Clinical Protocol AI447-029
A Phase 3, Open-Label Study with Asunaprevir and Daclatasvir Plus Peginterferon Alfa-2a (Pegasys) and Ribavirin (Copegus) (P/R) (QUAD) for Subjects Who Are Null or Partial Responders to Peginterferon Alfa 2a or 2b Plus Ribavirin with Chronic Hepatitis C Genotypes 1 or 4 Infection

Published: 25-05-2012
Last updated: 26-04-2024

Primary Objective:This research study is designed to assess the effectiveness of the combination of study drugs (ASV + DCV) being used to treat the hepatitis C virus (HCV). The best way to assess this aim is to measure the amount of virus in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON37569

Source
ToetsingOnline

Brief title
Open-Label Study: Asunaprevir/Daclatasvir + Peginterferon Alfa/Ribavirin

Condition

- Other condition
- Viral infectious disorders

Synonym
Chronic Hepatitis C, liver diseases

Health condition

Chronic Hepatitis C

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical company (Bristol-Myers Squibb)

Intervention

Keyword: Asunaprevir, Chronic Hepatitis C, Daclatasvir, Genotypes 1 and 4

Outcome measures

Primary outcome

Primary Endpoint

* Antiviral activity, as determined by the proportion of subjects with SVR-12,

defined as HCV RNA < LOQ at post-treatment Week 12, for all subjects infected

with HCV genotype 1.

Secondary outcome

Secondary Endpoints

* On-treatment safety, as measured by frequency of SAEs and discontinuations

due to AEs through the end of treatment (maximum of 24 weeks) plus 7 days;

* Proportion of subjects with SVR-12 (HCV RNA < LOQ at post-treatment Week 12)

by the rs12979860 single nucleotide polymorphisms (SNP) in the IL28 gene;

* Proportion of subjects with HCV RNA undetectable at each of the following timepoints: weeks 1, 2, 4, 6, 8 and 12; at both Weeks 4 and 12 [eRVR]; EOT (up to 24 weeks), post-treatment Week 12 or post-treatment Week 24;

* Proportion of subjects with HCV RNA < LOQ at each of the following timepoints: weeks 1, 2, 4, 6, 8 and 12; at both Weeks 4 and 12 [VR(4&12)]; End of Treatment (EOT) (up to 24 weeks), post-treatment Week 24 (SVR-24).

* Proportion of patients with SVR12 (HCV RNA < LOQ at post-treatment Week 12) for HCV genotype 4 subjects

Study description

Background summary

Approximately 170 million people worldwide are chronically infected with hepatitis C virus (HCV). The majority of individuals infected progress to chronic hepatitis, which can lead to cirrhosis, liver failure and hepatocellular carcinoma (HCC). HCV is the leading indication for liver transplantation in most countries and a major cause of HCC.

The standard of care therapy for patients with genotype 1 chronic HCV infection is the combination of a direct acting antiviral (DAA) and peg-Interferon plus ribavirin. The recently approved DAAs include the two NS3/4A protease inhibitors boceprevir (BOC) and telaprevir (TVR). These drugs are administrated for either 24 weeks (naive early responders) or 48 weeks (previous peg-Interferon Alfa-2 and ribavirin (P/R) treatment failures and naive late responders) achieving sustained virologic response (SVR) rates of ~60 - 80% in naive patients and ~30% - 80% among previous treatment P/R failures. Despite this improvement in SVR rates and the option of short treatment duration, adverse events occurred more frequently in patients treated with DAA + P/R than in those treated with P/R therapy alone.

