Multicenter, open*label, phase II study in patients with monoclonal gammopathy of unknown significance (MGUS) and anti Myelin Associated Gycoproteine (MAG) Neuropathy and Zanubrutinib Treatment * MAGNAZ trial

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Main objective:To improve the functional neurological outcome of patients, as measured on the Raschbuilt Overall Disability Scale (RODS) for inflammatory neuropathies (iRODS) with Zanubrutinib in combination with standard treatment with Rituximab or...

Ethical review	Not approved
Status	Will not start
Health condition type	White blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON52317

Source
ToetsingOnline

Brief title
Magnaz

Condition

- White blood cell disorders
- Peripheral neuropathies

Synonym
Neuropathy (nerve pain)

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,BeiGene Switzerland GmbH,Dr. C.J. Vaillantfonds

Intervention

Keyword: anti-MAG (myelin associated gycoproteine), IgM-related neuropathy, MGUS (monoclonal gammopathy of unknown significance), Zanubrutinib

Outcome measures

Primary outcome

To improve the functional neurological outcome of patients, as measured on the

RaschbuiltOverall Disability Scale (RODS) for inflammatory neuropathies (iRODS)

withZanubrutinib in combination with Rituximab or biosimilar treatment.

Secondary outcome

Safety of combined treatment with Rituximab or biosimilar and Zanubrutinib

* Changes in other neurological outcome parameters besides the iRODS, such as

ONLS

(Overall Neuropathy Limitations Scale), 10 meter walk test, ataxia score,

modified

INCAT (The Inflammatory Neuropathy Cause And Treatment) sensory sum score

(mISS), and grip strength (vigorimetry) 8,14*17

* Percentage of patients with >4 points difference measured with iRODS after 12

cycles

of therapy

* Hematological response

* Change of anti*MAG titers during treatment and follow up

* Molecular profiling and relation with response and immunological parameters

* Relation between neurological and immunological outcome parameters

* Quality of life assessment (EQ*5D*5L) before (at baseline), during and after

therapy

* Patients global impression of change (PGIC) during and after therapy

* Overall survival (OS)

* Progression free survival (PFS) (hematological)

Study description

Background summary

The trial will investigate whether adding Zanubrutinib to standard treatment (Rituximab or biosimilar)will improve the functional neurological outcome of patients with IgM related anti MAG neuropathies from baseline till after cycle 12.

Study objective

Main objective:To improve the functional neurological outcome of patients, as measured on the Raschbuilt Overall Disability Scale (RODS) for inflammatory neuropathies (iRODS) with Zanubrutinib in combination with standard treatment with Rituximab or biosimilar.

Secondary objectives:
The main secondary endpoint is to assess the safety of Zanubrutinb treatment in IgM related PNP as measured by Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.
- Changes in other neurological outcome parameters besides the iRODS, such as ONLS
(Overall Neuropathy Limitations Scale), 10 meter walk test, ataxia score, modified INCAT (The Inflammatory Neuropathy Cause And Treatment) sensory sum score
(mISS), and grip strength (vigorimetry)
- Percentage of patients with >4 points difference measured with iRODS after 12 cycles of therapy

- Hematological and immunological response
- Molecular profiling and relation with response and hematological and immunological parameters
- Relation between neurological and hematological and immunological outcome parameters
- Quality of life assessment (EQ*5D) before, during and after therapy
- Patients global impression of change (PGIC) during and after therapy
- Overall survival (OS)
- Progression free survival (PFS) (hematological)

Study design

Zanubrutinib is the study drug and will be used next to standard care. Standard care is 4 infusions IV of Rituximab or biosimilar infusion per week.
Zanubrutinib will start on the same day as start Rituximab or biosimilar.
Zanubrutinib will at least be given for 6 cycles. 1 cycle includes 28 days of orally Zanubrutinib capsules (4x80mg). Patients who achieve a hematological minimal response or better after 6 cycles continue with treatment.
After 12 cycles, if a very good partial response or complete hematological response is reached, Zanubrutinib can be continued. Otherwise Zanubrutinib will be stopped after 12 cycles.

Intervention

Zanubrutinib is the study drug and will be used next to standard care. Standard care is 4 infusions IV of Rituximab or biosimilar infusion per week.
Zanubrutinib will start on the same day as start Rituximab or biosimilar.
Zanubrutinib will at least given for 6 cycles. 1 cycle includes 28 days of orally Zanubrutinib capsules (4x80mg). If after 6 cycles a hematological response is measured treatment will be continued for another 6 cycles to monitor further hematological response and neurological improvement. After 12 cycles study treatment is completed but patients with a very good hematological response and willing to continue treatment are offered prolonged treatment with Zanubrutinib.

