An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 2 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease (InPedILD®-ON)

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The main objective of the trial is to assess the safety and tolerability of long-term treatment with nintedanib in pediatric patients with clinically significant fibrosing ILD.See section 2.1 and 2.2 of the protocol.

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54130

Source
ToetsingOnline

Brief title
What the long-term safety of nintedanib is in children with ILD

Condition

- Other condition

Synonym
interstitial lung disease, lungfibrose

Health condition

Respiratoire bronchiolitis-geassocieerde interstitiële longziekte

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: De opdrachtgever Boerhinger Ingelheim

Intervention

Keyword: Children, InPedILD®, Interstitial Lung Fibrosis, Nintedanib long-term dose exposure, safety and tolerability

Outcome measures

Primary outcome

The primary endpoint is the incidence of treatment emergent adverse events over

the whole trial.

See section 2.1 of the protocol.

Secondary outcome

N/A

Study description

Background summary

Childhood interstitial lung disease (chILD) is a term used to describe diffuse lung disease in children with non-specific respiratory symptoms. It consists of a heterogeneous group of rare respiratory diseases associated with varying morbidity and mortality. Although many of the ILDs present in children can also be found in adults, some chILDs are specific to paediatric populations and involve different pathophysiology.

There are no currently approved therapies for the treatment of ILD in children. Based on the mode of action of nintedanib and its demonstrated effects in adult

IPF and other chronic fibrosing ILDs with progressive phenotype, the use of nintedanib in fibrotic ILDs in children was considered to be of potential benefit.

In the Phase III trial, InPedILD® (BI trial 1199-0337; EudraCT no. 2018-004530-14), the parent trial to this open label study, the dose-exposure relationship and safety of nintedanib in children and adolescents with fibrosing ILD is investigated and information on the efficacy is collected as well.

If, the benefit/risk assessment based on the data of the InPedILD® trial justifies further exposure to nintedanib, all patients still on treatment will be offered to participate in this open label trial InPedILD®-ON (BI trial 1199-0378). Rollover of eligible patients from InPedILD® study to the current trial is planned to occur without treatment interruption, whenever possible.

The rationale of this open label trial is to collect additional safety and efficacy data of nintedanib in children and adolescents with clinically significant fibrosing ILD for at least 2 years (applies to patients rolling over from the parent trial) or until alternative treatment options become available or are made available (applies to new patients and to roll-over patients after 2 years).

See section 1.1 of the protocol.

Study objective

The main objective of the trial is to assess the safety and tolerability of long-term treatment with nintedanib in pediatric patients with clinically significant fibrosing ILD.

See section 2.1 and 2.2 of the protocol.

Study design

This is a multi-centre, multi-national, not randomised, open label clinical trial.

The patient population will include two cohorts:
1. Patients rolling over from the InPedILD® study and 2. Patients newly enrolled in the study.

Patients will be enrolled (screened) in the trial once they have signed the informed consent.
The roll-over patients will be screened (visit 1) on the same day as their first day of the treatmentperiod (visit 2) and the end of treatment (EoT) visit

from InPedILD® 1199-0337. These 3 visits will be combined on one day to prevent treatment interruption. Common procedures from the EoT from 1199-0337 and visit 1/ visit 2, will not be repeated. For medical reasons, the screening period for roll-over patients can last up to 8 weeks after the EoT from InPedILD®.
For new patients, the screening period can last up to 12 weeks.

After their eligibility has been confirmed at screening, patients will patients will be requested to stay in the trial with nintedanib for a minimum of 6 months to approximately 2 years.
Roll-over patients will receive treatment with nintedanib at their last dose of study medication in the parent trial, unless the patient*s weight has changed.
For new patients, the starting dose will be assigned based on the patient*s weight.
During treatment period, dose is adjusted based on patient*s weight. Dose reduction to the next lower dose is possible to manage adverse events.

The end of the trial will take place approximately when the last roll-over patient reaches 2 years of treatment in the follow-up study ensuring that nintedanib or alternative treatment options will be available for all remaining patients (roll-over and/or new patients) outside the trial at this time (this is expected to happen in in third quarter 2024). This can be earlier, if there are alternative treatment options become or are made available.

Calculated for 2 years, the patient will have approximately 13 scheduled visits.

See section 3.1 of the protocol.

