A Phase 2 Study Evaluating the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Narsoplimab in Paediatric Patients (28 Days to 18 Y.O.) with High Risk Haematopoietic Stem Cell Transplant Thrombotic Microangiopathy

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This study has been transitioned to CTIS with ID 2023-509710-11-00 check the CTIS register for the current data. Study Objectives:The purpose of this Phase 2 study is to evaluate the safety, efficacy, pharmacokinetics (PK),pharmacodynamics (PD), and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON56242

Source
ToetsingOnline

Brief title
OMS721

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)
- Immune disorders NEC
- Vascular disorders NEC

Synonym
thrombotic microangiopathies (TMA)

Research involving
Human

Sponsors and support

Primary sponsor: Omeros Corporation
Source(s) of monetary or material Support: Farmaceutische industrie.

Intervention

Keyword: Clinical trial, Narsoplimab, Paediatric, Phase 2

Outcome measures

Primary outcome

Primary

* Describe the 100-day survival rate following high risk HSCT-TMA diagnosis.

Study Endpoints:

Primary endpoint:

* 100-day survival rate from date of HSCT-TMA diagnosis

Secondary outcome

Main secondary endpoints:

* Survival at 52 weeks and median, mean, and overall survival from date of TMA

diagnosis

* Narsoplimab peak and trough PK and concomitant lectin pathway activation

measured

by ex vivo assay

* Safety will be evaluated by adverse events (AEs) and laboratory measures

* Anti-drug antibody response

* Responder rate based on clinical response criteria

Study description

Background summary

5.1. Background
5.1.1. Description of Narsoplimab
Omeros Corporation (Omeros, Sponsor) is developing narsoplimab (company code OMS721), a human IgG4 monoclonal antibody (mAb) that specifically binds to mannan-binding lectin-associated serine protease 2 (MASP-2) and inhibits the lectin
pathway of complement for the treatment of lectin complement pathway-mediated diseases.
The primary function of the complement system, a part of the innate immune system, is
to protect the host against infectious agents [Ricklin 2010]. This complex system targets
immune and inflammatory responses to surfaces that display molecular patterns not
usually present on healthy host cells. Activation of the complement system initiates a
series of proteolytic steps that culminate in the formation of a membrane attack complex,
which disrupts the membranes of targeted cells causing lysis and cell death. In addition,
complement activation triggers the release of anaphylatoxins to recruit leukocytes and
activate endothelium and many other cell types, as well as opsonization and activation of
phagocytic cells, to further engage the infectious agents.
Three pathways activate complement in response to distinct initiating events: the
classical, lectin, and alternative pathways. The classical pathway is triggered by immune
complexes and mediates important immune effector functions. The lectin pathway can be
activated by specific types of damage-associated molecular patterns (DAMPs) that are
usually found on microbes but not on healthy host cell surfaces. These DAMPS are also
found on injured host tissue. Lectin pathway activation is initiated by a group of enzymes
known as MASPs. These proteases are synthesized as proenzymes that form a

complex in
blood with lectins, such as the mannan-binding lectin (MBL), ficolins, and a lectin known
as Collectin 11. These lectins bind to carbohydrate patterns on foreign or injured host cell
surfaces, targeting MASPs to their site(s) of action and leading to activation of MASPs.
There are three known MASPs: MASP-1, MASP-2, and MASP-3 [Yongqing 2012]. MASP-2 is thought to be the key enzyme responsible for activation of the lectin pathway;
upon activation, it cleaves its substrates, C2 and C4, resulting in the formation of the
convertase C4b2a, which cleaves and activates C3, a central component of complement
activation. Narsoplimab blocks the action of MASP-2, thereby inhibiting the lectin
pathway of complement activation. The alternative pathway, by contrast, is continuously
activated at a low level and is kept in check by a series of regulatory proteins. The
alternative pathway also acts as an amplification loop, increasing the host immune
response following activation of the classical and the lectin pathways. While the
complement system supports innate host defense against pathogens, mutations in the
genome or tissue damage can cause inappropriate activation and lead to serious disease,
e.g., thrombotic microangiopathy (TMA), in which endothelial damage, as well as deposition of fibrin and platelet-rich thrombi in the microvasculature, leads to end organ
damage.

