
	Group A (24 Wk) N=50	Group B (12 Wk) N=49	Total N=99
Response ALT (EOT)			
No response	9 (18.0%)	13 (26.5%)	22 (22.2%)
Response	41 (82.0%)	36 (73.5%)	77 (77.8%)
p-VALUE (Chi^2)			0.3074
Response ALT (FU24)			
No response	15 (30.0%)	18 (36.7%)	33 (33.3%)
Response	35 (70.0%)	31 (63.3%)	66 (66.7%)
p-VALUE (Chi^2)			0.4773
Response AST (EOT)			

MISSING	1	0	1
No response	10 (20.4%)	13 (26.5%)	23 (23.5%)
Response	39 (79.6%)	36 (73.5%)	75 (76.5%)
p-VALUE (Chi²)			0.4746
Response AST (FU24)			
MISSING	1	0	1
No response	14 (28.6%)	17 (34.7%)	31 (31.6%)
Response	35 (71.4%)	32 (65.3%)	67 (68.4%)
p-VALUE (Chi²)			0.5146

Table 21: Response rated determined by ALT and AST (mITT)

Response as determined by ALT and AST (mITT)	Therapy arm		
	Group A (24 Wk) N=47	Group B (12 Wk) N=47	Total N=94
Response ALT (EOT)			
No response	6 (12.8%)	11 (23.4%)	17 (18.1%)
Response	41 (87.2%)	36 (76.6%)	77 (81.9%)
p-VALUE (Chi²)			0.1803
Response ALT (FU24)			
No response	12 (25.5%)	16 (34.0%)	28 (29.8%)
Response	35 (74.5%)	31 (66.0%)	66 (70.2%)
p-VALUE (Chi²)			0.3670
Response AST (EOT)			
MISSING	1	0	1
No response	7 (15.2%)	11 (23.4%)	18 (19.4%)
Response	39 (84.8%)	36 (76.6%)	75 (80.6%)
p-VALUE (Chi²)			0.3177
Response AST (FU24)			
MISSING	1	0	1
No response	11 (23.9%)	15 (31.9%)	26 (28.0%)
Response	35 (76.1%)	32 (68.1%)	67 (72.0%)
p-VALUE (Chi²)			0.3900

Table 22: Response rates determined by ALT and AST (completer)

Response as determined by ALT and AST (completer)	Therapy arm		
	Group A (24 Wk) N=38	Group B (12 Wk) N=34	Total N=72
Response ALT (EOT)			
No response	4 (10.5%)	0 (0.0%)	4 (5.6%)
Response	34 (89.5%)	34 (100.0%)	68 (94.4%)
p-VALUE (FISHER)			0.1168
Response ALT (FU24)			
MISSING	2	1	3
No response	3 (8.3%)	4 (12.1%)	7 (10.1%)
Response	33 (91.7%)	29 (87.9%)	62 (89.9%)
p-VALUE (FISHER)			0.7021
Response AST (EOT)			
MISSING	0	1	1
No response	5 (13.2%)	4 (12.1%)	9 (12.7%)
Response	33 (86.8%)	29 (87.9%)	62 (87.3%)
p-VALUE (FISHER)			1
Response AST (FU24)			
MISSING	2	2	4
No response	3 (8.3%)	3 (9.4%)	6 (8.8%)
Response	33 (91.7%)	29 (90.6%)	62 (91.2%)
p-VALUE (FISHER)			1

Laboratory values were log_{10}-transformed, if the distrubution was skewed. Missing values remained missing. Further analysis of laboratory data can be found in Appendix 16.2.1. The distribution of HCV RNA quantitative is skewed, however, transformation of HCV RNA was mostly not helpful as patients often had zero counts. Results on non- and log_{10} transformed HCV RNA is provided in the biometry report 16.2.1. For further comparisons of qualitative HCV RNA, categoriation of this variable could be used, e.g. according to quartiles or clinically relevant categorisations.

Efficacy results on analysis of quality of life (using questionnaire SF-36)

The SF-36 Mental and Physical Summary Scores were standardized to a mean of 50 and a standard deviation of 10 according to the U.S. general population. Differences between the German and the U.S. general population are, according to Ellert and Kurth (2004), only minimal. Choosing the American population gives internationally comparable results.

