A Phase I/II, Single-Arm, Open-label Study to Evaluate the Pharmacokinetics, Safety/Tolerability and Efficacy of the Selumetinib Granule Formulation in Children Aged >= 1 to < 7 Years with Neurofibromatosis Type 1 (NF1) Related Symptomatic, Inoperable Plexiform Neurofibromas (PN) (SPRINKLE)

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Primary objectives:- To determine the PK of selumetinib after administration of the selumetinib granule formulation. - To assess the safety and tolerability of the selumetinib granule formulation.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON56067

Source
ToetsingOnline

Brief title
SPRINKLE

Condition

- Congenital and hereditary disorders NEC
- Nervous system neoplasms benign

- Nervous system neoplasms benign

Synonym
A genetic disorder characterized by the presence of multiple, frequently symptomless but occasionally malignant, tumors formed on a nerve cell sheath

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Opdrachtgever/sponsor: AstraZeneca

Intervention

Keyword: Children, Granule Formulation, Neurofibromatosis Type I, Selumetinib

Outcome measures

Primary outcome

To determine the PK of selumetinib after administration of the selumetinib granule formulation the Selumetinib AUC0-12 will be derived after single dose administration.

Safety and tolerability of the selumetinib granule formulation will be evaluated in terms of AEs, clinical safety laboratory assessments (clinical chemistry, haematology, urinalysis), physical examination, weight, vital signs, ECG, ECHO, ophthalmologic assessment, knee (or wrist) MRI/X-ray, and performance status.

Secondary outcome

- To assess the palatability of the selumetinib granule formulation

- To further assess the PK of selumetinib and N-desmethyl selumetinib metabolite after administration of the selumetinib granule formulation.

- To evaluate the efficacy of the selumetinib granule formulation by assessment

of ORR as determined by ICR per REiNS criteria.

Study description

Background summary

Neurofibromatosis type 1 is an autosomal dominant disorder with an estimated prevalence of 2.13/10,000 individuals in Europe (OrphaNet Report Services 2020). There are no studies estimating the prevalence of NF1 in the US and most authors cite studies conducted in Europe. Neurofibromatosis type 1 is characterised by diverse, progressive cutaneous, neurological, skeletal, and neoplastic manifestations. Symptoms of NF1 generally manifest very early in life and the subsequent increase in morbidity can be severe. Neurofibromatosis type 1 arises from pathogenic variants of the NF1 gene encoding the tumour suppressor protein neurofibromin, a GTPase-activating protein whose normal function is to downregulate RAS activity (Ballester et al 1990, Bollag and McCormick 1991, Cawthon et al 1990, Martin et al 1990, Viskochil et al 1990, Wallace et al 1990). Constitutive activation of the RAS/RAF/MEK/ERK pathway is implicated in cell proliferation and is central to driving cancer growth and progression (Davies et al 2007). Neurofibromin 1 pathogenic variants lead to a failure to inactivate RAS, and can result in PNs (Basu et al 1992, Cichowski et al 2003). Affected individuals start life with one mutated (nonfunctional) copy and one functional copy of NF1 in every cell in their body. Although many of the clinical features of this syndrome are apparent from birth, complete loss of gene function is needed for tumour formation through acquisition of a somatic NF1 mutation in selected cells (Gutmann et al 2013, Ruggieri and Packer 2001). Plexiform neurofibromas develop in 20% to 50% of individuals with NF1. Plexiform neurofibromas in NF1 patients are histologically benign Schwann-cell tumours (Rutkowski et al 2000, Wu et al 2005) that, depending on the location and the growth rate, bear all the characteristics typical of cancers. Most NF1-related PNs are congenital or occur very early in life and are characterised by slow growth, complex shape, and sometimes very large size (up to 20% of body weight) (Korf 1999, Mautner et al 2008). Growth of PNs occurs more rapidly in young children (Akshintala et al 2020, Nguyen et al 2012, Tucker et al 2009). Spontaneous regression of PNs is uncommon and although occasionally seen in adolescents and young adults, it was not seen in young children (Akshintala et al 2020, Gross et al 2018). Consequently, there is a significant treatment need for young children with NF1-PN. These tumours can cause severe morbidity such as pain, neurological dysfunction, and disfigurement, and also have the potential to transform to MPNSTs (Nguyen et al 2011, Prada et al 2012). The lifetime incidence of MPNSTs in NF1 is 15.8%, and many MPNSTs arise in pre-existing PNs (Uusitalo et al 2016); MPNST is a rare disease in the general population with a lifetime incidence of 0.001% (Ferrari et al 2007). Selumetinib (AZD6244, ARRY 142886, AR00142886, AR-142886-X [where

