NCT03002818

Dr. Imma Fischer
Biostatistik - Tübingen

Quality of Life measurement using wrist actigraphy in HCV genotype 1 infected, treatment naïve patients suffering from fatigue and receiving ombitasvir, paritaprevir, and retonavir tablets and dasabuvir tablets (Viekirax®/Exviera®; 3D regimen): The HEMATITE Study

Statistical Analysis Plan (SAP)

02.05.2018

[redacted]

Table of Contents

Abbreviations

3D regimen	Ombitasvir, Paritaprevir, and Ritonavir tablets (Viekirax®); Dasabuvir tablets (Exviera®)
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
BMI	Body Mass Index
CRF	Case Report Form
DB	Database
DMP	Data Management Plan
EASL	European Association for the Study of the Liver
FSS	Fatigue Severity Scale
HCV	Hepatitis C Virus
SVR12	Sustained Virologic Response at 12 weeks after end of treatment

1 Introduction

As described in the HEMATITE study protocol (version V1.0, 09/20/2016) „... patients with Hepatitis C Virus (HCV) infection reported physical and mental fatigue as the most common symptom, highly impacting their overall quality of life. AASLD (American Association for the Study of Liver Diseases) and EASL (European Association for the Study of the Liver) guidelines therefore rate the treatment of HCV patients suffering from debilitating fatigue as a high priority. This cardinal symptom presents regardless of the stage of liver fibrosis and is difficult to quantify objectively. Similar to other potential reasons for physical fatigue, such as hepatic encephalopathy, increasing evidence suggests a direct viral impact on the central nervous system (CNS). Data demonstrating a longitudinal change of debilitating physical fatigue and increased daytime physical activity upon treatment with 3D regimen are missing to date and are anticipated by the Swiss scientific HCV community.

The rationale for this observational study is to observe the impact of therapy with 3D regimen on physical activity of HCV patients suffering from debilitating fatigue. Furthermore, this study supports the Swiss Hepatitis Strategy, which seeks for the elimination of viral hepatitis in Switzerland within the next 15 years by creating awareness for patients with extrahepatic manifestations."

Patients included in this study applied the following criteria:

- Male or female, aged ≥ 18 years
- Treatment-naïve
- Monoinfected with CHCV, GT 1 (confirmed within the last 36 months or at physicians discretion in case of risk factors)
- Non-cirrhotic (based on liver biopsy, fibroscan ≤ 9.6kPa and/or clinical signs)
- The decision to treat with 3D regimen is made by the physician in accordance with the local Swiss product label prior to any decision to approach the patient to participate in this study.
- Debilitating fatigue (FSS ≥ 4)
- Willing to participate in the study, and willing to wear an activity tracker.

Patients excluded from this study:

- With sources of fatigue other than HCV (especially, severe depression, cancer and hormonal disorders causing clinically significant fatigue).
- With conditions that do not allow to adhere to protocol and use of the device at investigator's discretion.
- Being wheelchair dependent.

Based on the HEMTATITE study protocol details of planned strategies for the data analysis will be documented in this SAP which will be established and finished by signatures of the statistician and the principle investigator before data base will be closed.

2 Data Sources

Data sources for the planned analyses are the data documented by the investigators on the case report forms (CRFs) for each patient. These CRFs were collected by the monitor and send to AbbVie Deutschland for electronically data collection in an OpenClinica data base.

Physical activity and sleep data will be collected by use of wrist-worn activity trackers (ActiGraph GT9X) which will be processed by device-specific software (ActiLife 6) to obtain the activity and sleep-related variables for analysis. These tracker variables will be transferred in csv format from ActiGraph to the Biostatistik – Tübingen. Dealing with and handling of the original data where described in detail in the Data Management Plan (DMP).

3 Data Management

3.1 Handling of Missing Data

- Missing data from CRFs will be proven within the data collection in OpenClinica and clarified by queries to the monitoring.
- For tracker variables datasets of two eligible weeks (10 working days) are needed. If less than two eligible weeks are available, daytimes variables of previous weeks will be used.
- No other replacement of missing data will take place.

4 Objectives

4.1 Primary Objective

According to the HEMATITE study protocol (version V1.0, 09/20/2016) the primary objective is "to observe changes in physical activity in patients with newly initiated therapy with 3D regimen between baseline (before treatment start) and post-treatment week 12".

4.2 Secondary Objectives

The secondary objectives include the following endpoints:

- To correlate subjective fatigue (assessed by means of FSS) and physical activity (measured with an electronic activity tracker) at baseline, during and after 12 weeks of treatment with 3D regimen.
- To observe the proportion of patients achieving sustained virologic response (SVR12) after treatment with 3D regimen (defined as HCV not detectable, 12 weeks after the last dose of 3D regimen).
- To observe sleep efficiency (assessed by means of activity tracker) at baseline, during and after 12 weeks of treatment with 3D regimen.

5 Populations

5.1 Overall Population (OP)

The overall population consists of all documented patients signing the informed consent and meeting all inclusion and no exclusion criteria. Descriptive and safety parameters will be analyzed for this population.

5.2 Analysis Populations (ITT and mITT)

The statistical analyses will be performed for the intention-to-treat population (ITT) and the modified ITT population (mITT) as well. The ITT consists of all documented patients of the overall population with treatment as intended to protocol and received study medication at least once. Additionally, mITT consists of all patients of the ITT which take part at all five visits. For ITT and mITT descriptive and safety parameters will be analyzed. Primary and secondary endpoints will be analyzed for mITT.