Questionnaire SF-36 was to be assessed at baseline, at treatment weeks 12 and 24 (only

group A) during study, as well as at FU12 and FU24. Questionnaires were provided with dates, but they were not allocated to a specific visit. Therefore, the questionnaires were assigned to the respective visits by calculating the date of SF-36 questionnaire +/- 2 days and then allocated to the corresponding visit. If this was not possible, the questionnaires were allocated to the closest visit. However, one patient (Screening number 036-001) had three SF-36 questionnaires at screening, but dropped out before baseline. As the difference to the screening visit was more than 4 weeks and no SF-36 questionnaire was assessed at screening, these questionnaires were not allocated to any visit and were not considered in the analysis.

T-tests were calculated to descriptively compare group A with group B, but only for scheduled assessments of SF-36 questionnaires. The results are summarized in Table 23. The results indicate that the patients of both groups assessed their quality of life as inferior to the reference population (mean=50).

Table 23: Results of SF-36 questionnaires

	Therapy arm		
	Group A (24 Wk) N=50	Group B (12 Wk) N=49	Total N=99
SF-36 Physical Health at Baseline			
N	37	32	69
MISSING	13	17	30
MEAN	39.55	41.36	40.39
STD	9.64	8.07	8.93
MIN	22.10	24.20	22.10
MEDIAN	39.88	39.79	39.84
MAX	57.35	60.21	60.21
p-VALUE (T-TEST)			0.4061
SF-36 Mental Health at Baseline			
N	37	32	69
MISSING	13	17	30
MEAN	38.25	38.12	38.19
STD	12.65	11.36	11.98
MIN	20.40	20.65	20.40
MEDIAN	35.98	36.95	36.02
MAX	60.32	57.44	60.32
p-VALUE (T-TEST)			0.9634
SF-36 Physical Health at Week 12			
N	30	32	62
MISSING	20	17	37
MEAN	39.96	42.81	41.43
STD	9.58	9.11	9.37

MIN	19.14	28.86	19.14
MEDIAN	38.18	43.50	39.34
MAX	55.78	57.01	57.01
p-VALUE (T-TEST)			0.2347

SF-36 Mental Health at Week 12

N	30	32	62
MISSING	20	17	37
MEAN	38.74	36.77	37.72
STD	12.75	12.27	12.44
MIN	19.15	16.62	16.62
MEDIAN	36.78	35.61	36.60
MAX	61.67	57.77	61.67
p-VALUE (T-TEST)			0.5369

SF-36 Physical Health at Week 24

N	36	0	36
MISSING	14	49	63
MEAN	40.34	.	40.34
STD	12.08	.	12.08
MIN	17.54	.	17.54
MEDIAN	40.30	.	40.30
MAX	58.85	.	58.85

SF-36 Mental Health at Week 24

N	36	0	36
MISSING	14	49	63
MEAN	39.98	.	39.98
STD	12.42	.	12.42
MIN	20.91	.	20.91
MEDIAN	39.24	.	39.24
MAX	57.83	.	57.83

SF-36 Physical Health at Follow Up Week 12

N	31	27	58
MISSING	19	22	41
MEAN	48.26	51.37	49.71
STD	9.47	8.11	8.93
MIN	25.19	26.69	25.19
MEDIAN	49.77	53.64	53.27
MAX	58.99	61.01	61.01
p-VALUE (T-TEST)			0.1883

SF-36 Mental Health at Follow Up Week 12

N	31	27	58
MISSING	19	22	41
MEAN	46.78	44.98	45.94

STD	12.05	12.08	11.99
MIN	18.81	17.68	17.68
MEDIAN	51.76	49.01	50.42
MAX	60.30	59.93	60.30
p-VALUE (T-TEST)			0.5734
SF-36 Physical Health at Follow Up Week 24			
N	30	24	54
MISSING	20	25	45
MEAN	49.64	52.08	50.72
STD	8.22	7.88	8.09
MIN	30.71	32.06	30.71
MEDIAN	52.52	54.54	53.16
MAX	59.26	60.79	60.79
p-VALUE (T-TEST)			0.2755
SF-36 Mental Health at Follow Up Week 24			
N	30	24	54
MISSING	20	25	45
MEAN	46.25	46.66	46.43
STD	11.88	11.37	11.55
MIN	17.72	17.40	17.40
MEDIAN	50	50.79	50.58
MAX	60.14	57.81	60.14
p-VALUE (T-TEST)			0.8994

11.4.3 Handling of Dropouts or Missing Data

Dropouts and missing data were handled as described in the protocol (see Appendix 16.1.1).

