A DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP, PHASE 2 STUDY TO INVESTIGATE THE EFFECT OF RO7049665 ON THE TIME TO RELAPSE FOLLOWING STEROID TAPERING IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Published: 22-02-2021
Last updated: 04-04-2024

Primary* To evaluate the effect of RO7049665 on time to relapse following forced CCS tapering as measured by the hazard ratio between 7.5 mg RO7049665 and placebo.Secondary* To assess changes in alanine aminotransferase (ALT), aspartate...

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

Summary

ID

NL-OMON51170

Source
ToetsingOnline

Brief title
Phase 2 Study for the Effect of RO7049665 in Patients with AIH

Condition

- Autoimmune disorders

Synonym
autoimmune condition, chronic inflammation

Research involving

Human

Sponsors and support

Primary sponsor: Covance
Source(s) of monetary or material Support: Hoffmann-La Roche Inc.

Intervention

Keyword: Autoimmune Hepatitis (AIH), Double-blinded, Parallel group, Phase 2

Outcome measures

Primary outcome

Primary Endpoints

- Time to relapse from randomization.

Secondary outcome

Secondary Endpoints

- ALT, AST, and IgG (for both absolute and relative [ULN]) over time.

- Time to relapse from randomization.

- Incidence and severity of adverse events.

- Changes in vital signs, physical examination, ECG parameters, and safety

laboratory parameters.

- ADA emergence and neutralizing potential.

Study description

Background summary

AIH may present as acute or chronic hepatitis or as well established cirrhosis; in rare cases, it presents as fulminant hepatic failure. Patients experience unspecific symptoms like fatigue, upper abdominal discomfort, mild pruritus, anorexia, myalgia, arthralgia, rashes (including acne), and amenorrhea. Untreated AIH can lead to liver cirrhosis, development of hepatocellular

carcinoma, and finally to death.

AIH is a rare disease with a prevalence of 16 to 18 affected people per 100 000 inhabitants in Europe (EASL 2015). It can affect people of all ages and sexes, though the female to male ratio is approximately four to one. AIH is characterized by a large heterogeneity of clinical, laboratory, and histological manifestations and therefore difficult to diagnose. If hypergammaglobulinemia is present, AIH should always be taken into consideration (EASL 2015). A simplified AIH score has been developed to facilitate the diagnosis in patients with histological evidence of hepatitis.

There is currently no approved treatment for AIH. Patients with AIH usually respond rapidly to immunosuppressive treatment (CCS +/- non-specific immunosuppressants [NSIs]) but relapse quickly after its tapering. Most patients need to be on immunosuppressive treatment for extended periods and often for life. Side effects of long-term immunosuppressive treatment can be quite severe and include osteoporosis, muscle wasting, skin manifestations, and endocrine effects like steroid-induced diabetes.

Therefore, there is an unmet medical need in patients with AIH to replace the current standard of care (SoC) with a less burdening maintenance.

Study objective

Primary
* To evaluate the effect of RO7049665 on time to relapse following forced CCS tapering as measured by the hazard ratio between 7.5 mg RO7049665 and placebo.

Secondary
* To assess changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and IgG over time and by dose.
* To evaluate the effect of RO7049665 on time to relapse following forced CCS tapering as measured by the hazard ratio between 3.5 mg RO7049665 and placebo.
* To evaluate the safety and tolerability of RO7049665 in participants with AIH.

Study design

This is an event-driven study, which means that participants stay in the study and on treatment until the participant experiences an event (e.g., ALT rises > 2 x upper limit of normal [ULN] or IgG increases > 1.5 x ULN), the necessary number of events (a total of 45 events) is reached, the participant stops for other reasons or withdraws consent, or the study ends.

Patients eligible for the study must be in biochemical remission for at least 2 years, be on stable treatment (CCSs * non-specific immunosuppressants [NSIs])

for at least 6 months prior to study entry, and show no signs of inflammation (HAI * 3) on a liver biopsy taken no more than 12 months prior to randomization. For eligible patients this will be the first attempt to taper out CCS completely.

