First in Human Study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.

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Primary objectiveTo assess the safety and tolerability after single and multiple intravenous administrations of PPSGG in patients suffering from anti-MAG neuropathy.Secondary objectives- To evaluate the PK of PPSGG after single and multiple...

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

Summary

ID

NL-OMON49059

Source
ToetsingOnline

Brief title
PN-1007-001

Condition

- Demyelinating disorders

Synonym
anti-MAG neuropathy, auto-immune

Research involving
Human

Sponsors and support

Primary sponsor: Polyneuron Pharmaceuticals AG
Source(s) of monetary or material Support: industry

Intervention

Keyword: anti-MAG neuropathy, First in Human study, placebo-controlled, safety

Outcome measures

Primary outcome

Safety endpoints:

- Frequency, duration, severity and outcome of AEs, treatment emergent AEs (TEAEs), and Serious AEs (SAEs) from time of informed consent signature to the EOS visit including follow-up as required.

- Any concomitant medications and relevant non-drug therapies.

- Signs and symptoms of infusion-related reactions on infusion days continuously during the infusion of the study drug until 1 hour after the end of infusion, and at 8 and 24 hours (Day 2) after the start of administration.

- Physical examination from screening, baseline, on infusion day (before dosing with the IMP), and 8 during SAD and EOS visit and during MAD during each visit until the EOS visit.

- Vital signs with the 12-lead ECG at screening, on infusion days predose, during the infusion of the IMP at 60 min (120 min for optional 3200 mg dose) and then at 2 hours and 8 hours after start of infusion during SAD and EOS visit. During the MAD, vital signs with the 12-lead ECG at each day of visit until the EOS.

- 1-lead ECG on infusion days continuously during the infusion of the IMP until

2 hours after start of infusion for both the SAD and MAD.

- Safety hematology, clinical chemistry and urinalysis at screening, baseline, on Day 8, and EOS during the SAD and on Day 8, 28, 42, 98 and EOS during the MAD.

- Blood sampling for anti-drug-antibodies (ADA) (immunogenicity) at screening and predosing, then Day 28 (EOS) in the SAD and Days 42 and EOS in the MAD.

Pharmacokinetic endpoints:

PPSGG*s PK will be determined in serum in the SAD phase on infusion Day 1 (30 min, 60 min, 2h, 6h, and 8h after start of administration), and on Day 2, 4, 8, 14 and 28 of the SAD phase. The sampling for the potential 3200 mg dose would be at 30 min, 60 min, 2h, 3h, 6h, 8h and 10h after start of infusion.

In the MAD phase on each of Days 1, 3, 5, and 42 at predose, at 30 min, 60 min, at 2h, 6h, and 8h after start of infusion. An additional PK sample will be taken on Day 150 (EOS). The time points for PK sampling for the MAD phase will be confirmed based on the PK data collected during SAD phase.

Pharmacodynamic endpoints:

PPSGG*s PD biomarkers will be determined in serum in the SAD phase during screening, baseline, on infusion day (30 min, 60 min, 2h, 8h after start on infusion) and on Day 2, 4, 8, 14 and EOS (Day 28). During the MAD phase on each of Days 1, 3, 5 and 42 at predose, at 30 min, 60 min, at 2h, and 8h after start of infusion. Then PD samples taken on Days 2, 4, 6, 7, 8, 9, 10 and Day 11 at

predose and 2h after start of infusion.

Efficacy endpoints:

Clinical efficacy assessments will be performed at screening, and Day 14, and

EOS during SAD and during MAD then every 8 weeks.

Clinical efficacy outcome for the SAD and MAD phases

- ONLS score.

- Time to walk 10 meters.

- RODS.

- Ataxia score.

End points for the MAD phase only:

All the above and then additionally every 8 weeks from Day 14 the following

ones:

- INCAT sensory sum score.

- Grip Strength.

Secondary outcome

Endpoints for the MAD phase only

- Neurofilament light chain (NfL) to measure the degree of axonal damage.

- B-cell activating factor (BAFF).

- Indirect immunofluorescence on sciatic nerves.

- Motor Unit Number Index (MUNIX) in selected sites.

Study description

Background summary

Anti-myelin-associated glycoprotein (MAG) neuropathy is a demyelinating polyneuropathy associated with a monoclonal immunoglobulin M (IgM) gammopathy with anti-MAG activity. Patients with anti-MAG neuropathy suffer from sensorimotor deficits, sensory ataxia, paresthesias, muscle weakness, neuropathic pain, and tremor.
Currently there is no treatment for anti-MAG neuropathy approved by the European Medicines Agency or the US Food and Drug Administration.