Narsoplimab is a fully human IgG4 mAb directed against MASP-2. Narsoplimab avidly
binds to recombinant MASP-2 (apparent Kd in the range of 100 pM) and exhibits greater
than 5000-fold selectivity over the homologous proteins C1s, C1r, and MASP-1. In functional assays, Narsoplimab inhibits the human lectin pathway with nanomolar potency (concentration leading to 50% inhibition [IC50] of approximately 3 nM), but it
has no significant effect on the classical or alternative complement pathways. An intact
classical and alternative complement pathway is important to prevent lethal infections
during complement inhibitory therapy, which has been a major concern that requires pretreatment

vaccination and/or prophylactic antibiotics. Narsoplimab administered either by intravenous (IV) or subcutaneous (SC) injection to mice and non-human primates resulted in high plasma concentrations that were associated with suppression of lectin
pathway activation in an ex vivo assay. Narsoplimab blocks the crosstalk between the
lectin pathway and the coagulation system (activation of Factor XII) and contact system
(activation of Kallikrein) (Omeros unpublished data). Narsoplimab treatment reduced
thrombus formation in a mouse model of TMA, thus demonstrating that narsoplimab is a
potential candidate for the treatment of haematopoietic stem cell transplant-associated
thrombotic microangiopathy (HSCT-TMA) that results from inappropriate lectin pathway
activation. Narsoplimab has also been shown to reduce platelet aggregation and endothelial cell death in models employing human sera from HSCT-TMA patients [Elhadad 2020].

Study objective

This study has been transitioned to CTIS with ID 2023-509710-11-00 check the CTIS register for the current data.

Study Objectives:
The purpose of this Phase 2 study is to evaluate the safety, efficacy, pharmacokinetics (PK),
pharmacodynamics (PD), and immunogenicity of narsoplimab in paediatric-aged patients with
thrombotic microangiopathies (TMA) following haematopoietic stem cell transplant (HSCT).

Study design

Methodology
This is the first study of narsoplimab in paediatric patients. This study is an open-label, multicenter
study evaluating the safety, efficacy, pharmacokinetic (PK), and pharmacodynamic (PD) of narsoplimab in male and/or female patients 28 days old to less than 18 years old who
received an allogeneic HSCT for the treatment of benign or malignant disease and have
high risk HSCT-TMA. The study has three periods: Screening (Days -28 to Day 0); Treatment
(Day 1 to Day 56); Follow-up (Days 57 to Day 365).

Screening Period
Patients will be evaluated for eligibility between Day -28 and Day 0 prior to the first drug
administration. If the ADAMTS13 activity response results are not available to confirm
eligibility before the Screening period ends, then Screening can be extended.
Treatment Period
Treatment with narsoplimab 4 mg/kg (not to exceed 370 mg) IV will be administered by IV
infusion twice a week, with 2 to 4 days between doses, with no more than 2 doses per week,
over 8 consecutive weeks, starting at Visit 1 (Day 1). If patient achieves all clinical response
criteria during the Treatment Period before 8 weeks, frequency will be reduced to narsoplimab
4 mg/kg IV once a week until patient completes the 8 full weeks of treatment.
See the Schedule of Events (Section 0) for the procedures to be done during the study. For
evaluation of laboratory assessments, local laboratory will be used for all of the sites because
paediatric patients are critically ill and will need lab results as soon as possible and because of
blood draw limitations based on regulatory guidelines. If study labs have already been drawn
as standard of care ± 48 to 72 hours of the screening and Day 1 visit, labs do not need to be
redrawn.
Narsoplimab is to be used in conjunction with standard of care treatments. Standard of care
treatments are not to be delayed or withheld from patients entering this study. These treatments
should be initiated according to local standard of care. For example, plasma exchange should
not be delayed while waiting for initiation of narsoplimab treatment if local standard of care is
to administer plasma exchange.
Depending on the patient*s clinical status at the completion of dosing for 8 weeks, the
Investigator may request compassionate use treatment with narsoplimab for the patient after
discussion with the Omeros medical monitor.
Follow-Up
All patients will enter Follow-up Period at the end of 8 weeks of study drug treatment. Followup
visits will begin at Day 60 and be completed 365 days after the first dose of study drug.