At study entry, the disease status of the participants should allow for a stepwise removal of all immunosuppressive treatment. Participants will start with study treatment on study Day 1 and start tapering CCS use from Day 8 onwards (see tapering schedule, Section 1.3, Table 3) to allow for complete CCS withdrawal within a maximum of 12 weeks, depending on the starting dose. Last dose of NSI therapy, if any, will be taken on study Day -1.

Randomization in a 1:1:1 fashion will occur after patient eligibility is confirmed and before the first dose of study drug is administered. Randomization will be stratified by equivalent prednisolone dose (* 7.5 mg daily versus > 7.5 mg daily or dual therapy [CCS any dose, plus RO7049665 NSI]). Two interim analyses are planned. The first is planned for futility once 25% of events (i.e.,12 events) are observed. The second interim analysis for efficacy and futility is planned once 50% of events (i.e., 23 events) are observed.

Intervention

See section E4 of the ABR form

Study burden and risks

RO7049665 has been tested in a study (WP39826) with 38 healthy volunteers. RO7049665 was given as a single injection, at doses ranging from 1.5 microgram (*g; one millionth of a gram) to 7500 µg (or 7.5 mg). The most frequently reported side effects of the study were injection site reactions (see Local Pain and Skin Reactivity), common colds and headache. Most of the side effects reported in this study were of mild intensity with no severe or serious events.

In another ongoing study (WP40161), doses of 3.5 mg and 7.5 mg of RO7049665 are tested in patients with ulcerative colitis. Patients receive 1 dose of RO7049965 (or placebo) every two weeks for a total of 4 doses. To date 30 patients have received RO7049965. The most frequently reported side effects to date are injection site reactions and eosinophilia (increase of a specific type of white blood cell [eosinophils] known to combat certain types of infections and parasites. These cells also control mechanisms around allergy and asthma). Most of the side effects reported in this study are of mild intensity with a low number of moderate to severe events.

In this study, the same two doses of RO7049665 will be tested (3.5 mg and 7.5 mg).

Side Effects due to Corticosteroid Tapering
The corticosteroid tapering is designed to minimize any possible withdrawal effects; however, it cannot be ruled out that the patient may experience any withdrawal effect, including weakness, fatigue, abdominal pain, nausea, vomiting and possibly disease flare.

Side Effects due to Immune Suppression
RO7049665 works by increasing regulatory T-cells, which may decrease the body*s natural defenses against infection and tumors (immunosuppression). Immunosuppression is not expected at the doses studied because the body naturally uses regulatory T-cells in controlling excessive immune activity, including during an infection. It is likely that the risk of immune suppression is greater in combination with other treatments targeting the immune system. Therefore the patient will not be allowed to use other immune suppressive treatments once he/she has stopped taking previous immunosuppressive treatment.

Allergic Reactions
Allergic reactions can occur with any drug and this can be in the form of itching, difficulty breathing, and a skin rash and/or drop in blood pressure. In very rare cases, the patient could suffer a life-threatening allergic reaction. If the patient does experience any such reaction, he/she should tell the study doctor immediately so that the patient can receive the appropriate treatment.

Antibodies to the drug
Antibodies which attach to the drug could occur, and could be without signs or symptoms, or could cause allergic reactions (see above), or a decrease in effectiveness or concentration of the drug. Very rarely, antibodies to drugs can also act like antibodies to similar proteins that the body makes normally. If antibodies to RO7049665 interact with the natural IL 2, a decrease or absence of IL-2 may occur, which has been associated with autoimmune conditions such as autoimmune thyroiditis (inflammation of thyroid gland) or Type 1 Diabetes. Antibodies to RO7049665 have been seen in the two previous studies (WP39826 and WP40161), however, these had no impact on safety and were not directed against natural IL-2. The patient will be monitored closely for the possibility of antibodies against the drug in this study and for potential outcomes such as allergic reactions.

In studies in animals with RO7049665, it was observed that RO7049665 caused a temporary increase in heart rate, so the heart activity will be monitored during this study. No increase in heart rate was observed in the two previous studies.

Risks Associated with Drug Administration

Local Pain and Skin Reactivity
Administration of study drug will be done by injecting under the skin in the

lower belly (abdomen). Local pain and injection site reactions can occur and include burning, bleeding, itching, bruising, redness, and hive formation. Injection site reactions of mild intensity were the most frequently reported side-effect in the two previous studies. If the patient develops a reaction around the injection site, the study doctors may ask to take a photograph of the reaction.