11.4.4 Interim Analyses and Data Monitoring

An interim analysis was done in October 2013 (see Appendix 16.1.10). The results of this analysis were presented as a poster at the AASLD (2.-5. November, 2013; see Appendix 16.1.11). It was concluded that approximately 30% of G2/3 patients did not achieve RVR in a real life patient registry. However, subsequent recruitment in a treatment-extension study was difficult. Prolonged therapy was well tolerated and 36 versus 48 weeks treatment did not result in higher drop out rates. EOT and SVR were similar.

Data monitoring was done as described in the protocol (see Appendix 16.1.1).

11.4.5 Examination of subgroups

Subgroup analyses are given under section 11.4.2.

11.4.6 Efficacy Conclusions

The primary aim of the study that SVR24 improved with a treatment prolongation of 24 weeks was not achieved. This was also true for an extension of therapy by 12 weeks. Based on the data of the OPTEX study we conclude that treatment prolongation in patients with

genotypes 2/3 and non-RVR cannot be recommended. Due to the current developmets of new direct acting antivirals such as the NS5B polymerase inhibitor sofosbuvir, we recommend treating patients with non-RVR with new DAA combinations.

12. SAFETY EVALUATION

Analysis of safety parameters was performed in all randomized patients per treatment group. Absolute and relative frequencies are displayed. Groups were descriptively compared using the Chi^2-test or Fisher test, respectively.

12.1 Extent of Exposure

During the course of the study, adherence to therapy and changes in dosage were collected and descriptevely compared between both groups. The Table 24 displays dosages of and compliance to study medication.

Table 24: Doses of and compliance to study medication

	Therapy arm	
	Group A (24 Wk) N=50	Group B (12 Wk) N=49
Dosis Peginterferon before study		
80	6 (12.0%)	2 (4.1%)
90	0 (0.0%)	2 (4.1%)
100	13 (26.0%)	19 (38.8%)
105	1 (2.0%)	0 (0.0%)
120	16 (32.0%)	16 (32.7%)
135	1 (2.0%)	0 (0.0%)
150	13 (26.0%)	10 (20.4%)
p-VALUE (FISHER)		0.2617
Dosis Ribavirin before study		
800	9 (18.0%)	9 (18.4%)
1000	23 (46.0%)	22 (44.9%)
1200	14 (28.0%)	15 (30.6%)
1400	4 (8.0%)	3 (6.1%)
p-VALUE (FISHER)		1
Compliance to therapy before study		
ja	50 (100.0%)	49 (100.0%)
Dosis Peginterferon at baseline		
MISSING	3	2
80	4 (8.5%)	2 (4.3%)
90	5 (10.6%)	6 (12.8%)

100	9 (19.1%)	12 (25.5%)
105	3 (6.4%)	4 (8.5%)
120	12 (25.5%)	12 (25.5%)
135	1 (2.1%)	1 (2.1%)
150	13 (27.7%)	10 (21.3%)
p-VALUE (FISHER)		0.9466

Dosis Ribavirin at baseline

MISSING	3	2
800	12 (25.5%)	10 (21.3%)
1000	20 (42.6%)	24 (51.1%)
1200	10 (21.3%)	11 (23.4%)
1400	5 (10.6%)	2 (4.3%)
p-VALUE (FISHER)		0.6246

Last dose Peginterferon in study

MISSING	2	3
80	2 (4.2%)	2 (4.3%)
90	5 (10.4%)	7 (15.2%)
100	12 (25.0%)	10 (21.7%)
105	5 (10.4%)	5 (10.9%)
120	8 (16.7%)	10 (21.7%)
135	2 (4.2%)	1 (2.2%)
150	14 (29.2%)	11 (23.9%)
p-VALUE (FISHER)		0.9721

Tolerability of last dose Peginterferon in study

MISSING	3	3
sehr gut	2 (4.3%)	6 (13.0%)
gut	21 (44.7%)	23 (50.0%)
befriedigend	17 (36.2%)	10 (21.7%)
ausreichend	6 (12.8%)	6 (13.0%)
schlecht	1 (2.1%)	1 (2.2%)
p-VALUE (FISHER)		0.3942