Intervention

Investigational Product, Dosage, and Mode of Administration:
* Narsoplimab for injection, formulated in 20 mM citrate, 200 mM arginine, and 0.01%
polysorbate 80, pH 5.8, 185 mg/mL
* IV infusion: appropriate volume of narsoplimab added to 0.9% sodium chloride for
injection (normal saline or NS) or dextrose in water (D5W), infused over 30 to 90
minutes

Study burden and risks

5.3. Potential Risk and Benefits
5.3.1. Known and Potential Risks
5.3.1.1. Human MASP-2 Deficiency
A MASP-2 deficiency has been reported to occur in humans, and the clinical phenotype
of MASP-2 deficiency may be relevant to risk assessment of MASP-2 inhibition with
narsoplimab. The literature contains conflicting reports as to whether patients with
MASP-2 deficiency are at risk for adverse effects.
Two case reports described individuals with MASP-2 deficiency due to a homozygous
mutation (D120G) with clinical associations with autoimmunity or recurrent bacterial
infections; 1 patient was healthy until 13 years of age, and the other patient had cystic
fibrosis [Olesen 2006, Stengaard-Pedersen 2003]. A genetic screen of 335 Polish children
with recurrent respiratory tract infections identified 1 child with MASP-2 deficiency
[Cedzynski 2004]. In contrast, in a genetic screen of 868 healthy Spaniards, 2 homozygous D120G individuals were identified; both patients were healthy without
clinical evidence of recurrent infections or autoimmune disorders, and both had normal levels of circulating complement [Garcia-Laorden 2006].
The gene frequency of the D120G mutation is 2% to 4% in European populations, which would predict that approximately 1 in 625 to 2000 individuals in this population would be homozygotes with MASP-2 deficiency [Garcia-Laorden 2006, Thiel 2007]. Polymorphisms in the MASP-2 gene as well as the plasma concentration of MASP-2 are influenced by race. For example, the D120G mutation is the most common one in Caucasians, but it is not found in Chinese or Africans [Thiel 2007, Urbano-Ispizua 2011]. Moreover, the circulating levels of

MASP-2 were lowest in Africans (median 196 ng/mL), followed by Chinese (262 ng/mL) and Native American (290 ng/mL), and highest in Caucasian Danes (416 ng/mL) [Thiel 2007]. The initial studies were in Danes, and a plasma concentration below 100 ng/mL was suggested as indicating MASP-2 deficiency because only individuals homozygous for the D120G mutation had this level. Subsequent studies in broader populations showed that this cutoff was inappropriate because 5% of Chinese and 19% of Africans tested had values below 100 ng/mL.
Several studies have examined the relationship between MASP-2 concentration and susceptibility to infections. In a Swiss study of 94 paediatric cancer patients, MASP-2 deficiency, defined as serum levels below 200 ng/mL, was identified in 9 children [Schlapbach 2007].
Patients with low MASP-2 levels had significantly more episodes of febrile neutropenia with no identified microbial etiology and had longer duration of IV antibacterial therapy than those with normal MASP-2 levels. In a Polish study of 1788 neonates, cord blood serum MASP-2 concentration correlated with gestational age and birth weight and was significantly lower in premature babies and other pre-term babies compared with term babies [St Swierzko 2009]. Neonates with low MASP-2 concentrations did not have a higher incidence of perinatal infections when compared with those with normal MASP-2. Indeed, there was a trend toward higher MASP-2 concentrations among babies with infections. A study in Spain evaluated the frequency of D120G mutation in 868 healthy individuals as well as 967 adult patients with community-acquired pneumonia, 43 children with recurrent respiratory infections, and 130 patients with systemic lupus erythematosus and found that the allelic frequency of the D120G mutation was similar in all of these clinical groups [Garcia-Laorden 2006]. These investigators conducted a follow-up study in which they evaluated the significance of MASP-2 deficiency in the susceptibility and outcome of community-acquired pneumonia in adults and found similar MASP-2 alleles and genotypes among patients and control individuals, leading to the conclusion that MASP-2 deficiency was not associated with an increased risk of community-acquired pneumonias [Garcia-Laorden 2008] .
In summary, the literature does not provide a clear indication as to the risk for increased susceptibility to infections in individuals with MASP-2 deficiency. The researchers in Denmark who were the first to describe MASP-2 deficiency and have done the most work in this area stated in 1 article [Thiel 2007] that *One must conclude that (MASP-2) deficiency in itself does not result in disease, rather, it is a modifier, which may penetrate when also other elements are compromised.*