Risks Associated with Study Procedures

Blood Sampling
During this study, small amounts of blood will be drawn from a vein and used for tests that allow the study doctors to see how the patient is doing. Drawing blood may cause pain where the needle is inserted, and there is a small risk of bruising or infection at the place where the needle is inserted. Very rarely, a blockage of the vein or a small nerve injury can occur, resulting in numbness and pain. However, this will resolve with time. Some people experience dizziness, upset stomach, or fainting when their blood is drawn.
On days when several blood samples will be taken, we may use a cannula (small plastic tube) inserted in the arm using a small needle. This cannula may remain in place for the day and will be taken out before the patient goes home. There is a small chance of infection by placing the cannula in the arm, but every medical precaution will be taken to avoid an infection.

Electrocardiogram (ECG)
The patient will have small, soft pads, placed temporarily on different parts of his/her body. There is no pain or discomfort during an ECG; however, the area of skin in which the ECG pads will be stuck may need to be shaved, and the pads may cause a skin reaction such as redness or itching. Taking the pads off may cause localized irritation to the skin and/or hair loss, similar to having a plaster taken off.

Biopsies
The patient may feel some amount of pain or discomfort during the biopsy, including slight stinging pain when a local anesthetic is injected by needle to numb the area, pressure and dull pain where the biopsy needle is inserted, discomfort from lying still for an extended time, and soreness at the biopsy site. If a general anesthetic is used, the patient will not feel pain during the procedure because he/she will be asleep. There is a risk of injury to adjacent organs and infection. If the patient chooses to allow collection of his/her fresh liver tissue, the doctor will explain the risks of the biopsy procedure to the patient for his/her to decide if you want to participate.

Reproductive Risks

Reproductive Risks for Women
If the patient is pregnant or become pregnant, or if she is currently breastfeeding, she cannot take part in this study because she or her child may

be exposed to an unknown risk.
If the patient is a woman who can become pregnant, she must have a test that shows she is not pregnant before she can be enrolled in this study. The patient may also have further pregnancy tests during the course of the study. If her urine pregnancy test is positive, a repeat (blood) pregnancy test will be taken to confirm the result. If the blood test is positive, the patient will not receive any more study medication.
If the patient can become pregnant, she must agree to remain abstinent or use birth control methods that are judged to be effective by the study doctor during this study and within 28 days after the final dose of RO7049665. The patients should check with the study doctor about the methods of birth control to use.
The patient should tell the study doctor right away if she suspect that she have become pregnant during the study (including the 28-day follow up period). The study doctor will ask for patient's permission to follow up with her on the outcome of the pregnancy and collect information on the baby.

Possible Risks Associated With Loss Of Privacy
Although the genetic information will not contain any personal identifying information, there is a very small risk that it could be linked to an outside public database and used to help identify the patient and his/her blood relatives. Because some genetic differences can help to predict future health problems experienced by the patient or his/her blood relatives, this information might be of interest to health care providers, life insurance companies, and others. It is possible that genetic information could be used in ways that would cause the patient or his/her family distress, such as by revealing that the patient or a blood relative carries a genetic disease.

Contacts

Public
Covance

Avenue Marcel Thiry 77
Bruxelles 1200
NL
Scientific
Covance

Avenue Marcel Thiry 77
Bruxelles 1200
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:
Informed Consent
1. Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonisation (ICH) and local regulations.

Age
2. Between 18 to 75 years of age, inclusive, at the time of signing the informed consent.

Type of Participants and Disease Characteristics
3. Patients with a definite diagnosis of AIH (type 1, 2 and 3) as per simplified or revised original diagnostic criteria (including response to CCSs) (Hennes et al 2008).
4. Patients who have been in biochemical remission (complete normalization of serum transaminases and IgG levels) for * 2 years prior to randomization.
5. Patients who have been on stable treatment (CCSs * NSIs) for at least 6 months prior to randomization.
6. No signs of liver inflammation (HAI * 3) on a liver biopsy taken no more than 12 months prior to randomization.
7. Patients with AIH who have previously not attempted to taper CCS to 0 mg/day.

Weight
8. Body mass index within the range of 18-35 kg/m2 (inclusive).