Intervention

Children and young adolescent:
13.5 kg to <23.0 kg receive 50mg or 25mg nintedanib 2x a day
23.0 kg to <33.5 kg receive 75mg or 50mg nintedanib 2x a day
33.5 kg to <57.5 kg receive 100mg or 75mg nintedanib 2x a day
>=57.5 kg receive 150mg or 100mg nintedanib 2x a day

Patients will receive the medication dose as indicated above. The lower dose is to manage adverse events. For roll over patients, they will receive the same dose as they received for the parent trial, unless their weight has changed. If dose already reduced in InPedILD® or if dose reduction is needed at visit 2. In these cases, no further reduction will be possible. The lowest possible dose in this study is 25mg nintedanib 2x a day.

See section 4.1 of the protocol.

Study burden and risks

Burden
- Patient will be asked to participate for a minimum 6 months to approximately 2 years (approximately 6-13 scheduled visits). The length of the study varies depending on when the patient starts participating and when nintedanib or alternative treatment options become available outside of this trial. Patients will be asked to follow the visits according to protcol.
- Female patients will have to do a pregnancy test every 4-6 weeks. When they do not have to come to the hospital, they can do a provided urine test at home. The outcome will have to be administered in a patient diary.
- A maximum of 13 visits with blood sampling. In total, 100ml of blood per patient will be drawn at scheduled visits over a participation of 2 years in the study.
- 1x CT scan - when there is no CT scan available from within a year form the screening date a new CT scan is done. This is
about 9,5 mSv per scan.
- Imaging of the physes in the knee will be done with an MRI around every 12 weeks in the first year of the study and thereafter around every 24 weeks.
If the patient does not consent with having an MRI done an X-ray is allowed per protocol. An X-ray from the knee is about 0,01 mSv per time. When the physis is closed, no more imaging of the knee is needed.
- The teeth will be monitored by panoramic X-ray (every around 24 weeks in the first year and thereafter around every 48 weeks) and regular dental check-ups (around every 12 weeks in the first year and thereafter around every 24weeks) by a dentist. The amount of radiation that comes with a panoramic X-ray is 0,007 mSv per photo.
- The PedsQL and the 6 MWT are done a maximum of 6 times per protocol.
- The patients will be asked 2x to complete a questionnaire about the IMP acceptability.
- For the 2x PK visits, patients will have to complete a diary about the 3 days of IMP intake before this visits.

Risk/benefit *
Given the high unmet need for treatment options in paediatric fibrosing ILDs, the established clinical benefit and known safety profile of nintedanib in adults as well as the expected benefit of nintedanib in the paediatric fibrosing ILD, the benefitrisk of nintedanib in the target population is considered acceptable. Importantly, this open label trial InPedILD®-ON (BI trial 1199-0378) will only be implemented if the benefit/risk assessment based on the data of the InPedILD® trial justifies further exposure to nintedanib. The planned trial procedures in this extension study, which is the same as for the parent trial, and the associated-risk are therefore deemed acceptable. Also, timely identification of potential risks allow for discontinuation of treatment and possible reversal of adverse drug reactions.

Criteria for dose reduction
If a patient experiences a drug related adverse event, the dose can be reduced as described in Table 4.1.2: 1. The original the dose can be re-started after

recovery.The dose can be reduced without prior interruption, i.e. immediately stepping down from one dose to the next dose.

See protocol sections: flowchart, 1.4, 3.1, 4.1 and 5.

The use of Nintedanib post-study
The overall end of trial will take place approximately when last roll-over patient reaches 2 years of treatment ensuring that nintedanib or alternative treatment options will be available for all remaining patients (roll-over or new patients) outside the trial. This is expected in the third quarter of 2024. Should the patient in the Netherlands withdraw his/her consent from trial participation before end of trial, then there is the possibility of implementing a type of compassionate use for Nintedanib called *Artsenverklaring*. This will be only given when Nintedanib is considered beneficial for the patient and thus will be determined on a case-by-case basis between the investigator and sponsor.

