Quality of Life measurement using wrist actigraphy in HCV genotype 1 infected, treatment naive patients suffering from fatigue and receiving ombramvir, paritaprevir, and ritonavir tablets and dasabuvir tablets (Victiva®/Exviera®). Statistical Analysis Plan (SAP): The HEMATITE Study
Sustained Virologic Response at 12 weeks after end of treatment
Hepatitis C Virus
HCV
Fatigue Severity Scale
FSS
European Association for the Study of the Liver
EASL
Data Management Plan
DMP
Database
DB
Case Report Form
CRF
Body Mass Index
BMI
Adverse event
AE
American Association for the Study of Liver Diseases
AASLD
3D regimen
Combivir® Pr sustained and Recognitr tablets (Viekirax®); Daclacort tablets

Abbreviations

Table of contents

1 Introduction
2 Data Sources
3 Data Management
4 Primary Objective
5 Objectives
4.1 Handling of Missing Data
5.1 Overall Population (OP)
5.2 Analysis Population (AP)
4.2 Secondaries Objectives
4.1 Primary Objective
4.2 Secondaries Objectives
3.1 Handling of Missing Data
2 Data Management
1 Introduction

Abbreviations
stabilization and the principle investigator before data is closed.

Based on the HEMATITTE study protocol, details of planned strategies for the data analysis:

- **Patients excluded from this study:**
  - With conditions that do not allow to adhere to protocol and use of the device at will.
  - With concomitant diseases causing clinically significant fatigue.
  - With sources of fatigue other than HCV (especially: severe depression, cancer and...)

- **Patients included in this study:**
  - With concomitant (besides liver biopsy: fibrosis > 3 and/or clinical signs)
  - With CHC, CT 1 (confirmed within the last 36 months or physicians...)
  - Male or female, age > 18 years

The rationale for this observational study is to observe the impact of therapy with 3D regimen on physiochemical 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 ceasing awareness for patients with hepatitis C. Furthermore, this study addresses the Swiss Hepatitis Strategy, which seeks for the elimination of viral hepatitis in Switzerland within the next 15 years by ceasing awareness for patients with hepatitis C.

**Introduction**

*Dr. Föster, Biostatistik - Tubingen*

*Statistical Analysis Plan*
During and after 12 weeks of treatment with 3D regimen:

- To observe sleep efficiency (assessed by means of activity tracker) at baseline and 12 weeks after the last dose of 3D regimen.
- To observe the proportion of patients achieving sustained virologic response (SVR12) after treatment with 3D regimen.
- To measure with an electrocardiographic activity tracker (at baseline, during and after 12 weeks).
- To correlate subjective fatigue (assessed by means of FSS) and physical activity.

The secondary objectives include the following endpoints:

4.2 Secondary Objectives

Regimen between baseline (before treatment start) and post-treatment week 12:

- To observe the changes in objective activity in patients with newly initiated therapy with 3D regimen as per the HEMATEME study protocol (version V1.0, 09/20/2016) as the primary objective.

4.1 Primary Objective

- No other replacement of missing data will take place.

3.1 Handling of Missing Data

Data Management

Handling of the original data where described in detail in the Data Management Plan (DMP).

Data sources for the planned analyses are the data documented by the investigators on the.

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HEMATEME Study

Statistical Analyses PLAN

Dr. L. Fischer
For the secondary endpoints, "change of FSS between baseline, during and after 12 weeks,"

6.3.2 Secondary Endpoints

The difference between baseline and the respective follow-up visits will be calculated and

The primary endpoint, the change of the mean daily physical activity between baseline

6.3.1 Primary Endpoint

6.3 Statistical Analyses

The results of descriptive analyses will be shown in common tables for the populations OP.

6.2 Descriptive Analyses

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

6.1 Flowchart

6 Statistical Methods

Secondary endpoints will be analyzed for MI IV.

Secondary endpoints will be analyzed for MI IV.

Primary and all secondary endpoints will be analyzed for MI IV. Additionally, MI IV consists of all patients of MI IV which take part in all five groups of MI IV population with randomization as intended in protocol and received study medication at intake. MI IV population (MI IV) as well as MI IV consists of all documented patients of the

5.2 Analyses Populations (III and IV)

The statistical analyses will be performed for the intervention-to-healthy ratio population (P)

5.1 Overall Population (OP)

Populations

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HEMATITE Study

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Bischofstr. – Tübingen

STATISTICAL ANALYSES PLAN
The following temporary periods of time are planned:

<table>
<thead>
<tr>
<th>Time Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

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

Additionally, for patients with GTT vs. patients with GTT and FSS will be compared at each visit:

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

Daily time activity, FSS, and sleep efficiency will be compared between the following groups:

Regimen: These analyses will be performed for ITT and MITT. Additional analyses will be provided for patients who achieve or do not achieve SVR12 after treatment with 3D according to the HEMATITE study protocol (version 1.0, 09/20/2016). Subgroup analyses will be performed for the following variables:

- SVR12: The proportion of patients achieving SVR12 will be calculated and shown with 95% confidence intervals.
- Coefficient correlation: The correlation between mean daytime physical activity and FSS will be analyzed for each baseline, during the study and after 12 weeks.
- Furthermore for daytime activity, FSS and sleep efficiency 95%-CI will be provided at
- Subgroup analyses: daytime activity and sleep efficiency shown with 95% confidence intervals (95%-CI).
| Database 1 | Database 1 - Visit 5 (Day 166, SVR12) | Smoke/gender/ethnic status | 5 (Day 166, SVR12) |
| Database 1 and database 2 | Database 1 - Visit 4 (Day 84) and Visit 5 (Day 166, SVR12) | Physical examination | 7 |
| Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Laboratory | 6 |
| Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Visual signs | 5 |
| Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Score of CD regimen / CD regimen | 4 |
| Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Figeley Severity Scale (FSS) | 3.3 |
| Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | STELAR and concomitant medication | 3.2 |
| Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Activity tracker data | 3.1 |

3 Patients characteristics during study

| Database 1 - Visit 1 (Day 26) | Database 1 - Visit 1 (Day 26) | Concomitant medication | 2.9 |
| Database 2 - Tracker data | Database 2 - Tracker data | Activity tracker | 2.8 |
| Database 1 - Visit 1 (Day 26) | Database 1 - Visit 1 (Day 26) | Smoke/gender/ethnic status | 2.7 |
| Database 1 - Visit 1 (Day 26) | Database 1 - Visit 1 (Day 26) | Laboratory | 2.6 |
| Database 1 - Visit 1 (Day 26) | Database 1 - Visit 1 (Day 26) | Visual signs | 2.5 |
| Database 1 - Visit 1 (Day 26) | Database 1 - Visit 1 (Day 26) | HOV history | 2.4 |
| Database 1 - Visit 1 (Day 26) | Database 1 - Visit 1 (Day 26) | Figeley Severity Scale (FSS) | 2.3 |
| Database 1 - Visit 1 (Day 26) | Database 1 - Visit 1 (Day 26) | Medical history | 2.2 |
| Database 1 - Visit 1 (Day 26) | Database 1 - Visit 1 (Day 26) | Demographics | 2.1 |

2 Patinets baseline characteristics

| Database 1 - Visit 1 (Day 26) | Database 1 - Visit 1 (Day 26) | Patient eligibility criteria | 1.3 |
| Database 1 - Visit 1 (Day 26) | Database 1 - Visit 1 (Day 26) | Study visits and study termination | 1.2 |
| Database 1 - Visit 1 (Day 26) | Database 1 - Visit 1 (Day 26) | Enrollment/dropout if patients | 1.1 |

1 Information to the study course

### 4 Statistical analysis

<p>| Database 1 - Visit 5 (Day 166, SVR12) | Database 1 - Visit 4 (Day 84) and Visit 5 (Day 166, SVR12) | Secondary endpoints - Proportion of SVR12 | 4.4 |
| Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Secondary endpoints - Correlations | 4.3 |
| Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Change of parameters | 4.2 |
| Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Database 1 - Visit 2 (Day 1) - Visit 5 (Day 166, SVR12) | Primary endpoint | 4.1 |</p>
<table>
<thead>
<tr>
<th>Database 1 and Database 2</th>
<th>FSS for patients with G1 vs. G1b</th>
<th>5.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Database 1 and Database 2</td>
<td>Patients with different age categories</td>
<td>5.4</td>
</tr>
<tr>
<td>Database 1 and Database 2</td>
<td>Daytime activity, FSS and sleep efficiency for</td>
<td>6.3</td>
</tr>
<tr>
<td>Database 1 and Database 2</td>
<td>Patients with different Arousals Stages</td>
<td>5.2</td>
</tr>
<tr>
<td>Database 1 and Database 2</td>
<td>Women vs. men</td>
<td>5.1</td>
</tr>
<tr>
<td>Database 1 and Database 2</td>
<td>Daytime activity, FSS and sleep efficiency for</td>
<td>5.1</td>
</tr>
<tr>
<td>Database 1 and Database 2</td>
<td>Patients with/without Rhabdomyolysis</td>
<td>5.1</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Database/Variables</th>
<th>Number</th>
<th>Items</th>
</tr>
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**Bostick - Ludwig**

**HEMATITE Study**

**STATISTICAL ANALYSIS PLAN**

**Dr. L. Fischer**

**Dr. Toger Adams**