X refers to a sequential lot number], KOSELUGO®) is an oral, potent, and highly selective, allosteric MEK1/2 inhibitor with a short half-life (Banerji et al 2010, Denton and Gustafson 2011). It is licensed for development by AstraZeneca Pharmaceuticals from Array BioPharma and is being co-developed by AstraZeneca and Merck & Co. Selumetinib can inhibit PN growth by blocking RAS signaling (Gross et al 2018, Gross et al 2020, Weiss et al 1999, Widemann et al 2014). Analysis of volumetric MRI data by NCI POB central review from a Phase I open-label, single-arm, Investigator-sponsored study (Study 8799 [NCI 11-C-0161; SPRINT; NCT01362803]) in paediatric patients (aged 3 to 18 years at enrolment) with NF1-related inoperable PN demonstrated durable tumour shrinkage with confirmed tumour volume decreases of >= 20% from baseline (Dombi et al 2016). These observations led to the addition of a Phase II part to the study to further evaluate the effect of selumetinib capsules on tumour response, pain, quality of life, and physical functioning in paediatric patients (aged 2 to 18 years at enrolment) with NF1-related symptomatic inoperable PN. Analysis of volumetric MRI data by NCI POB central review from SPRINT Phase II Stratum 1 showed durable tumour shrinkage along with clinical benefit (Gross et al 2020). The NCI POB central analysis-assessed ORR was 66% (95% CI: 51.2 to 78.8) in the SPRINT study. The median time to onset of response was 7.2 months (range 3.3 months to 1.6 years). The median DoR from onset of response was not reached; at the time of DCO the median follow-up time was 22.1 months. Of the 33 patients who had confirmed PR, 27 (81.8%) remained in response after 12 months; the remaining 6 patients were censored and had not progressed. The median time from treatment initiation to disease progression while on treatment was not reached. At the time of DCO, 28 (56%) patients remained in confirmed PR, 2 (4%) had unconfirmed PRs, 15 (30%) had stable disease and 3 (6%) had PD. Clinical Outcome Assessments were generally improved with an overall reduction in pain, improvement in motor function and mobility, improved bowel and bladder function and overall improvement in quality of life assessments. Selumetinib showed good tolerability with mainly mild or moderate AEs which were manageable long term via supportive therapy and/or dose interruption or reduction. Selumetinib (KOSELUGO®) capsules were approved for the treatment of paediatric patients >= 2 years of age with NF1 who have symptomatic, inoperable PN in the US on 10 April 2020 and a Conditional Marketing Authorisation was granted in Europe/EEA for paediatric patients 3 years of age and older, via the European Centralised Procedure in the EU on 17 June 2021. A detailed description of the chemistry, pharmacology, efficacy, and safety of selumetinib is provided in the Investigator*s Brochure.

Study objective

Primary objectives:
- To determine the PK of selumetinib after administration of the selumetinib granule formulation.
- To assess the safety and tolerability of the selumetinib granule formulation.

Study design

This is a Phase I/II, Single-Arm, Open-label Study to Evaluate the Pharmacokinetics, Safety/Tolerability and Efficacy of the Selumetinib Granule Formulation in Children Aged >= 1 to < 7 Years with Neurofibromatosis Type 1 (NF1) Related Symptomatic, Inoperable Plexiform Neurofibromas (PN).