Study objective

Primary objective
To assess the safety and tolerability after single and multiple intravenous administrations of PPSGG in patients suffering from anti-MAG neuropathy.

Secondary objectives
- To evaluate the PK of PPSGG after single and multiple intravenous administrations.
- To investigate PD of PPSGG in reducing anti-MAG IgM levels.
- To obtain preliminary efficacy data from neurological evaluations and clinical outcomes using different clinical scores.

Study design

Phase I: First in Human, open label, SAD escalation study in anti-MAG neuropathy patients to assess the safety, tolerability, PK and PD parameters of PPSGG.
After completion and evaluation of the SAD phase a MAD phase will follow.

Phase IIa: randomized, dose escalation, double blind (patient and investigator blinded), placebo-controlled MAD in anti-MAG neuropathy patients to assess the safety, immunogenicity, tolerability, PK, PD and preliminary efficacy parameters of PPSGG.

- Phase I: Single Ascending Dose (SAD)
The single rising dose escalation phase will enroll 6 patients in each of the 4 or 5 ascending dose cohorts. The first administration of PPSGG of any cohort will be provided to a single patient (sentinel patient). The decision to continue dosing the remaining patients in a given cohort will be based on all available safety data collected during the first 72 hours after treatment of the sentinel patient. The decision to escalate to the following dose (once a cohort is completed) will be based on all available safety data, collected

during a minimum of 72 hours after the start of the infusion for all patients, where no stopping rules are met and analyzed by an Independent Data Monitoring Committee (IDMC). The study drug will be administered as a 60 min (120 min for optional 3200 mg dose) IV infusion.
In the SAD phase each patient will have, within 2 months, the following 8 visits: Screening, Baseline, Treatment (4 visits), end of study (EOS) and Follow-up.

- Phase IIa: Multiple Ascending Dose (MAD) - adaptive trial
The multiple rising dose phase will enroll 2 dose cohorts of at least 12 patients each (10 on active and 2 on placebo). Dose levels will be determined based on the safety, tolerability, PK and PK/PD outcome (anti-MAG IgM titers) from the SAD phase. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD. The dosing frequency will be defined based on the PK/PD relationship established during the SAD phase (PPSGG half-life, anti-MAG IgM kinetic) and simulation of it. The study drug will be administered for up to 11 times (as a 60 min (120 min for optional 3200 mg dose) IV infusion) for six weeks to explore the effect on anti-MAG antibody levels. For safety purposes the first 2 patients in each cohort of the MAD phase will be randomized to receive active or placebo treatment in a double-blind fashion. The decision to continue dosing in a given cohort will be based on safety data of the first 2 patients collected during 2 weeks (minimum) after the start of the infusion. The decision to escalate to the following dose will be based on safety data collected during the first 2 weeks after the start of infusion and analyzed by an IDMC.

In the MAD phase each patient will have, within 6 months, up to 17 visits: Screening, Baseline, Treatment (up to 14 visits), EOS and Follow-up.

The MAD phase dosing regimen will be adapted for accordance with PK/PD modeling, safety and tolerability data collected during the SAD phase. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD. Dosing regimen includes the dose level administered, the frequency of dosing and the duration of dosing, i.e. the number of doses administered. Based on the safety toxicology studies performed in animals the maximum doses is 11 infusions in 6 weeks. The goal is to define a potential dose and regime to reliably, safely and sustainably reduce anti-MAG IgM antibody levels by at least 50%.

The following assessments will be performed in each of the two phases (SAD and MAD):
- Safety and tolerability (adverse events (AEs), vital signs, laboratory data, electrocardiograms (ECGs), and local tolerability assessment).
- Blood sampling for anti-drug antibodies (ADA) development (immunogenicity).
- Blood sampling for PPSGG pharmacokinetics.

- Blood sampling for pharmacodynamics: (anti-MAG titers (Bühlmann Titer Units), paraprotein levels, anti-human natural killer- 1 antibodies (anti-HNK-1 Titers) and total IgM.
- Clinical assessments based on overall neuropathy limitations scale (ONLS) score, time to walk 10 meters, and Rasch-built overall disability scale (RODS) and Ataxia scores.

The following assessments will be performed in the MAD phase only :
o INCAT sensory sum score (ISS)
o Motor Unit Number Index (MUNIX) in selected sites only.
o Grip strength
o Neurofilament light chain (NfL) to measure the degree of axonal damage.
o B-cell activating factor (BAFF).
o Indirect immunofluorescence on sciatic nerves.

