CHAT Study Report according to §42b AMG

Study code: TPVAHC2012

EudraCT-Nr.: 2012-001419-21

ClinicalTrials.gov Identifier: NCT02006745 (UK part)

1) Name of Sponsor/Company: Prof. Dr. Jürgen K. Rockstroh c/o Medizinische Klinik und Poliklinik I, Universitätsklinikum Bonn, Rheinische Friedrich-Wilhelms-Universität, Sigmund-Freud-Str. 25, 53105 Bonn, Germany

2) Name of Finished Product: Incivo® (Zulassungsnummer EU/1/11/720/001)

3) Name of Active Substance: Telaprevir

4) Individual Study Table: Not applicable

5) Title of Study: An open label, randomised, non-inferiority trial of pegylated interferon, ribavirin and telaprevir versus pegylated interferon and ribavirin alone in the response guided treatment of acute hepatitis C genotype 1 virus infection in patients with HIV-1 co-infection (CHAT Study).

CHAT study protocol Version 10, 15th July 2013

Amendment 3, final version 19 March 2014 (Amendments solely due to changes in numbers of participating study centres)

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7) Study centre(s):

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8) Publication (reference):

https://pubmed.ncbi.nlm.nih.gov/28240597/

https://pubmed.ncbi.nlm.nih.gov/29493385/

9) Studied period (years): date of first enrolment: 04.09.2013, date of last completed: 16.09.2015

Enrolment was stopped prematurely on 31.12.2014 due to slow recruitment.

10) Phase of development: Phase IV

11) Objectives :

Primary objective: Sustained virological response (SVR): Negative HCV RNA 24 weeks after end of treatment (Comparison of SVR between arms by intention to treat analysis)

Secondary objectives:

Negative HCV RNA 12 weeks after end of treatment

Negative HCV RNA at end of treatment (EOT)

Reduction in HCV RNA from baseline to week 4

CD4 count change from baseline to EOT

HIV RNA change from baseline to EOT

Total grade III / IV adverse events by EOT

Adherence to medication

(Comparison of respective parameters between arms by intention to treat analysis)

12) Methodology: The CHAT study is a parallel arms, open label, randomized, controlled trial of pegylated interferon (Peg-IFN) and ribavirin (RBV) plus TPV versus Peg-IFN and RBV alone in the response guided treatment of patients with AHC genotype (GT) 1 infection and HIV-1 co-infection at 6 centres in Germany (n=14) and 1 centre in Great Britain (n=20). After screening 34 HIV-infected male patients from the United Kingdom and Germany who were diagnosed with acute HCV infection were randomized to one of two study arms:

- Peg-IFN and weight-based RBV (arm 1)
- Peg-IFN and weight-based RBV plus TPV (arm 2)

Telaprevir was given 750mg tid (if efavirenz containing ART telaprevir dose was increased to 1125mg tid) p.o., Peg-IFN was given as either Peg-IFN alfa-2a (180μg) or Peg-IFN alfa-2b (1.5mg/kg) once weekly s.c., ribavirin was given 1000mg qd (body weight <75kg) or 1200mg qd (weight ≥ 75kg) p.o.
Patients achieving an undetectable HCV RNA at 4 weeks (RVR) were treated for 12 weeks in arm 2 and 24 weeks in arm 1. Patients without RVR were treated for 24 weeks in arm 2 (12 weeks of TPV/PR followed by 12 weeks of PR) and 48 weeks in arm 1. Patients in arm 2 with a HCV-RNA >1000 IU/ml at week 4 were discontinued from Telaprevir and continued with PR for an additional 44 weeks. Stopping rules as per Telaprevir product information were used (Discontinuation of TPV when HCV-RNA above 1000 IU/ml at week 4 or week 12). Occurrence of any contraindication for Telaprevir, ribavirin or pegylated interferon lead to treatment discontinuation.
All patients were evaluated for virological response: A negative HCV-RNA 12 weeks after end of treatment was considered a SVR (sustained virological response; SVR12).
Abbott Realtime HCV PCR assay and COBAS® AmpliPrep/COBAS® TaqMan® HCV assay by Roche were used for HCV quantification at local laboratories.

13) Number of patients (planned and analysed): Planned: 40; analysed: 34

14) Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Documented current acute hepatitis C genotype 1 infection with detectable HCV-RNA (PCR-assay) with an estimated duration less than 24 weeks as defined below:
   a. First HCV RNA positive AND
   b. Prior negative anti-HCV antibody or HCV RNA test within 6 months OR
   c. rise of liver transaminases above 2.5 x ULN within the past 6 months with prior normal transaminases during the year before AND
   d. exclusion of other causes of acute hepatitis
2. Confirmed HIV infection
3. Receiving a atazanavir-, etravirine-, rilpivirine-, efavirenz- or raltegravir-based ART regimen or able to switch regimen to these agents with an undetectable HIV viral load for at least 3 months, or not receiving ART with no immediate plans to start ART during the first 6 months of study
4. CD4 T cell count >200/µl at screening in patients under ART, CD4 T cell count >500/µl at screening in patients without ART
5. Patients who are 18 years or older
6. Able to give informed consent

Exclusion criteria:

1. HCV infection with non-1 genotype
2. Acute opportunistic infection requiring treatment

3. Malignancy requiring chemotherapy or radiotherapy
4. Active HBV infection (HBs Ag + with positive hepatitis B DNA unless tenofovir containing ART)
5. Known autoimmune disease
6. Hepatic failure
7. History of ischaemic heart disease or other serious cardiac disease
8. Current symptoms of depression, or past history of depression for which the patient is currently taking medication, or history of other serious psychiatric disease
9. Haemoglobinopathy or severe anaemia of any cause
10. Serious abnormality on screening blood tests including, but not limited to: Hemoglobin <8g/dl, absolute neutrophil count <750/mm3, platelets <50000/mm3, creatinine >2mg/dl, creatinine clearance <50ml/min
11. Pregnancy or breast feeding
12. Known hypersensitivity to one of the trial drugs or its excipients
13. Other contraindicated concomitant treatment
14. Active drug abuse that would make it difficult to comply with the protocol
15. Any other reason why, in the opinion of the investigator, the patient should not be enrolled in the trial.

15) Test product, dose and mode of administration, batch number: Telaprevir 750mg tid p.o., batch numbers: DAL6R00, VX-4007_JC_Bonn_140227, CAL7Y00.

16) Duration of treatment: 12-24 weeks (response guided)

17) Reference therapy, dose and mode of administration, batch number: Peg-IFN alfa-2a (180μg) or Peg-IFN alfa-2b (1.5mg/kg) once weekly s.c.; Ribavirin 1000mg qd (body weight <75kg) and 1200mg qd (weight ≥ 75kg) p.o.; batch number: not available (prescription medication via individual pharmacies)

18) Criteria for evaluation: Efficacy, Safety:

Efficacy: HCV RNA quantification will be performed at the local laboratory. After screening, the coordinating CTU will communicate to the treating physician the randomised treatment arm for each patient. The local laboratories at each site will all use a standard methodology for measuring HCV VL and must be shown to be participating in a recognised quality control programme.

Safety: A symptom evaluation and basic physical examination (vital signs and targeted examination according to any reported symptoms) will be performed at each visit. Stage of disease will be classified according to the WHO criteria. Blood will be drawn at designated study visits to assess laboratory safety parameters (see table of study assessments). Additional safety blood tests will be performed to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated. All safety blood tests will be performed at the local site laboratory and the results returned to the treating physician in real time. Adverse events (clinical and laboratory) will be graded using the 1992 Division of AIDS toxicity grading scale. Serious adverse events will be defined as in ICH GCP.

19) Statistical methods: Eligible patients were randomised in a 1:1 ratio to PR (arm 1) or PR + TPV (arm 2). Enrolment was closed before 40 participants had been randomised due to slow recruitment. Fisher's exact, chi-square and Mann-Whitney U test were used for statistical analysis.

20) Summary – Conclusions: Efficacy Results, Safety Results, Conclusion:

Efficacy: All 34 patients were male, median age was 41 years. Main route of HIV transmission was MSM (100%). 53% had an IL28B C/C HCV genotype (GT). Median baseline HCV-RNA was 291.227 IU/mL and median CD4+ T cell count 676 cells/µL. 88% of all patients received cART, 88% had baseline suppressed HIV-RNA (<40 copies/mL). Median ALT was 105 U/l. Median time from HCV diagnosis to screening was 16 weeks. 15 patients were randomized to arm 1, 19 to arm 2.

Primary endpoint: Overall SVR_{12} rate was 79.4% (27/34). SVR_{12} was seen in 80% patients (12/15) receiving PR alone and in 78.9% patients (15/19) receiving TPV + PR. Of the 4 patients without SVR_{12} receiving TPV one experienced a viral breakthrough, 2 were non-responders; in one case HCV protease inhibitor associated mutations were selected under TPV (V36M, R155K; detailed resistance analyses will be reported separately). 3 out of 4 patients had baseline HCV-RNA >6 Mio IU/ml.

Safety

No SAE occurred throughout the study period. TPV containing treatment had to be stopped in one case of severe epidermolysis (the event did not fulfil SAE criteria). All other adverse events were grade 1. Ribavirin dose reduction occurred in 0% in arm 1 and 27% in arm 2 (p=0.113), anemia in 7% vs. 21% (p=0.355), rash in 20% vs. 26% (p=0.494), pruritus in 20% vs. 63% (p=0.017), fatigue in 73% vs. 53% (p=0.269), mood disorders in 20% vs. 11% (p=0.634), and headache was seen in 20% in arm 1 vs. 16% in arm 2 (p=0.548).

Conclusions

In summary, although Telaprevir containing triple therapy offers the advantage of shortened treatment duration in acute HCV coinfection treatment is associated with additional toxicities while not leading to higher SVR rates. Therefore, with the AHC epidemic still ongoing additional studies are needed assessing which all oral DAA combination should best be used for treatment of acute HCV and what would be the optimal treatment duration. Hopefully this will eventually lead to a registration of DAAs for treatment of AHC and corresponding recommendation in hepatitis treatment guidelines.

21) Date of report: 21.10.2016, revised 08.11.2020