Intervention

The study is open-label and single arm; there is no randomisation. Participants will receive selumetinib for 25 cycles (or until they meet discontinuation criteria). Enrolment into the initial dose-finding phase will be stratified by age group: - Cohort 1: participants aged between >= 4 and < 7 years - Cohort 2: participants aged between >= 1 to < 4 years Selumetinib will be administered using BSA-based dosing. The granule formulation dose schema to be used in the study will be established in the dose-finding phase, as described in section 6.1.2 on page 43 of the protocol and this is summarized in figure 2 on page 16 of the protocol. At enrolment participants must have a BSA within the range 0.40 to 1.09 m2; once participants attain a BSA between 1.10 and 1.29 m2 they will be encouraged to transition to the capsule formulation, if feasible, although all participants must remain on the granule formulation until after they have completed their third cycle of treatment.

Study burden and risks

Patients need to come to the hospital more often and visits are longer.
Patients will undergo the following actions during the study:
- History (including medical history)
- Physical examination (including standard neurological assessments)
- Vital signs (temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, measurement of weight and length)
- 12-lead ECG
- ECHO
- AE/SAE assessments
- Lansky performance status assessments
- Blood - and urine collections
- Questionnaires: FLACC/FPS-R, GIS-pNF, GIC-pNF, Pain medicatoin survey, PedsQL.
- Neurodevelopmental tests
- Palatability assessments
- Ophthalmology assessments
- MRI/Röntgen of knees (or wrists)
- Volumetric MRI (PN assessments)

The study drug can also cause side effects. Potential risks associated with selumetinib:
- Gastrointestinal effects; diarrhoea, nausea and vomiting

- Retinal toxicity; vision blurred (reported in 10% of patients receiving treatment with selumetinib), Central Serous Retinopathy, Retinal Pigment Endothelial Detachment, Retinal Vein Occlusion
- Creatinine phosphokinase increase
- Skin toxicity; rash, dermatitis acneiform, dry skin
- LVEF decreases
- Transaminase increase
- Increased blood pressure
- Physeal dysplasia
- Fatigue
- Peripheral oedema
- Stomatitis
- Pyrexia

Potential risks associated with selumetinib in paediatric patients:
- (Blood) CK increase
- Rash maculo-papular
- Urticaria
- Vulval Cellulitis
- decreased ejection fraction
- Vomiting
- Diarrhoea
- Nausea
- Dry skin
- Fatigue
- Pyrexia
- Dermatitis acneiform
- Hypoalbuminaemia
- Stomatitis
- Headache
- Oropharyngeal pain
- AST increase
- Paronychia
- Pruritus
- Mucositis
- Dyspnoea

Contacts

Public
Astra Zeneca

Prinses Beatrixlaan 582
Den Haag 2595BM

NL
Scientific
Astra Zeneca

Prinses Beatrixlaan 582
Den Haag 2595BM
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

- Male and female participants aged >= 1 to < 7 years of age at the time their legally authorised representative (parent or guardian) signs the informed consent. - All participants must have a diagnosis of NF1 with symptomatic inoperable PN where: a) Participants must have PN and at least one other diagnostic criterion for NF1 b) Inoperable is defined as a PN that cannot be completely surgically removed without a risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN; or unacceptable risk from the general anaesthetic as assessed by the investigator c) Symptomatic is defined as clinically significant symptoms or complications caused by the PN, as judged by the investigator; symptoms may include, but are not limited to, pain, motor dysfunction and disfigurement (examples of complications include PN displacing trachea, or PN causing bladder obstruction and hydronephrosis). - Participants must have at least one measurable PN, defined as a PN of at least 3 cm measured in one dimension, which can be seen on at least 3 imaging slices and have a reasonably well*defined contour. Participants who have undergone surgery for resection of a PN are eligible provided the PN was incompletely resected and is measurable. - Performance status: Participants must have a Lansky performance of >= 70 except in participants who are wheelchair bound or have limited mobility secondary to a need for mechanical breathing support (such as an airway PN requiring tracheostomy or continuous positive airway pressure) who

must have a Lansky performance of >= 40 - Participants must have a BSA >= 0.4 and <= 1.09 m2 at study entry (date of ICF signature). - Mandatory provision of consent for the study signed and dated by a participant*s legally authorised representative (parent or guardian) along with the paediatric assent form, when applicable