Compliance to Peginterferon in study

MISSING	3	3
sehr gut	32 (68.1%)	37 (80.4%)
gut	13 (27.7%)	7 (15.2%)
befriedigend	2 (4.3%)	1 (2.2%)
ausreichend	0 (0.0%)	1 (2.2%)

p-VALUE (FISHER)		0.3827

Last dose Ribavirin in study

MISSING	2	3
800	14 (29.2%)	8 (17.4%)
1000	19 (39.6%)	25 (54.3%)
1200	10 (20.8%)	11 (23.9%)
1400	5 (10.4%)	2 (4.3%)
p-VALUE (FISHER)		0.3079

Tolerability of last dose Ribavirin in study

MISSING	3	3
sehr gut	2 (4.3%)	5 (10.9%)
gut	22 (46.8%)	24 (52.2%)
befriedigend	20 (42.6%)	13 (28.3%)
ausreichend	2 (4.3%)	3 (6.5%)
schlecht	1 (2.1%)	1 (2.2%)
p-VALUE (FISHER)		0.5375

Compliance to Ribavirin in study

MISSING	3	3
sehr gut	30 (63.8%)	33 (71.7%)
gut	15 (31.9%)	10 (21.7%)
befriedigend	2 (4.3%)	2 (4.3%)
ausreichend	0 (0.0%)	1 (2.2%)
p-VALUE (FISHER)		0.5898

Some patients had changes of study drug during the course of the study, but no major differences were seen between both groups.

12.2 Adverse events

The treatment and the observational time differed between the two groups by 12 weeks. Therefore, various analyses to compare both groups were performed at either

- the same time points (12 weeks and 24 weeks) or
- same visits (EOT and FU24).

Details of all adverse events that occurred during the study with the use of MedDRA-Coding System are displayed in Appendix 16.2.3. Four patients had records of the same AE but with either different, partially overlapping time points or different outcomes or actions. They were summarized according to a Note to File (29th April 2014, in Appendix 16.2.3). Subject 37 appears twice in the listing of AEs, because of differing severity. It was counted as one AE in

the analysis.

Table 25 illustrates a summary of adverse events for both treatment groups at week 12 (36 week therapy for group A and EOT for group B). At this time point, both groups had received a total of 36 weeks of therapy. This table illustrates the total number of AEs and SAEs recorded in each group at this time point. Comparison between groups in more detail were performed on a patient level, which have to be interpreted as e.g. 2 out of 50 (group A) and 2 out of 49 patients had an AE leading to change of dose.

Table 25: Adverse and serious adverse events at 36 weeks of treatment (week 12 of study)

Adverse events [Treatment Week12 (Group A and Group B)]			
	Therapy Arm		
System Organ Class Preferred Term	Group A (24 wk) N=50	Group B (12 wk) N=49	Total N=99
Total number of AEs	130	95	225
Number of patients with at least one AE	40 (80.0%)	34 (69.4%)	74 (74.7%)
General disorders and adminstration site conditions	16 (32.0%)	14 (28.6%)	30 (30.3%)
Asthenia	-	1 (2.0%)	1 (1.0%)
Fatigue	8 (16.0%)	7 (14.3%)	15 (15.2%)
Pyrexia	2 (4.0%)	1 (2.0%)	3 (3.0%)
Flu-like Symptoms	1 (2.0%)	2 (4.1%)	3 (3.0%)
Inflammation at injection site	1 (2.0%)	-	1 (1.0%)
Feeling cold	1 (2.0%)	-	1 (1.0%)
Perfomance impaired	1 (2.0%)	-	1 (1.0%)
Irratability	1 (2.0%)	3 (6.1%)	4 (4.0%)
Shivering	1 (2.0%)	-	1 (1.0%)
Eye disorders	2 (4.0%)	2 (4.1%)	4 (4.0%)
Infalmmation of the eye	-	1 (2.0%)	1 (1.0%)
Ocular hyperemia	-	1 (2.0%)	1 (1.0%)
Increased tear secretion	1 (2.0%)	-	1 (1.0%)
Dry eye	1 (2.0%)	-	1 (1.0%)
Endocrine disorders	3 (6.0%)	2 (4.1%)	5 (5.1%)
Hyperthyroidism	1 (2.0%)	-	1 (1.0%)
Hypothyreosis	2 (4.0%)	1 (2.0%)	3 (3.0%)
Immunthyreoiditis	-	1 (2.0%)	1 (1.0%)
Respiratory, thoracic, and mediastinal disorders	6 (12.0%)	3 (6.1%)	9 (9.1%)
Stress dyspnea	3 (6.0%)	2 (4.1%)	5 (5.1%)
Dyspnea	1 (2.0%)	1 (2.0%)	2 (2.0%)
Cough	2 (4.0%)	-	2 (2.0%)
Skin and subcutaneous disorders	23 (46.0%)	20 (40.8%)	43 (43.4%)
Alopecia	7 (14.0%)	6 (12.2%)	13 (13.1%)
Rash	2 (4.0%)	3 (6.1%)	5 (5.1%)
Eczema	3 (6.0%)	3 (6.1%)	6 (6.1%)
Erythema anulare	1 (2.0%)	-	1 (1.0%)
Skin disease	1 (2.0%)	-	1 (1.0%)