Sex and Contraception/Barrier Requirements
9. Male and female participants are eligible.
The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. Therefore, the reliability of sexual abstinence for female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.
A female participant is only eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
Women of non-childbearing potential (WONCBP),
OR
Women of childbearing potential (WOCBP), who:
Agree to remain abstinent (refrain from heterosexual intercourse) or use at least one acceptable contraceptive methods during the treatment period and for at least 28 days after the final dose of study drug.
The following are acceptable contraceptive methods: bilateral tubal occlusion/ligation, male sexual partner who is sterilized, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices, male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

Exclusion criteria

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:
Medical Conditions
1. Patients with cirrhosis (F4 fibrosis by Fibroscan®) with significant impairment of liver function (Child Pugh category B or C).
2. Any other autoimmune disease (including overlap syndrome) requiring immunomodulating treatment.
3. History of infection with hepatitis B (hepatitis B surface antigen [HBsAg] positive and/or anti-HBc positive; HBV vaccinated patients are eligible), human immunodeficiency virus (HIV; positive HIV antibody test), active hepatitis C virus (HCV) infection (detectable HCV RNA), detection of replicating CMV or Epstein-Barr virus.
4. Active infections requiring systemic therapy with antibiotic, antiviral or antifungal treatment or febrile illness within 7 days before Day *1.
5. History of primary or acquired immunodeficiency.
6. Female patients: Pregnant or lactating.
7. Symptomatic herpes zoster within 3 months prior to screening.
8. History of active or latent tuberculosis or a positive Quantiferon* Gold test.

9. History of clinically significant severe drug allergies, multiple drug allergies, allergy to any constituent of the product, or intolerance to topical steroids.
10. Lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years and in situ carcinoma of the cervix that was completely removed surgically. Breast cancer within the past 10 years.
11. Significant uncontrolled comorbidity, such as cardiac (e.g., moderate to severe heart failure New York Heart Association [NYHA] Class III/IV), pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders (excluding UC).
12. Any condition or disease detected during the medical interview/physical examination that would render the patient unsuitable for the study, place the patient at undue risk or interfere with the ability of the patient to complete the study in the opinion of the Investigator.

Prior/Concomitant Therapy
13. CCSs of * 5 mg/day (prednisolone-equivalent dose), or < 2.5 mg CCSs (prednisolone-equivalent dose) plus immune suppressant, or < 3 mg/day budesonide with or without immune suppressant.
14. CCSs * 20 mg/day (prednisolone-equivalent dose) or > 9 mg/day budesonide.
15. NSI daily dose higher than recommended standard of care therapy.
16. T or B cell-depleting therapy (e.g., rituximab) within the last 12 months or T- or B-cell number below normal due to depleting therapy.

Prior/Concurrent Clinical Study Experience
17. Leukocyte apheresis within 12 weeks of screening.
18. Donation of blood or blood products in excess of 500 mL within 3 months prior to screening.
19. Exposure to any investigational treatment within 6 months prior to Day 1.

Laboratory Abnormalities
20. Abnormal hematologic values:
* Anemia (hemoglobin * 9 g/dL)
* Leukocytosis (white blood cells * 2 * ULN)
* Thrombocytopenia (platelet count * 100,000/*L)
* Thrombocytosis (platelet count * 2 * ULN)
* Eosinophilia (eosinophil count * 2 * ULN)
21. Abnormal hepatic enzyme or hepatic function values:
* ALT, AST, or alkaline phosphatase, above normal range
* Total bilirubin * 2 * ULN
* International normalized ratio (INR) * 1.7
* Albumin * 3 g/dL
22. Abnormal biochemistry values:
* IgG above normal range

Other Exclusions
23. History of regular alcohol consumption within 2 months of screening defined as:
An average weekly intake of * 14 drinks for men or * 7 drinks for women. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine, or 1.5 ounces (45 mL) of 80 proof distilled spirits (equivalent to 40 vol%).
24. Any suspicion or history of illicit drug use.
25. Patients under judicial supervision, guardianship, or curatorship.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-04-2021
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Placebo
Product type:	Medicine
Brand name:	RO7049665

Ethics review

Approved WMO Date:	22-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-04-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2020-003990-23-NL
CCMO	NL75913.056.21