A multicenter, Phase 1b, open label, nonrandomized, single dose study evaluating the safety, tolerability and activity of BIVV020 in adults with cold agglutinin disease

Published: 21-07-2020
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Primary: The safety and tolerability of BIVV020Secondary: - The effect of BIVV020 on complement mediated hemolysis.- The pharmacodynamics (PD) of BIVV020 relating to complement inhibition.- The pharmacokinetics (PK) of BIVV020.- The immunogenicity...

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

Summary

ID

NL-OMON55174

Source
ToetsingOnline

Brief title
PDY16370

Condition

- Autoimmune disorders

Synonym
CAD, cold agglutinin disease

Research involving
Human

Sponsors and support

Primary sponsor: Genzyme Europe BV
Source(s) of monetary or material Support: Sanofi

Intervention

Keyword: Autoimmune hemolytic anemia (AIHA), BIVV020, cold agglutinin disease

Outcome measures

Primary outcome

Safety

* Assessment of adverse events (AE)/treatment-emergent adverse events (TEAE).

* Clinical laboratory evaluations including hematology, biochemistry, systemic

lupus erythematosus (SLE) panel testing, and urinalysis.

* Electrocardiographic (ECG) intervals (heart rate, PR, QRS, QT, and QTcF).

* Vital signs (blood pressure and heart rate).

Secondary outcome

Hematologic BA

* Total bilirubin.

* Hemoglobin.

Pharmacodynamics

* CP.

* Complement alternative pathway (AP).

* CH50.

* Total C4.

Pharmacokinetics

* Parameters (not limited to): Cmax, tmax, tlast, AUClast, AUC0-*, t1/2z, CL,

Vd.

Immunogenicity

* Anti-BIVV020 antibodies (ADA).

Study description

Background summary

BIVV020 is a humanized monoclonal antibody that binds to and selectively inhibits the activated form of human serine protease complement component 1, s subcomponent (C1s). By binding to activated C1s, BIVV020 prevents enzymatic action of the C1 complex on its substrates, complement factors C4 and C2, and thereby blocks formation of the C3 convertase. The result of this mechanism is inhibition of complement classical pathway (CP) activity proximal in the complement activation pathway to C3 which allows the alternative and lectin pathways to remain functionally intact for the purpose of host defense. The CP has been implicated in many diseases that are driven by the presence of a pathogenic antibody;
primary Cold Agglutin Disease is one such example.
Cold agglutinin disease is an autoimmune hemolytic anemia caused by IgM-induced CP activation.
This study will provide clinical data on the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of BIVV020 in adults with CAD to facilitate the dose/dosing regimen selection for future clinical studies with BIVV020.

Study objective

Primary:
The safety and tolerability of BIVV020

Secondary:
- The effect of BIVV020 on complement mediated hemolysis.
- The pharmacodynamics (PD) of BIVV020 relating to complement inhibition.
- The pharmacokinetics (PK) of BIVV020.

- The immunogenicity of BIVV020.

Study design

The study initiates with an IV cohort and on-study decisions about selection of the next cohort and/or expansion within a cohort are made based on clinical response (total bilirubin and hemoglobin) and variability of response across patients.
The study design includes up to three IV cohorts. The study will begin dosing in Cohort 1a at a dose of 30 mg/kg. Following Cohort 1a, additional IV dose levels, specifically Cohort 1b (higher dose) and/or 1c (lower dose), may be used up to a maximum of 50 mg/kg IV or the highest tolerated dose tested in normal healthy volunteers.

Intervention

Dosing will begin with a single dose of 30 mg/kg IV. Dosing will not exceed 50 mg/kg or the highest tolerated dose tested in normal healthy volunteers in any cohort.

Study burden and risks

Risks and burdens related to blood collection, study procedures and possible adverse events of study medication.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male and/or female patients, * 18 years of age with cold agglutinin disease as defined by:
a) Chronic hemolysis per Investigator*s judgement,
b) Polyspecific direct antiglobulin test (DAT) positive,
c) Monospecific DAT strongly positive for C3d,
d) Cold agglutinin (CAg) titer * 64 at 4°C; and,
e) IgG DAT *1+.
- A hemoglobin level *11 mg/dL.
- A total bilirubin level above the normal reference range that is thought to be due to hemolysis.
- Documented vaccinations against encapsulated bacterial pathogens (Neisseria meningitidis,
including serogroup B meningococcus and Streptococcus pneumoniae) within five years of
screening or willing to complete protocol specified vaccinations.
- Having given written informed consent prior to undertaking any study-related procedure.

Exclusion criteria

- Cold agglutinin syndrome secondary to infection, rheumatologic disease, or known high grade
hematologic malignancy, or known solid organ tumor.
- Clinically relevant infection of any kind within one month preceding screening.
- Treatment with anti-CD20 monotherapy within three months or anti CD20 combination therapies
within six months prior to screening.
- Concurrent treatment with systemic immunosuppressive agents targeting B- or T-cell function
and/or cytotoxic agents within 3 months prior to screening. Concurrent

treatment with other
systemic immunosuppressants within 5.5 half-lives of the drug prior to screening.
- Any specific complement system inhibitor within three months prior to screening.
- Concurrent treatment with systemic corticosteroids other than a stable daily dose equivalent to
*10 mg/day prednisone within three months prior to screening.
- If female, pregnant or lactating.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-02-2021
Enrollment:	2
Type:	Actual

Ethics review

Approved WMO Date:	21-07-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	10-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2021
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
Other	2019-001844-22
EudraCT	EUCTR2019-001844-22-NL
CCMO	NL74337.018.20

Study results

Date completed: 06-01-2022

Results posted: 21-11-2022

First publication
29-08-2022