Clinical experience with narsoplimab has not demonstrated safety concerns. Infections,
some severe and fatal, have been reported in clinical trials; however, these infections
have been similar to infections occurring in the respective patient populations who have
not received narsoplimab. The independent Data Monitoring Committee (DMC) of the

adult TMA study has not observed an increased signal of infection.

5.3.1.2. Animal Models of Infection
The role of MASP-2 in bacterial infection has been evaluated in animal models, and the
results vary depending on the model, ranging from disease worsening to no effect to
protection. In a murine model of pneumococcal infection, inhibition of MASP-2 with a
MASP-2 mAb prior to nasal inoculation of Streptococcus pneumonia resulted in
increased severity of disease compared to isotype control mAb [Ali 2012]. In this model,
antibiotic treatment was effective in MASP-2 mAb-treated animals, resulting in a similar
outcome to that in untreated controls. In contrast, in a murine model of pneumococcal
meningitis, MASP-2-deficient mice had a better outcome compared to wild-type
littermates [van de Beek D, unpublished observations]. In a murine model of
Pseudomonas aeruginosa infection, MASP-2-deficient mice had no significant survival
disadvantage compared to wild-type littermates [Kenawy 2012]. In a murine model of
meningococcal infection, treatment with a MASP-2 mAb prior to bacterial challenge
resulted in increased survival compared to treatment with isotype control mAb,
demonstrating a protective effect [Omeros unpublished observations].
5.3.1.3. Adult TMA Infections

Based on complement pathway inhibition, a potential risk is an increased susceptibility to
systemic infection or worsening of an existing infection. Infections, some severe and
fatal, have been reported in clinical trials, but these infections have been similar to
infections occurring in the respective corresponding patient populations who have not
received narsoplimab.

Patients should be monitored closely for the development of infections, and appropriate antimicrobial treatment should be promptly initiated in the
event of a suspected infection. However, because lectin pathway (MASP-2) inhibition
does not impact innate/acquired immunity, vaccination for encapsulated bacteria is not
required.

The most commonly reported AEs were infections. Twenty out of 28 treated patients
reported an infection. All reported infections Grade 2 or greater have been reviewed for
temporal relationship to narsoplimab treatment, severity, other potential risk factors, and
outcome. Temporal relationship was defined as infection onset occurring between the
first narsoplimab dose and 37 days following the last narsoplimab dose (AE evaluation
period). Risk factors were considered only when they were present at the start of the
infection and included corticosteroid treatment, other immunosuppressive treatment,
neutropenia, and venous catheterization (only for catheter-related infections).

Three patients died of infection during the HSCT-TMA Core Study period. Three died of sepsis. All were receiving corticosteroids and had neutropenia. One was receiving cyclosporin and another was receiving sirolimus.
The infections were typical for this seriously ill population. All fatal infections were associated with corticosteroid treatment. The fatal infections in HSCT-TMA patients were also associated with neutropenia. Almost all severe infect