6 Statistical Methods

6.1 Flowchart

The formation of the populations will be described by a Consort-Flowchart.

6.2 Descriptive Analysis

The results of descriptive analyses will be shown in common tables for the populations OP, ITT and mITT where quantitative parameters will be shown with number (N), number of missings (miss), mean, standard deviation, minimum, maximum and quartiles (q1, q2 = median and q3). Qualitative parameters will be presented with number (N), number of missings (miss), total and relative frequency.

6.3 Statistical Analysis

6.3.1 Primary Endpoint

The primary endpoint, the change of the mean daytime physical activity between baseline (before treatment start) and post-treatment week 12, will be calculated and analyzed by t-test or Wilcoxon-test, depending from the distribution of the data (normal or not). The significance level will be set to $\alpha = 0.05$, the test will be performed two-sided.

6.3.2 Secondary Endpoints

For the secondary endpoints „change of FSS between baseline, during and after 12 weeks“ the difference between baseline and the respective follow-up visits will be calculated and

shown with 95% confidence intervals (95%-CI). This analysis will also be performed for the parameters daytime activity and sleep efficiency.

Furthermore for daytime activity, FSS and sleep efficiency 95%-CI will be provided at baseline, during the study and after 12 weeks.

The correlation between mean daytime physical activity and FSS will be analyzed for each visit and for the changes between baseline and follow-up visits using Spearman's rank correlation coefficient.

The proportion of patients achieving SVR12 will be calculated and shown with 95 % confidence interval.

6.3.3 Subgroup Analyses

According to the HEMATITE study protocol (version 1.0, 09/20/2016) „subgroup analyses will be provided for patients who achieve/do not achieve SVR12 after treatment with 3D regimen". These analyses will be performed for ITT and mITT.

Daytime activity, FSS and sleep efficiency will be compared between following groups:

- Patients with Ribavirin vs. patients without Ribavirin at visit V2, V3, V4 and V5.
- Women vs. men at each visit.
- Patients with different fibrosis stages (F0, F1, F2 or F3) at each visit.
- Patients with different age categories (median split) at each visit.

Additionally for patients with GT1a vs. patients with GT1b FSS will be compared at each visit.

All statistical analyses will be performed by SPSS® for Windows, version 22.0.

7 Time table

The following temporary periods of time are planned:

Last patient out	April 2018
Data input until	May 2018
Cleanfile	June 2018
Statistical analyses	Juli/August 2018
Integrated Clinical Study Report	September 2018

Deviations from this plan because of unexpected occurence are possible.

8 Planned tables for the statistical part

Number	Items	Database/Variables
1 Information to the study course		
1.1	Enrolled/dropped out patients	Database 1 – Visit 1 (Day -28)
1.2	Study visits and study termination	Database 1 – Visit 1 (Day -28) – Visit 5 (Day 168, SVR12)
1.3	Patient eligibility criteria	Database 1 – Visit 1 (Day -28)
2 Patients baseline characteristics		
2.1	Demographics	Database 1 – Visit 1 (Day -28)
2.2	Medical history	Database 1 – Visit 1 (Day -28)
2.3	Fatigue severity scale (FSS)	Database 1 – Visit 1 (Day -28)
2.4	HCV history	Database 1 – Visit 1 (Day -28)
2.5	Vital signs	Database 1 – Visit 1 (Day -28)
2.6	Laboratory	Database 1 – Visit 1 (Day -28)
2.7	Smoking/alcohol status	Database 1 – Visit 1 (Day -28)
2.8	Activity tracker	Database 2 – Tracker data
2.9	Concomitant medication	Database 1 – Visit 1 (Day -28)
3 Patients characteristics during study		
3.1	Activity tracker	Database 2 – Tracker data
3.2	(S)AEs and concomitant medication	Database 1 – Visit 2 (Day 1) – Visit 5 (Day 168, SVR12)
3.3	Fatigue severity scale (FSS)	Database 1 – Visit 2 (Day 1) – Visit 5 (Day 168, SVR12)
3.4	Start of 3D regimen / 3D regimen	Database 1 – Visit 2 (Day 1) – Visit 4 (Day 84)
3.5	Vital signs	Database 1 – Visit 2 (Day 1) – Visit 5 (Day 168, SVR12)
3.6	Laboratory	Database 1 – Visit 2 (Day 1) – Visit 5 (Day 168, SVR12)
3.7	Physical examination	Database 1 – Visit 4 (Day 84) and Visit 5 (Day 168, SVR12)
3.8	Smoking/alcohol status	Database 1 – Visit 5 (Day 168, SVR12)
4 Statistical analysis		
4.1	Primary endpoint	Database 2 – Tracker data
4.2	Secondary endpoints – Change of parameters	Database 1 (visit data) and database 2 (tracker data)
4.3	Secondary endpoints - Correlations	Database 1 and database 2
4.4	Secondary endpoints – Proportion of SVR12	Database 1

Number	Items	Database/Variables
5 Subgroup analyses		
5.1	Daytime activity, FSS and sleep efficiency for patients with/without Ribavirin	Database 1 and database 2
5.2	Daytime activity, FSS and sleep efficiency for Women vs. men	Database 1 and database 2
5.3	Daytime activity, FSS and sleep efficiency for patients with different fibrosis stages	Database 1 and database 2
5.4	Daytime activity, FSS and sleep efficiency for patients with different age categories	Database 1 and database 2
5.5	FSS for patients with GT1a vs. GT1b	Database 1 and database 2