Daclatasvir (DCV) and asunaprevir (ASV) are man-made experimental drugs, in tablet and capsule form respectively, that work by inhibiting hepatitis C virus (HCV) proteins called NS5a and NS3 respectively. The NS5a and NS3 proteins have a key function in the replication of HCV and modulation of viral cellular

signalling/communication pathways and are also important in blocking the hosts IFN or immune response to the infection. IFN, named after their ability to "interfere" with viral replication also function to activate immune cells, increase the recognition of infected cells and increase the ability of uninfected host cells to resist new infection by virus. By inhibiting this IFN signalling or communication pathways, the NS5a and NS3 proteins impair the host*s immune response to infection. Thus, DCV and ASV work by interfering with viral replication and preventing the virus from impairing the immune response to infection a double benefit. It is hoped that NS5a and NS3 protein inhibitors such as the study drugs, DCV and ASV, will result in improved response and also shorter treatment times. DCV and ASV have been studied intensively in laboratory and animal studies and its effectiveness against HCV has been demonstrated. DCV and ASV are not currently licensed but clinical studies have shown that they may be effective in treating hepatitis C virus infection.

The addition of ASV + DCV in combination with P/R will potentially have even greater success in the treatment of null responders of both sub-types of genotype 1 (1a & 1b). In a Phase 2 study (AI447-011) evaluating *QUAD* therapy in prior null responders SVR rates of 90% have been achieved (n = 51). Although this data has yet to be confirmed in larger studies, it suggests that ASV combined with DCV plus P/R may provide significant benefit to prior null responders, and potentially also for partial responders of P/R, compared to single direct acting antivirals (DAA) plus P/R regimens in subjects infected with genotype 1 or genotype 4.
The purpose of this study is to assess the efficacy and safety of ASV and DCV in combination with P/R (QUAD therapy) in a larger patient population.

Research Hypothesis: In subjects who are prior null/partial responders to P/R, co-administration of ASV and DCV with P/R for 24 weeks for the treatment of chronic HCV genotype 1 infection is safe, tolerable and efficacious where efficacy is based on SVR12, defined as HCV RNA < LOQ at post-treatment Week 12.

Study objective

Primary Objective:
This research study is designed to assess the effectiveness of the combination of study drugs (ASV + DCV) being used to treat the hepatitis C virus (HCV). The best way to assess this aim is to measure the amount of virus in patients* blood 12 weeks after ceasing study the study medication which is 24 weeks in duration. If a patient has achieved undetectable HCV in their blood 12 weeks after ceasing treatment they are said to have achieved a "Sustained Virological Response" (Abbreviated as SVR-12).

Secondary Objectives:
* To assess the safety of the study medications. This will be assessed by measuring the number of serious adverse events (SAEs) and study medication discontinuations*

* To assess the relationship between the efficacy of the study drugs and changes in the HCV genome responsible for drug resistance.
* To assess the efficacy of the study drugs as determined by:
* Undetectable HCV RNA at the following time points throughout the trial: weeks 1, 2, 4, 6, and 8 and 12; at both Weeks 4 and 12 [Extended rapid virological response (eRVR) - which means that the virus is undetectable at treatment weeks 4 and 12.]; End-Of-Treatment (up to 24 weeks), post-treatment Week 12 or post-treatment Week 24;
* To evaluate antiviral activity endpoints for HCV genotype 4 subjects.

Study design

Approximately 390 HCV subjects (approximately 350 genotype 1 and up to approximately 40 genotype 4), who failed prior P/R treatment, will be treated in this single arm, open-label study. Genotype 4 subjects will be capped at 10% (maximum up to approximately 40 subjects will be enrolled). Enrollment in this study may be closed once approximately 350 genotype 1 subjects are treated. The study will enroll a minimum of 40% of genotype 1 subjects for each HCV Subtype: 1a and non-1a (ie, subtype will be capped at 60%).
All subjects will be treated for 24 weeks and will receive 100 mg BID of ASV soft capsule, 60 mg QD of DCV, and P/R for 24 weeks and subjects will then be followed-up for 24 weeks after completion of treatment or early discontinuation. It is expected that all subjects who are in the study will complete the protocol-defined durations for treatment and follow-up.
If alternative HCV therapy is initiated in the post treatment period for any reason, the subject must withdraw from the study once the post-treatment Week 4 visit has occurred.
The last visit will be considered the date of the last post-treatment visit.
The end of the study will be considered the last subject*s last visit date or when the last data point required for statistical analysis is received from the last subject, whichever is later.
Following completion of the post-treatment period of the study, subjects will then be asked to enroll into a separate observational study (AI444-046) for an additional 3-year follow-up to assess long-term SVR, natural history of the HCV resistance and liver-related complications.
The primary analysis will occur when all subjects complete post-treatment Week 12, and a final analysis will occur once all subjects complete post-treatment Week 24.