Night sweats	-	3 (6.1%)	3 (3.0%)
Onychoclasia	1 (2.0%)	-	1 (1.0%)
Pruritus	7 (14.0%)	3 (6.1%)	10 (10.1%)
Dry skin	1 (2.0%)	2 (4.1%)	3 (3.0%)
Blood and lymphatic system disorders	4 (8.0%)	8 (16.3%)	12 (12.1%)
Anemia	1 (2.0%)	4 (8.2%)	5 (5.1%)
Hemolytic anemia	-	1 (2.0%)	1 (1.0%)
Leukopenia	1 (2.0%)	1 (2.0%)	2 (2.0%)
Lymphadenitis	-	1 (2.0%)	1 (1.0%)
Pancytopenia	-	1 (2.0%)	1 (1.0%)
Thrombocytopenia	2 (4.0%)	-	2 (2.0%)
Gastrointestinal disorders	13 (26.0%)	6 (12.2%)	19 (19.2%)
Abdominal pain	1 (2.0%)	1 (2.0%)	2 (2.0%)
Blood in stool	1 (2.0%)	-	1 (1.0%)
Hemorrhoides	1 (2.0%)	-	1 (1.0%)
Dry mouth	2 (4.0%)	-	2 (2.0%)
Constipation	1 (2.0%)	1 (2.0%)	2 (2.0%)
Pain upper abdomen	1 (2.0%)	2 (4.1%)	3 (3.0%)
Nausea	6 (12.0%)	2 (4.1%)	8 (8.1%)
Nervous system disorders	12 (24.0%)	10 (20.4%)	22 (22.2%)
Attention impairment	3 (6.0%)	1 (2.0%)	4 (4.0%)
Dysgeusia	-	1 (2.0%)	1 (1.0%)
Headache	8 (16.0%)	6 (12.2%)	14 (14.1%)
Dizziness orthostatic	1 (2.0%)	-	1 (1.0%)
Dizziness	-	2 (4.1%)	2 (2.0%)
Ear and labyrinth disorders	1 (2.0%)	3 (6.1%)	4 (4.0%)
Hearing disorder	-	1 (2.0%)	1 (1.0%)
Middle ear infection	-	1 (2.0%)	1 (1.0%)
Morbus Meniere	-	1 (2.0%)	1 (1.0%)
Tinnitus	1 (2.0%)	-	1 (1.0%)
Infections and infestations	7 (14.0%)	5 (10.2%)	12 (12.1%)
Airway infection	1 (2.0%)	-	1 (1.0%)
Abszess	-	1 (2.0%)	1 (1.0%)
Atemwegsinfektion	1 (2.0%)	-	1 (1.0%)
Bronchitis	1 (2.0%)	-	1 (1.0%)
Boil	1 (2.0%)	-	1 (1.0%)
Helminthosis	1 (2.0%)	-	1 (1.0%)
Nasopharyngitis	1 (2.0%)	1 (2.0%)	2 (2.0%)
Ear infection	-	1 (2.0%)	1 (1.0%)
Oral Herpes	-	1 (2.0%)	1 (1.0%)
Pneumonia	-	1 (2.0%)	1 (1.0%)
Sinusitis	1 (2.0%)	-	1 (1.0%)
Psychiatric disorders	21 (42.0%)	12 (24.5%)	33 (33.3%)
Aggression	2 (4.0%)	-	2 (2.0%)
Anxiety	1 (2.0%)	-	1 (1.0%)
Apathia	-	1 (2.0%)	1 (1.0%)
Depression	5 (10.0%)	3 (6.1%)	8 (8.1%)
Depressive disorder	1 (2.0%)	2 (4.1%)	3 (3.0%)
Hallucinations, mixed	-	1 (2.0%)	1 (1.0%)
Nervositaet	1 (2.0%)	-	1 (1.0%)
Psychological disorder due to general	1 (2.0%)	-	1 (1.0%)