Each phase (SAD and MAD) will be split in two parts: (1) an active administration phase with single (SAD) or multiple (MAD) infusions and (2) an observation phase of 1 and 3 months respectively for the SAD and MAD. After this, patients whose antibody levels have not returned to baseline will enter in the follow-up phase, the duration of which will depend on the evolution of the anti-MAG IgM antibody levels.

Intervention

Subjects in the first phase, SAD, who comply with all the inclusion criteria and do not meet any of the exclusion criteria will be assigned to a single dose escalation study.
SAD phase: Single IV infusion of 200, 400, 800 mg and 1600 mg per patient in 4 cohorts. A higher dose (3200 mg) may be administered if safe to do and satisfactory antibody reduction has not been demonstrated in previous cohorts.

The study will enroll 6 patients per cohort (4 or 5 cohorts).

The study drug will be administered as a single 60 min IV infusion on Day 1 in the morning (between 7 AM and 10 AM).
The potential dose of 3200 mg will require a 120 minutes infusion.

The MAD phase that consists of two sequential and ascending cohorts.
The MAD phase dosing regimen will be adapted for in accordance with PK/PD modelling, safety and tolerability data collected during the SAD phase. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD. Based on the safety toxicology studies performed in animals the maximum number of doses is 11 infusions in 6 weeks.

Study burden and risks

In the SAD phase each patient will have the following 8 visits over about 2 months: Screening, Baseline, Treatment (4 visits), Follow-up and end of study (EOS).
In the MAD phase each patient will have up to 17 visits over about 6 months: Screening, Baseline, Treatment (for 6 weeks, max 11 infusions), Follow-up and EOS.

A visit will take approximately 2 hours, except for the dosing days, where over a period of 8 hours PK samples are taken.

During these visits the following actions occur:
physical examination, collection of demographic data, discussion of medical history, checking eligibility criteria, making a 12-lead ECG & continues heart monitor, blood collection, urinalysis, pregnancy test (if applicable), discussing adverse events, discussing concomitant medication. During these visits the
subject will complete various test and questionnaires.

All female subjects of childbearing potential must use adequately acceptable methods of birth control to prevent pregnancy. Male subjects have to use adequate contraception to prevent pregnancy of their partners.

Blood sampling related risks:
During the hospital visits blood samples will be taken. The insertion of the needle can be painful or there may be blue spots developing at the injection site. In addition, the subject may suffer from dizziness, light headedness or fainting.

Medication-related risks:
This study is the first administration of PPSGG in humans; therefore, no prior human safety and tolerability data are available. As with any drug, it is possible that adverse reactions are caused by PPSGG. There may be unknown or unforeseeable risks. However, the risk to patients in this study will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring in an hospital setting, strict adherence to standard practice including training of staff and provision of manuals for study procedures, infusion procedure, stopping rules for an individual patient, as well as a safety review after the first part of the study and monitoring by an IDMC. Key safety data will be reviewed by Polyneuron in an open manner on an ongoing basis. The IDMC will regularly review safety data to assess whether the benefit/risk of each treatment arm remains acceptable.

Evaluation of the safety of PPSGG in dogs and rats demonstrated a favorable toxicity profile (see IB). In a 6-week repeat-dose study in rats and dogs of

doses from 20 mg/kg up to 200 mg/kg IV of 11 infusions over 6 weeks followed by a 2-week recovery, there were no clinical signs, no effects on organ weight or macroscopic observations, and no safety pharmacology findings; clinical chemistry and hematology results were remarkable. Neither microscopic findings were reported.

Based on the experimental animal studies that were carried out, investigation of the safety and tolerability of PPSGG showed no special dangers for humans. Therefore, based on the safety profile of PPSGG the risks in participating in the trial are considered acceptable. However, they include the usual risks of participating in clinical trials, which are related to possible allergic reactions, infusion related adverse event, blood drawing via venepuncture. Patients* safety will be observed during all study phases. Before the drug administration, participants will be informed about the potential and/or observed adverse effects, if any, that occurred in the previous cohort.

Medical progress is based on research which ultimately must rest in part on experimentation involving humans. Eligible patients may consider participation in this clinical trial because they want to contribute to the advancement of medical knowledge. Still, considerations related to the well-being of the individual patients enrolled into this clinical study must take precedence over the interests of science and society. Based on the available information and the design of the study, Polyneuron and the Principal investigator consider the trial to be ethically acceptable. The duration of hospitalization and the medical surveillance are considered adequate to ensure safety of the patients

There are preclinical findings of undetermined clinical relevance that will be mitigated by careful clinical monitoring. Thus, vital signs and ECG will be monitored before and after the first dose during the SAD phase and before and after the doses during the MAD phase and at other visits throughout the study.