Intervention

All subjects will be treated with QUAD therapy (DCV + ASV + pegIFN*-2a + RBV) for 24 weeks and will receive 24 weeks of follow-up after treatment or early discontinuation.

Subjects will receive the following doses:

* pegIFN*-2a: Subjects will self-administer 180 *g pegIFN*-2a injection subcutaneously once weekly throughout the entire dosing period.
* RBV: Subjects will take RBV twice daily with food. For subjects weighing < 75 kg the total dose is 1000 mg per day and for those weighing * 75 kg the dose is 1200 mg per day. Therefore, subjects should take either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects * 75 kg) in the morning with food and 600 mg (3 tablets) in the evening with food.
* ASV: ASV soft capsules should be taken twice daily (1 capsule per dose) for the duration of assigned treatment.
* DCV: DCV tablets should be taken once daily (1 tablet) for the duration of assigned treatment. DCV may be taken with or without a meal, and may be taken with RBV.

Subjects who do not tolerate therapy with P/R during the study may continue on ASV and DCV alone (DUAL) for a total treatment duration of 24 weeks. Any subject with genotype non-1a is permitted to continue on DUAL therapy alone; however, subjects with genotype 1a or genotype 4 must have HCV RNA < LOQ at the last assessment before proceeding to DUAL therapy.

It is expected that all subjects who are on study will complete the protocol defined durations for treatment and follow-up. If alternative HCV therapy is initiated in the post-treatment period for any reason, subject must withdraw from the study once the post treatment Week 4 visit has occurred.

Study burden and risks

RISKS:
As for any relatively new drug or new drug combination, there might be unknown side effects. Based on what we have learned up to this point, the following adverse drug reactions are known:

a) Side effects seen for the combination of DCV and ASV (alone or with P/R):
In clinical trials with HCV infected subjects receiving the combination of DCV and ASV alone or with P/R:
AI447-011 is an ongoing Phase 2a, parallel, open label, randomized, multiple-dose study to evaluate the safety, pharmacokinetics and pharmacodynamics of DCV and ASV in combination alone or with P/R in chronically infected subjects with HCV genotype 1 who were previous null responders to P/R. Subjects received this *QUAD* therapy for 24 weeks. Based on preliminary safety data, there were no deaths, SAEs or discontinuation due to AE/SAEs. The most frequently reported AEs were diarrhea in 15/21 (71.4%), fatigue in 13/21 (62%), headache 11/21 (52.4%), nausea 7/21 (33%), and cough 5/21 (23.8%). Six (6/21) subjects were identified with elevations in ALT above 3x upper limit of normal (ULN) (47 U/L). Two (2) of the subjects received DCV and ASV alone, and 4 received DCV and ASV in addition to P/R.
ALT values in all subjects showed improvement without intervention, dose reduction or drug discontinuation. The etiology of these findings is not

understood: however, they appear similar to observations made from data as part of a 12 week on-treatment database lock performed in study AI447-016. Continued close monitoring of liver function tests during treatment is justified.
In addition to potential risks based on pre-clinical and early clinical studies, the possibility of drug-induced liver injury (DILI) may be increased with DAAs, which are concentrated and metabolized by the liver, and administered to a population (chronic HCV) at increased risk for DILI. The type of liver injury that leads to severe DILI is predominantly hepatocellular, and is therefore associated with a rise in ALT and AST, but is extensive enough to affect the liver*s functional ability to clear bilirubin or to synthesize coagulation factors. Therefore increased total bilirubin and/or INR associated with marked ALT/AST elevation should warrant consideration of DILI, and subject interventions should include discontinuation of study drugs.