Exclusion criteria

- Participants with confirmed suspected malignant glioma or MPNST. Participants with optic glioma not requiring chemotherapy or radiation therapy are permitted. - History of malignancy except for malignancy treatment with curative intent with no known active disease >= 2 years before the first dose of study intervention and of low potential risk of recurrence. - Refractory nausea and vomiting, chronic gastrointestinal disease, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption, distribution, metabolism, or excretion of selumetinib. - A life*threatening illness, medical condition, organ system dysfunction or laboratory finding which, in the Investigator's opinion, could compromise the participant's safety, interfere with the absorption or metabolism of selumetinib, or put the study outcomes at undue risk. - Participants with clinically significant cardiovascular disease - As judged by the Investigator, any evidence of disease (such as severe or uncontrolled systemic disease, known moderate or severe hepatic impairment, active infection, active bleeding diatheses, or renal transplant, including any participant known to have hepatitis B, hepatitis C, or HIV) which, in the Investigator*s opinion, makes it undesirable for the participant to take part in the study. - Participants with the following ophthalmological findings/conditions: • Current or past history of RPED/CSR or RVO; • Intraocular pressure >21 mmHg (or ULN adjusted by age) or uncontrolled glaucoma (irrespective of IOP). • Participants with known glaucoma and increased IOP who do not have meaningful vision (light perception only or no light perception) and are not experiencing pain related to the glaucoma, may be eligible after discussion with the Medical Monitor. • Participants with any other significant abnormality on ophthalmic examination should be discussed with the Sponsor for potential eligibility. • Ophthalmological findings secondary to long*standing optic pathway glioma (such as visual loss, optic nerve pallor or strabismus) or longstanding orbito* temporal PN (such as visual loss, strabismus) will NOT be considered a significant abnormality for the purposes of the study. - Have any unresolved chronic toxicity with CTCAE Grade >= 2 which are associated with previous therapy for NF1*PN (except hair changes such as alopecia or hair lightening) - Participants who have previously been treated with a MEKi (including selumetinib) and have had disease progression, or due to toxicity have either discontinued treatment and/or required a dose reduction. - Have had major surgery within 4 weeks of the first dose of study intervention, with the exception of surgical placement for vascular access. Have planned major surgery

during the treatment period. - Have received or are receiving an IMP or other systemic NF1*PN target treatment (including MEKi) within 4 weeks prior to the first dose of study intervention, or within a period during which the IMP or systemic PN target treatment has not been cleared from the body (eg, a period of 5 'half*lives'), whichever is longer. - Has received radiotherapy in the 6 weeks prior to start of study intervention or any prior radiotherapy directed at the target or non*target PN. - Has received growth factors in the 7 days prior to study entry (date of ICF signature). - Receiving herbal supplements or medications known to be strong or moderate inhibitors or inducers of the CYP2C19 and CYP3A4 enzymes unless such products can be safely discontinued at least 14 days or 5 half*lives (whichever is longer) before the first dose of study medication. - Inability to undergo MRI and/or contraindication for MRI examinations. Prosthesis or orthopaedic or dental braces that would interfere with volumetric analysis of target PN on MRI.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-10-2022
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Selumetinib
Generic name:	Koselugo

Ethics review

Approved WMO Date:	21-10-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-01-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	15-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2020-005608-20-NL
CCMO	NL79097.078.21
Other	volgt