A two-part randomized, double-blind, placebo-controlled multicenter dose ranging and confirmatory study to assess the safety and efficacy of VAY736 in autoimmune hepatitis patients with incomplete response to or intolerance of standard therapy (AMBER)

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Part 1 - To determine effects of different ianalumab doses on ALT normalization at Week 24 in patients with AIH who are incomplete responders or intolerant to standard therapy.Part 2 - To confirm the efficacy (biochemical and histological remission...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON48945

Source
ToetsingOnline

Brief title
CVAY736B2201 (AMBER)

Condition

- Autoimmune disorders

Synonym
Autoimmun hepatitis

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: Auto-immun hepatitis, fase 2, placebo, VAY736

Outcome measures

Primary outcome

Part 1:

To determine effects of different ianalumab doses on ALT normalization at Week

24 in patients with AIH who are incomplete responders or intolerant to standard

therapy.

Part 2:

To confirm the efficacy (biochemical and histological remission) and safety of

the dose determined from Part 1 in this population.

Secondary outcome

Part 1:

To evaluate the dose-response relationship of VAY736 with respect to

normalization in ALT at Week 24.

Part 2:

To demonstrate that VAY736 improves normalization of ALT at Week 52 relative to

placebo

To demonstrate histological remission with VAY736 at Week 52 relative to placebo

To demonstrate the effect of VAY736 on FACIT-F patient reported outcome measure

at Week 52 relative to placebo

Study description

Background summary

Autoimmune hepatitis (AIH) is a chronic autoimmune disease of unknown etiology characterized by hypergammaglobulinemia, aminotransferase elevations, histological changes and specific autoantibodies. AIH is a rare (approximately 20 prevalent cases per 100,000, Lohse 2015) but potentially devastating disease burdened by significant morbidity and potentially lethal outcomes (untreated mortality at 5 years is 75%.
The treatment goal in AIH is suppression of liver inflammation, thereby preventing progression to cirrhosis and liver failure. Serum transaminases are utilized as surrogate markers for severity of inflammation.
Guidelines for treatment include use of corticosteroids, combination of corticosteroids with azathioprine or azathioprine alone, and use of mycophenolate mofetil (MMF) as a second line therapy. Non-adherence to treatment because of intolerance is a wellrecognized issue.
Not all patients respond completely to conventional treatment with predniso(lo)ne and azathioprine, and others may develop treatment-related side effects, requiring drug withdrawal. Therefore, new and better tolerated targeted treatments are needed to better control disease activity in these AIH patients.

Study objective

Part 1 - To determine effects of different ianalumab doses on ALT normalization at Week 24 in patients with AIH who are incomplete responders or intolerant to standard therapy.

Part 2 - To confirm the efficacy (biochemical and histological remission) and safety of the dose determined from Part 1 in this population.

Study design

Part 1 is a randomized, placebo-controlled, double-blind, multicenter, parallel group study in approximately 80 adult patients with Type 1 autoimmune hepatitis. Patients will be randomized into four study arms, treated as follows:
Arm 1: VAY736 5 mg s.c. every four weeks (q4w);
Arm 2: VAY736 50 mg s.c. q4w;
Arm 3: VAY736 300 mg s.c. q4w;
Arm 4: Placebo s.c. q4w
while continuing to receive corticosteroids and/or azathioprine.

At the end of 24 weeks of treatment, the primary analysis and dose-response modeling will be performed to determine the dose to be evaluated in Part 2. Patients in the placebo arm, who remain on treatment to Week 28, will be reassigned to VAY736 150 mg s.c. q4w treatment at the Week 28 visit. Patients from the VAY736 arms will continue on the assigned dose of active drug every 4 weeks, with the last dose being administered at Week 48.

Part 2 is a randomized, placebo-controlled, double-blind multicenter, parallel group study in approximately 280 AIH patients to confirm the efficacy and safety of VAY736 at the selected dose from Part 1, as outlined in Figure 3-2. The Part 2 population differs from Part 1 in the inclusion of (i) any type of AIH patient, and (ii) AIH pati ents from 16 to 75 years of age. Part 2 Patients will be randomized in a 5:2 ratio to VAY736 (at the dose determined from dose - response modeling in Part 1) or placebo.
Part 2 will start only after an appropriate dose of VAY736 is identified from Part 1 of the study and incorporating any changes to the study design necessitated by the results of Part 1 and agreed to by Regulatory Authorities. For Part 2 a different group of patients will be enrolled (i.e. no patients from Part 1 will participate in Part 2).

Intervention

VAY736 or placebo

Study burden and risks

- Minimum of 22 (part 2) and 23 (part 1) site visits with duration of 1 to 4 hours. Duration of study is minimum 76 weeks, depending on recovery of B-cells.
- Day 1 visit lasts around 8 hours so the physician can monitor patient after first injection of study medication. This is also the case at Week 28 visit in Part 1 of study.
- Full physical exam: Prescreening (in case treated with MMF/MPA), Screening, Baseline, Week 24 and 52
- Short physical exam: All other visits.
- Liver biopsy in part 1: Screening and week 24
- Liver biopsy in part 2: Screening and week 52
- Subcutaneous injections: starting at baseline every 4 weeks two injections.

Before first study medication injection intraveneous prednisolone will be administered.
- Blood samples: each visit.
- Completion of PRO: 4 times
- Heart rate, blood pressure and weight: almost each visits.
- Urine dipstick: almost each visits.
- Fibroscan: 3 times.
- ECG: 4 times.
- Optional: 1 extra blood sample for pharmacogenetics

Risks of VAY736 injections:
- First-dose mild-to-moderate injection reactions were observed in the phase 1/2a studies in a substantial subset of patients.
- An increase in mild-to-moderate upper respiratory tract infections compared to placebo has been associated with use of VAY736.
- Neutropenia as result of depletion of B-cells. This has not yet been observed with VAY736.
- Although no allergic reactions following i.v. or s.c. administration were observed so far, the potential to develop an allergic reaction in a predisposed subject cannot entirely be ruled out.
- Liver biopsy is associated with some discomfort like mild to moderate pain occurring in the upper abdomen or the right shoulder.

Contacts

Public
Novartis

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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

- AIH diagnosed per International Autoimmune Hepatitis Group
- Liver biopsy with Ishak modified HAI score equal or above 5
- Incomplete response to OR intolerance of standard therapy (per AASLD)

Exclusion criteria

- Prior use of any B-cell depleting therapy
- Required regular use of medications with known hepatotoxicity
- Decompensated cirrhosis
- Diagnosis of overlap syndrome with AIH (e.g., AIH+PBC, AIH+PSC)
- Drug related AIH at screening or a history of drug related AIH
- History of drug abuse or unhealthy alcohol use
- History of malignancy of any organ system
- Pregnant or nursing (lactating) women

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:	Will not start
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	ianalumab

Ethics review

Approved WMO

Date:	18-10-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	26-04-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	13-08-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	15-08-2018

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	01-11-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	28-11-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	14-02-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	23-08-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	18-10-2019

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-10-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2017-001555-32-NL
ClinicalTrials.gov	NCT03217422
CCMO	NL63270.058.17