b). Side effects seen for the combination of P/R:
i). Side effects seen in 1 in 10 or more of subjects:
Anaemia (low red blood cell count), loss of appetite, feeling depressed (feeling low, feeling bad about oneself or feeling hopeless), anxiety, inability to sleep, headache, difficulty concentrating and dizziness, cough, shortness of breath, Diarrhoea, nausea, abdominal pain, loss of hair, and skin reactions (including itching, dermatitis and dry skin), pain in joints and muscles, fever, weakness, tiredness, shaking, chills, pain, injection site irritation and irritability (getting easily upset)
ii). Side effects seen in less than 1 in 10 but more than 1 in 100 patients:
Fungal, viral and bacterial infections. Upper respiratory infection, bronchitis, fungal infection of the mouth and herpes (a common recurring viral infection affecting the lips, mouth), low platelet count (affecting the clotting ability) and enlarged lymph glands, overactive and underactive thyroid gland, mood /emotion changes, aggression, nervousness, decreased sexual desire, poor memory, fainting, decreased muscle strength, migraine, numbness, tingling, burning sensation, tremor, changes in the sense of taste, nightmares, sleepiness, blurry vision, eye pain, eye inflammation and dry eyes, sensation of room spinning, ear pain, rapid heart rate, pulsation of the heart beats, swelling in the extremities, flushing, shortness of breath with activity, nose bleeds, nose and throat inflammation, infections of the nose and sinuses (airfilled spaces found in the bones of the head and face), runny nose, sore throat, vomiting,indigestion, difficulty swallowing, mouth ulceration, bleeding gums, inflammation of tongue and mouth, flatulence (excess amount of air or gases), dry mouth and loss of weight, rash, increased sweating, psoriasis, hives, eczema, sensitivity to sunlight, night sweats, back pain, joint inflammation, muscle weakness, bone pain, neck pain, muscle pain, muscle cramps, impotence (inability to maintain an erection), chest pain, flu-like illness, malaise (not feeling well), lethargy, hot flushes, thirst.
iii). Side effects seen in less than 1 in 100 but more than 1 in 1,000 patients:
Lower respiratory tract infections, urinary tract infection, skin infections, liver tumour, sarcoidosis (areas of inflamed tissue occurring throughout the body), inflammation of the thyroid, diabetes (high blood sugar), dehydration,

thoughts of suicide, hallucinations (abnormal perceptions), anger, hearing loss , peripheral neuropathy (disorder of the nerves affecting the extremities), bleeding in the retina (back of the eye), high blood pressure, wheezing, gastrointestinal bleeding, inflammation of the lips, inflammation of the gums, poor functioning of the liver.
This risk will be minimised by frequently monitoring the safety of the participant during and after treatment, and providing a list of prohibited medications to the subjects, and their GPs to prevent possible drug to drug interactions.

Risks for patients if they are able to become pregnant: Participating patients must not become pregnant or breastfeed whilst they are taking the study treatments and for 6 months after stopping treatment. Patients who are woman of child bearing potential must be using two adequate methods to avoid pregnancy for the duration of this study and are advised to immediately contact their study doctor if there is a change in the method to avoid pregnancy or if patients start any prescription drug or other medication (including over-the-counter drugs and herbal supplements) not prescribed by the study doctor.
The reasons for these precautions are because taking peg-IFN* in combination with ribavirin can cause death, serious birth defects or other harm to an unborn child or breastfeeding infant.