disease			
Insomnia	1 (2.0%)	-	1 (1.0%)
Sleep disorder	7 (14.0%)	4 (8.2%)	11 (11.1%)
Mood swings	2 (4.0%)	-	2 (2.0%)
Nervousness	-	1 (2.0%)	1 (1.0%)
Musculoskleletal and connective tissue disorders	10 (20.0%)	5 (10.2%)	15 (15.2%)
Arthralgia	1 (2.0%)	2 (4.1%)	3 (3.0%)
Discopathy	1 (2.0%)	-	1 (1.0%)
Resilience impaired	1 (2.0%)	-	1 (1.0%)
Bone pain	1 (2.0%)	-	1 (1.0%)
Muscle disease	-	1 (2.0%)	1 (1.0%)
Myalgia	4 (8.0%)	2 (4.1%)	6 (6.1%)
Neckache	1 (2.0%)	-	1 (1.0%)
Backache	1 (2.0%)	-	1 (1.0%)
Social circumstances	1 (2.0%)	-	1 (1.0%)
Pregnancy of partner	1 (2.0%)	-	1 (1.0%)
Metabolism and nutrition disorders	4 (8.0%)	2 (4.1%)	6 (6.1%)
Appetite reduced	4 (8.0%)	1 (2.0%)	5 (5.1%)
Dehydratation	-	1 (2.0%)	1 (1.0%)
Investigations	6 (12.0%)	3 (6.1%)	9 (9.1%)
Weight reduced	4 (8.0%)	2 (4.1%)	6 (6.1%)
Glucose in blood increased	1 (2.0%)	-	1 (1.0%)
Thyreotropin in blood increased	-	1 (2.0%)	1 (1.0%)
Transaminases increased	1 (2.0%)	-	1 (1.0%)
Injury, poisoning, and procedural complications	1 (2.0%)	-	1 (1.0%)
Dizziness during a procedure	1 (2.0%)	-	1 (1.0%)

Patients in group A experienced more events leading to concomitant medication. Also, more patients had ongoing AEs compared to group B. Similar tables, but at different time points (week 24, EOT, total (FU24)) are displayed in Appendix 16.2.3.

12.3 Deaths, other SAE, and other significant AE

12.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

Overall 10 serious adverse events were recorded in the study with four considered to be related to the study drug by the investigator and sponsor (Table 26).

Table 26: List of serious adverse events

	Gender	Age	Arm	SAE term	Patient no.	Causality	Outcome
1	F	41	B	Morbus meniere, anemia, dehydration (exsiccosis)	17	Anemia problably related; Exsiccosis possibly related	Study medication stopped, anemia resolved
2	F	39	B	Biliary pancreatitis due to gallstones	6	Not related	Pancreatitis resolved, gallstones removed

2	F	39	B	Gastric lymphoma	6	Not related	SAE occurred during FU; study drug already terminated
3	M	46	B	Intracerebral bleeding, epilesia	35	Not related	Patient was no longer receiving medication
4	M	42	B	Effusion of pericard and pleura	58	Possible	Study medication terminated
5	M	31	A	Pregnancy of partner	73	Not related	Patient was informed about birth control
6	M	40	A	Epigastralgia	76	Not related	Stent placement
7	M	40	A	Pyrexia, cholecystisis	76	Possible	Was no longer recieiving treatment
8	M	40	A	Epigastralgia	76	Possible	Ribavirin discontinued for 6 days
9	M	40	A	Death	76	Not related	Death

12.3.2 Narratives of SAE and deaths

Four of the 10 SAEs were considered to be possibly or probably related to the study medication by the investigator and/or the sponsor. One patient died, but this was not related to the study treatment.