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

1. Age at least 28 days and less than 18 years prior to informed consent (Visit 0).
2. Have informed consent from at least one parent or legal guardian as required by local law and regulation. Patient informed consent will be required if the patient has reached the local legal age of majority.
3. Assent from patients as required by local law and regulation.
4. Have received an allogeneic haematopoietic stem cell transplant for the treatment of non-malignant or malignant disease. All donor cell sources are allowed (i.e., matched, mismatched, and haploidentical; related and unrelated; bone marrow, peripheral blood stem cells, and umbilical cord blood).
5. Have a diagnosis of HSCT-TMA defined as having both of the following:
-Platelet count < 50,000/µL or a decrease in platelet count > 50% from the highest value obtained following transplant.
-Evidence of microangiopathic hemolysis (presence of schistocytes, serum lactate dehydrogenase [LDH] > upper limit of normal ([ULN], or haptoglobin < lower limit of normal [LLN])
6. Have at least one of the following HSCT-TMA high-risk criteria:
- HSCT-TMA persistence > 2 weeks following modification of calcineurin inhibitors or sirolimus
OR
- Have evidence of high-risk HSCT-TMA defined as at least one of the following:
- Spot protein/creatinine ratio > 2 mg/mg
- Serum creatinine > 1.5 x the creatinine level prior to TMA development
- Biopsy-proven gastrointestinal TMA
- TMA-related neurological abnormality (e.g., confusion, stroke, transient ischemic attack [TIA] or seizures)
- Pericardial or pleural effusion without alternative explanation
- Pulmonary hypertension without alternative explanation
- Have Grade III or Grade IV graft-versus-host disease (GVHD) or, in the opinion of the Investigator, risk for development of Grade III or Grade IV GVHD

if immunosuppression were to be modified
- Have elevated serum C5b-9 (> 244 ng/mL)
7. If sexually active and of childbearing potential, must agree to practice a highly effective method of birth control throughout the study drug treatment and for at least 12 weeks after the last dose of study drug, such method of birth control defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence (abstinence is acceptable when it is in line with the patient*s preferred and usual lifestyle and is defined as complete abstinence of sexual intercourse, not periodic abstinence or withdrawal), or vasectomized partner.
8. Male patients must be willing to avoid fathering children for at least 12 weeks following the last dose of study medication.

Exclusion criteria

1. All treatments for HSCT-TMA are allowed except eculizumab, ravulizumab, and defibrotide within 3 months prior to informed consent, unless failure of therapy can be documented.
a. Patients may not be on eculizumab, ravulizumab, or defibrotide for any indication at screening.
2. Have Shiga toxin-producing Escherichia coli haemolytic uraemic syndrome (STEC-HUS). Test results obtained within 28 days prior to informed consent may be used.
3. Have ADAMTS13 activity < 10%. Test results obtained within 28 days prior to informed consent may be used.
4. Have a severe, uncontrolled systemic bacterial or fungal infection requiring antimicrobial therapy (prophylactic antimicrobial therapy administered as standard of care is allowed).
5. Have malignant hypertension (blood pressure [BP] > 99th percentile plus 5 mmHg with bilateral hemorrhages or *cotton-wool* exudates on fundoscopic examination).
6. Due to conditions other than HSCT-TMA, have a poor prognosis with a life expectancy of less than 3 months in the opinion of the Investigator.
7. If pregnant or lactating
8. Have received treatment with an investigational drug or device within 4 weeks of entering study.
9. Have abnormal liver function tests defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times ULN within 28 days prior to informed consent through prior to the first dose.
10. Have a positive test by antigen, antibody, or polymerase chain reaction (PCR) for human immunodeficiency virus (HIV); if negative within 28 days prior to informed consent, the test does not need to be repeated.
11. Patients or their parents or legal guardians are an employee of Omeros, Clinical Research Organization (CRO), an Investigator, a study staff member, or

an immediate family member.
12. Have a known hypersensitivity to any constituent of the product.
13. Presence of any condition that the Investigator believes would put the patient at risk.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-03-2024
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Narsoplimab
Generic name:	Narsoplimab

Ethics review

Approved WMO Date:	15-02-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-06-2023

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-11-2023
Application type:	Amendment
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
EU-CTR	CTIS2023-509710-11-00
EudraCT	EUCTR2021-002727-38-NL
CCMO	NL82077.041.23