Patients will return to the study site on a regular basis. During these visits, safety, tolerability, efficacy, and PK/PD data will be collected. Standard safety assessments will include vital signs, ECGs, clinical laboratory evaluations (hematology, blood chemistry and urinalysis), and AEs as outlined in the Schedule of Assessments. In addition to the standard clinical laboratory assessments, patients will be regularly monitored for signs and symptoms, inflammation, and hematologic and hepatic function. Patients will be informed to report any symptoms to the clinical staff to assure proper assessment and so that care can be administered in a timely manner.

In addition, the clinical opinion of the Investigator will be used to protect individual patient safety during the trial.

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

- Written informed consent.
- Age between 18 and 80 years, male and female.
- Patient with a confirmed diagnosis of monoclonal IgM associated with monoclonal gammopathy of undetermined significance (MGUS) with anti-MAG activity (titer of > 10*000 Bühlmann Titer units [BTU]) and demyelinating neuropathy defined by electrophysiological criteria according to European Federation of Neurological Societies/Peripheral Nervous System paraproteinemic demyelinating neuropathy (EFNS/PNS PDN) guideline, 2010.
- Clear clinical signs of disability: with at least ONLS * 2 in lower extremities.
- Inflammatory Neuropathy Cause and Treatment sensory sum score (ISS) * 2.
- Patients must have adequate hepatic function as evidenced by total bilirubin

< 26 µmol/l (1.5 mg/dL), and alkaline phosphatase and aspartate transaminase/alanine aminotransferase < 2X the upper limit of normal (ULN).
- Absence of cause of neuropathy independent from anti- MAG activity: e.g. diabetes, hypothyroidism, past or current dependence on alcohol, past or current treatment with neurotoxic drugs.
- Patients must have adequate renal function as evidenced by serum creatinine <2 mg/dL or calculated creatinine clearance of *60 mL/min within 28 days before the first investigational medicinal product (IMP) administration using the Modification of Diet in Renal Disease (MDRD) formula.
- Capability to meet the requirements of the study.

Exclusion criteria

- Patients with total serum IgM levels >30 g.
- Hematological malignancy (e.g. known multiple myeloma or confirmed Waldenström's macroglobulinemia based on bone marrow analysis).
- Patients with any history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Previous immunosuppressive treatment with intravenous immunoglobulin (IVIG) or apheresis/plasmapheresis in the preceeding 3 months, and/or cyclophosphamide and biologicals (e.g. rituximab): in the preceeding 6 months prior to enrolment.
- Other neurological, neuromuscular, rheumatologic or orthopedic conditions with significant impact on the capability of walking preventing evaluation of neurological scores.
- Anti-MAG neuropathy patients with persistent clinically significant laboratory abnormalities not related to the anti-MAG neuropathy, such as significant renal dysfunction, hepatic dysfunction, cardiac disease or other significant neurological disorder.
- Anti-MAG neuropathy patients with a modified Rankin Scale (mRS) score > 4.
- Participation in another interventional clinical trial.
- Any other significant finding that would increase, according to the Investigator, the risk of having an adverse outcome from participating in the study.
- Any other medical condition, including mental illness or substance abuse deemed by the investigator(s) to likely interfere with the patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.
- Patients who have undergone major surgery * 2 weeks prior to starting study drug or who have not recovered from the side-effects of surgery.
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening:
PR > 200 msec.; QRS complex > 120 msec.; QTcF > 450 msec (males); QTcF > 460 msec (females); History of familial long QT syndrome or known family history of

Torsades de Pointes; Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study.
- Sexually active males must use a condom during intercourse after the start of the IMP administration and for at least one week after stopping study medication and should not father a child in this period after completion of the study medication (SAD and MAD phases). A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants should not donate sperm for the time period specified above.
- Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or within 30 days, whichever is longer; or longer if required by local regulations.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after discontinuation of the investigational drug.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	04-11-2020
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A

Generic name:	Placebo (phosphate buffered saline (PBS)
Product type:	Medicine
Brand name:	N/A
Generic name:	PPSGG: Poly phenyl (disodium 3-O-sulfo-beta-D-glucopyranuronate)-(1-3)-beta-D-galactopyranoside.

Ethics review

Approved WMO Date:	23-04-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-07-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2020-000067-23-NL
CCMO	NL72912.041.20

Study results

Date completed: 23-09-2021

Results posted: 08-02-2022

Summary results
Trial ended prematurely

First publication
03-02-2022