BENEFITS:
The study drugs (ASV + DCV + P/R) will hopefully help research participants to achieve a virologic response to treatment, and hence, prevent their HCV from progressing to liver cirrhosis (scarring), liver cancer or end stage liver disease which may require a liver transplant. However, this cannot be guaranteed.
The addition of two DAAs (ASV, DCV) to P/R will potentially have even greater success than the addition of a single DAA in the treatment of genotypes 1 and 4 null responders and, by extension, all genotypes 1 and 4 non-responders. Results from the Phase 2a study (AI447-011) evaluating *Quad* therapy in prior null responders has achieved SVR rates approaching > 90% (n = 51). Although this data has yet to be confirmed in larger studies, it suggests that DCV combined with ASV plus P/R may provide significant benefit to prior null responders of P/R compared to single direct-acting antiviral (DAA) plus P/R regimens in subjects infected with genotype 1. It is anticipated that the *Quad* regimen will be at least equally efficacious in other P/R non-null responder groups (partials, relapsers, and breakthrough). Finally, DCV and ASV not only have potent and selective activity against genotypes 1b and 1a, but also have potent activity against genotype 4. Therefore the unprecedented response in the re-treatment of genotype 1-infected subjects is anticipated to translate into the genotype 4-infected population.

During the study, subjects will be monitored closely by the study doctor (who is an experienced clinician) and his/her team. Subjects may benefit from being

seen more frequently by a experienced clinicians and nursing staff, and from receiving increased emotional support from the research team.

Although not of direct benefit to research participants, the information learned from this study may help other subjects with chronic HCV infection in the future.

Contacts

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NL
Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Males and females, * 18 years of age;
* HCV Genotype 1 or 4 who previously failed treatment with P/R, classified as previous null and partial responders based on previous therapy;
* HCV RNA > 10,000 IU/mL;

* Seronegative for HIV and HBsAg;
* Subjects with compensated cirrhosis are permitted (compensated cirrhotics are capped at approximately 25% of treated population). If a subject does not have cirrhosis, a liver biopsy within
three years prior to enrollment is required to demonstrate the absence of cirrhosis. If cirrhosis is
present, any prior liver biopsy is sufficient. For countries where liver biopsy is not required prior to
treatment and where non-invasive imaging tests (Fibroscan® ultrasound) are approved for staging of liver disease, non-invasive imaging test results may be used to assess the extent of liver disease.

Exclusion criteria

* Prior treatment of HCV with HCV direct acting agent (DAA);
* Evidence of a medical condition contributing to chronic liver disease other than HCV;
* Evidence of decompensated liver disease including, but not limited to, a history or presence of
ascites, bleeding varices, or hepatic encephalopathy;
* Diagnosed or suspected hepatocellular carcinoma or other malignancies;
* Uncontrolled diabetes or hypertension;
* Total bilirubin * 34 *mol/L (or * 2 mg/dL) unless subject has a documented history of Gilbert*s
disease;
* Confirmed ALT * 5x ULN;
* Confirmed Albumin * 3.5 g/dL (35 g/L)
* Confirmed ANC < 0.5 x 109 cells/L
* AFP > 100 ng/mL OR * 50 and * 100 mg/mL requires a liver ultrasound and subjects with findings suspicious of HCC are excluded;
* Neutrophil count < 1500 cells/*L (<1,200 cells/*L for Black/African-Americans);
* Platelet count < 90,000 cells/*L;
* Hemoglobin < 12 g/dL for females or <13 g/dL for males;
* Any criteria that would exclude the subject from receiving P/R;
* Hematologic, biochemical and serologic criteria (growth factors may not be used to achieve trial
entry requirements)

Study design

Design

Study phase: 3

Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-09-2012
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	asunaprevir
Generic name:	asunaprevir
Product type:	Medicine
Brand name:	Copegus
Generic name:	Ribavirin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	daclatasvir
Generic name:	daclatasvir
Product type:	Medicine
Brand name:	Pegasys
Generic name:	Peg-Interferon-alpha-2a
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	25-05-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	11-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-005422-21-NL
ClinicalTrials.gov	NCT01573351
CCMO	NL39758.018.12