One SAE was observed in a female patient who had a history of Morbus Meniere. She suffered from dehydration and anemia. The former was possibly related to both study drugs and the latter probably resulted from ribavirin. The patient was hospitalized and treatment stopped.

Another SAE possibly related to both study drugs was effusion of pericard and pleura. The male patient was hospitalized. This SAE occurred during follow-up.

A male patient with a history of liver cirrhosis, cholelithiasis, Mellory-Weiß-lesions, and esophageal varices had epigastralgia, an SAE possibly related to ribavirin. The patient was hospitalized and ribavirin discontinued for 6 days. PEG-intron treatment was continuously given. The same patient had another SAE (fever and cholecystisis) possibly related to the study drugs during follow-up. He was hospitalized again. He finally died of hepatocellular carcinoma as a result of liver cirrhosis. This was not related to the study drugs and also occured during follow-up.

The narritives of the other SAEs that were considered not related to the study drugs can be found in the appendix (16.3).

12.4 Clinical Laboratory Evaluation

Laboratory data were collected during the study at various time points (see Appendix 16.2.1). These data were analyzed with and without last observation carried forward (LOCF). Those variables that showed skewed distribution were $\log_{10}$.transformed. Transformed variables were also analyzed untransformed. These variabels were bilirubin, GGT, GOT, GPT, and leukocytes. Differences between both groups were only explored for leukocytes and bilirubin.

However, these differences were explored before study start.

12.5 Vital signs

Results of physical examinations during the study are summarized in Appendix 16.2.1.

12.6 Safety conclusions

One problem for the comparison of both groups was the different time points of assessment. Therefore, different analyses were performed to account for these differences and to assess safety variables at equal time points. However, even when comparing both groups at equal times points with equal time of exposure to study drug, group A had more AEs compared to group B. Group A also experienced more SAEs compared to group B except for the time point 12 weeks. Group A had more AEs which were ongoing or which led to concomitant medication. As expected, treatment prolongation of 24 weeks compared to 12 weeks seems to be increasingly physically demanding.

13. DISCUSSION AND OVERALL CONCLUSIONS

The primary efficacy analysis was conducted on the ITT population. The primary aim of this study was to show improved SVR24 with a treatment prolongation of an additional 24 weeks compared to standard duration. SVR24-rate was compared to a reference level of 70%. In group A 34 of 50 patients were HCV negative 24 weeks after EOT [68.00%; 95% Wald-CI: 55.07%;80.93%]. The Wald-CI shows that the primary aim was not achieved in this study. Group B showed a similar result with 28 out of 49 patients being negative 24 weeks after EOT [57.14%; 95% Wald-CI: 43.29%;71.00%].

For sensitivity analysis further populations were considered. In the completer analysis with no imputation of missing values, SVR-rates were improved in group A at all time points and in group B at EOT compared to the historical control group. However, this population might be overoptimistic as this is a selection of patients that were willing or able to follow the drug regimen according to the protocol. This analysis was missing in the historical control group.

It should be pointed out that for the primary aim of the study group A was compared to a historical control group with slightly different baseline charactersitics. However, the control cohort was also from Nothern Europe and the treatment regimen was similar.

For the comparison of both randomized groups the analysis was adjusted for a set of stratication variables. Additional sensitivity analyses were performed for a different set of stratification variables. Due to the differences in treatment, various analyses with equal study duration or at equal visits were performed. Differences in SVR-rates between both groups were only observed when comparing the groups at equal time points, which was study week 24. However, differences diminish at later time points, and also in the completer analysis. Sensitivity analyses with another set of stratification variables gave similar results.

Analysis of safety variables indicates that prolonged treatment duration is more physically demanding. Group A had more AEs, more SAEs, an increased number of ongoing AEs, and more AEs leading to concomitant medication. As before, comparisons between both groups were performed at different times points. The results are consistent except for treatment week 12, where group A experienced 1 SAE compared to 3 SAEs in group B.

14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

There are no tables, figures, or graphs referred to but not included in the text.