Study burden and risks

By participating in this study patients will receive a treatment they usually would not receive. IgM-related neuropathy is usually treated with 4 gifts of Rituximab or biosimilar. By lowering the toxic IgM M protein in the blood the effect on the neurons is diminished. Zanubrutinib targets the IgM M protein and thereby this treatment can possibly improve neuropathy complaints and with that improve quality of life of patients. There are no guarantees that treatment will result in direct benefits for the patient.

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

- Able to provide written informed consent and understand and comply with the requirements of
the study
- Demyelinating polyneuropathy defined by electrophysiological criteria according to EFNS/PNS
PDN guideline, 201019
- Some functional impairment; defined as an iRODS * 44 at baseline
- Age * 18 years
- IgM MGUS, defined as the presence of an IgM M protein (detectable but < 30 g/L) AND elevated total IgM level in serum
- Presence of anti MAG antibodies * 10.000 titer units, measured with the Bühlmann ELISA

- ECOG performance score 0, 1, or 2
- Adequate hematological laboratory values defined as
hemoglobin * 5.0 mmol/L neutrophils > 1.0 × 10^9/L and platelets > 100 × 10^9/L
- Adequate hepatic and renal function laboratory values defined as ASAT/ALAT
< 3 × ULN, bilirubin < 2.0 × ULN and creatinine clearance * 30 ml/min
- No history of severe bleeding disorder such as hemophilia A, hemophilia B,
von Willebrand
disease, or history of spontaneous bleeding requiring blood transfusion or
other medical intervention
- Previous treatment with intravenous immunoglobulins is allowed if > 3
months before inclusion
- Previous treatment for PNP with Anti CD20 MoAb and/or cyclophosphamide is
allowed only if
given > 6 months before inclusion

Exclusion criteria

- Hematological malignancy e.g known Multiple Myeloma or confirmed Waldenstrom*s Macroglobulinemia based on bone marrow analysis
- Any history of malignancy of any organ system (other than localized basal or
squamous cell
carcinoma of the skin, superficial bladder cancer or carcinoma in situ of the
cervix or breast),
treated or untreated within the last 3 years
- History of ischemic stroke within 180 days before first dose of Zanubrutinib.
- History of CNS hemorrhage.
- History of inherited or acquired hemorrhagic disorder
- Prior treatment with purine analogues (fludarabine or cladribine)
- Prior treatment with a BTK inhibitor
- Major surgery within 4 weeks of study treatment
- Participation in another interventional clinical trial
- Women with child*bearing potential (WOCBP) not able or willing to prevent
pregnancy and
lactating women as well. WOCBP will agree to use highly effective contraception
for the duration of the trial treatment and for 120 days after treatment stop
- Other known concomitant causes of chronic (demyelinating) PNP, including Charcot Marie Tooth Disease, other hereditary neuropathies, diabetes mellitus, use of amiodarone, past or current dependence on alcohol, other lymphoma or malignant blood dyscrasias, previous Guillain*Barré syndrome
- Currently active, clinically significant cardiovascular disease such as
uncontrolled arrhythmia,
congestive heart failure, any Class 3 or 4 cardiac disease (congestive heart
failure) as defined by
the New York Heart Association (NYHA) Functional Classification, or history of
myocardial

infarction within 6 months of screening
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities
at screening:
o QTcF >450 msec (males)
o QTcF >460 msec (females)
o History of familial long QT syndrome or known family history of Torsades de Pointes
o Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study
o second degree atrioventricular (AV) block Type II, or third*degree AV block
* Controlled atrial fibrillation is allowed
- Unable to swallow capsules or disease significantly affecting gastrointestinal function such as
malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory
bowel disease, or partial or complete bowel obstruction
- Uncontrolled active systemic infection or recent infection requiring parenteral anti*microbial
therapy that was completed * 14 days before the first dose of study drug. Active tuberculosis
- Known infection with human immunodeficiency virus (HIV), or serologic status reflecting active
hepatitis B or hepatitis C infection as follows: Presence of hepatitis B surface antigen (HBsAg) or
anti*hepatitis B core antibody (anti*HBc). Patients with anti*HBc, but absence of HBsAg, are
eligible if hepatitis B virus (HBV) DNA is undetectable and if they are willing to undergo monthly
monitoring for HBV reactivation
- Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV ribonucleic acid (RNA) is ndetectable
- At time of study entry, taking any medications which are strong cytochrome P450, family 3,
subfamily A (CYP3A) inhibitors or strong CYP3A inducers
- Intolerance to previous Anti CD20 MoAb or other anti CD20 MoAb treatment
- History of intolerance to the active ingredients or other ingredients of Zanubrutinib

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Zanubrutinib
Generic name:	Brukinsa

Ethics review

Approved WMO

Date:	08-08-2022
Application type:	First submission
Review commission:	METC NedMec

Not approved

Date:	14-12-2022
Application type:	First submission
Review commission:	METC NedMec

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	EUCTR2021-003066-12-NL
CCMO	NL78826.041.22