15. REFERENCE LIST

Aghemo, A., M. G. Rumi, R. Soffredini, R. D'Ambrosio, G. Ronchi, N. E. Del, S. Gallus, and M. Colombo. 2006. Impaired response to interferon-alpha2b plus ribavirin in cirrhotic patients with genotype 3a hepatitis C virus infection. Antivir. Ther. **11**:797-802.

Choo, Q. L., G. Kuo, A. J. Weiner, L. R. Overby, D. W. Bradley, and M. Houghton. 1989. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science **244**:359-362.

Cornberg, M., K. Deterding, and M. P. Manns. 2006. Present and future therapy for hepatitis C virus. Expert. Rev. Anti. Infect. Ther. **4**:781-793.

Dalgard, O., K. Bjoro, H. Ring-Larsen, E. Bjornsson, M. Holberg-Petersen, E. Skovlund, O. Reichard, B. Myrvang, B. Sundelof, S. Ritland, K. Hellum, A. Fryden, J. Florholmen, and H. Verbaan. 2008. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. Hepatology **47**:35-42.

Dalgard, O., K. Bjoro, K. B. Hellum, B. Myrvang, S. Ritland, K. Skaug, N. Raknerud, and H. Bell. 2004. Treatment with pegylated interferon and ribavarin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. Hepatology **40**:1260-1265.

Davis, G. L., J. E. Albright, S. F. Cook, and D. M. Rosenberg. 2003. Projecting future complications of chronic hepatitis C in the United States. Liver Transpl. **9**:331-338.

Ellert, U. & Kurth, B.M. 2004 Methodische Betrachtungen zu den Summenscores des SF-36 anhand der erwachsenen bundesdeutschen Bevölkerung. Bundesgesundheitsbl - Gesundheitsforsch -Gesundheitsschutz 47:1027–1032.DOI 10.1007/s00103-004-0933-1.

Hoofnagle, J. H. 1997. Hepatitis C: the clinical spectrum of disease. Hepatology **26**:15S-20S.

Hoofnagle, J. H. 2002. Course and outcome of hepatitis C. Hepatology **36**:S21-S29.

Lauer, G. M. and B. D. Walker. 2001. Hepatitis C virus infection. N. Engl. J. Med. **345**:41-52.

Mangia, A., R. Santoro, N. Minerva, G. L. Ricci, V. Carretta, M. Persico, F. Vinelli, G. Scotto, D. Bacca, M. Annese, M. Romano, F. Zechini, F. Sogari, F. Spirito, and A. Andriulli. 2005. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N. Engl. J. Med. **352**:2609-2617.

Manns, M. P., H. Wedemeyer, and M. Cornberg. 2006. Treating viral hepatitis C: efficacy, side effects, and complications. Gut **55**:1350-1359.

Senn, S., Weir, J., Hua, T.A., Berlin, C., Branson, M., and Glimm, E. 2011 Creating a suite of macros for meta-analysis in SAS®: a case study in collaboration.Statistics and Probability Letters, 81 (7): 842-851. ISSN 0167-7152 (doi:10.1016/j.spl.2011.02.010).

Shepard, C. W., L. Finelli, and M. Alter. 2005. Global epidemiology of hepatitis C virus infection. Lancet Infectious Diseases **5**:558-567.

Shiffman, M. L., F. Suter, B. R. Bacon, D. Nelson, H. Harley, R. Sola, S. D. Shafran, K. Barange, A. Lin, A. Soman, and S. Zeuzem. 2007. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N. Engl. J. Med. **357**:124-134.

von Wagner, M., M. Huber, T. Berg, H. Hinrichsen, J. Rasenack, T. Heintges, A. Bergk, C. Bernsmeier, D. Haussinger, E. Herrmann, and S. Zeuzem. 2005. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterology **129**:522-527.

16. APPENDICES

16.1 Study information

16.1.1 Protocol and protocol amendments

16.1.2 Sample CRF (unique pages only)

16.1.3 Patient info and consent form

16.1.4 BfArM and ethics committee trial approval

16.1.5 Changes in study onduct documents

16.1.6 Dose modifications

16.1.7 Amendment Approval

16.1.8 Intermim analysis

16.1.9 Important publications and publications based on study

16.2 Patient listings

16.2.1 Biometry report

16.2.2 List of adverse and serious adverse events