See section 1.3 and 3.1 of the protocol.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

For new patients:
1. Children and adolescents 6 to 17 years old at Visit 2.
2. Signed and dated written informed consent and assent, where applicable, in accordance
with ICH-GCP and local legislation prior to admission to the trial.
3. Male or female patients. Female of childbearing potential (WOCBP1) must confirm that
sexual abstinence is standard practice and will be continued until 3 months after last drug
intake, or be ready and able to use a highly effective method of birth control per ICH M3
(R2) that results in a low failure rate of less than 1% per year when used consistently and
correctly, in combination with one barrier method, from 28 days prior to initiation of
study treatment, during treatment and until 3 months after last drug intake. Sexual
abstinence is defined as abstinence from any sexual act that may result in pregnancy. A
list of contraception methods meeting these criteria is provided in the parental
information and in CTP Section 4.2.2.3.
4. Patients with evidence of fibrosing ILD on HRCT within 12 months of Visit 1 as assessed
by the investigator and confirmed by central review.
5. Patients with FVC % predicted >=25% at Visit 2.
6. Patients with clinically significant disease at Visit 2, as assessed by the investigator based
on any of the following:
* Fan score >=3, or
* Documented evidence of clinical progression over time based on either:
o a 5-10% relative decline in FVC% predicted accompanied by worsening symptoms, or
o a >=10% relative decline in FVC % predicted, or
o increased fibrosis on HRCT, or
o other measures of clinical worsening attributed to progressive lung disease

(e.g.
increased oxygen requirement, decreased diffusion capacity).

For roll-over patients from the InPedILD® study:
Only criteria 2 and 3 listed for new patients are applicable with the following additional
inclusion criterion:
7. Patients who completed the InPedILD® trial as planned and who did not permanently
prematurely discontinue study treatment.

For patients who prematurely discontinued treatment permanently in 1199-0337 but are potentially
eligible and for completed patients from parent trial not able to roll-over
into the extension trial within 12 weeks following their End of Treatment visit:
Inclusion criteria for new patients are applicable except criteria 4, and 6 (as eligibility for these criteria has been done in 1199-0337 and does not need to be repeated) and also except inclusion criteria 1 for completed patients from parent trial not able to roll over within 12 weeks following their End of Treatment Visit in the parent trial.

See protocol section 3.3.2.

Exclusion criteria

For new patients:
1. AST and/or ALT >1.5 x ULN at Visit 1.
2. Bilirubin >1.5 x ULN at Visit 1.
3. Estimated Glomerular Filtration Rate (eGFR) <30 mL/min /1.73m² at Visit 1.
4. Patients with underlying chronic liver disease (Child Pugh A, B or C hepatic impairment) at Visit 1.
5. Other investigational therapy received within 1 month or 5 half-lives (whichever is
shorter but >=1 week) prior to Visit 2 except investigational therapy received in InPedILD® trial.
6. Significant pulmonary arterial hypertension (PAH)
7. In the opinion of the Investigator, other clinically significant pulmonary abnormalities.
8. Cardiovascular diseases
9. Bleeding risk
10. History of thrombotic event within 12 months of Visit 1.
11. Known hypersensitivity to the trial medication or its components (i.e. soya lecithin).
12. Patients with documented allergy to peanut or soya.

13. Other disease that may interfere with testing procedures or in the judgment of the
investigator may interfere with trial participation or may put the patient at risk when
participating in this trial.
14. Life expectancy for any concomitant disease other than ILD <2.5 years (investigator
assessment).
15. Female patients who are pregnant, nursing, or who plan to become pregnant while in
the trial.
16. Patients not able or willing to adhere to trial procedures, including intake of study
medication.
17. Patients who must or wish to take any drug considered likely to interfere with the safe
conduct of the trial according to investigator*s benefit-risk assessment for the individual
patient.
18. Patients with any diagnosed growth disorder such as growth hormone deficiency or any
genetic disorder that is associated with short stature and/or treatment with growth hormone therapy
within 6 months before Visit 2.
19. Patients <13.5 kg of weight at Visit 1

For roll-over patients from the InPedILD® study:
Only criteria 11, 12, 13, 15, 16, 17 and 19, listed for new patients are applicable with the
following additional exclusion criterion:
20. Patient not compliant in parent trial (InPedILD®), with trial medication or trial visits,
according to investigator*s judgement.
Roll-over patients may qualify for participation even though other exclusion criteria may
have been met during the participation in InPedILD®, if the investigator*s benefit-risk
assessment for the individual patient remains favourable. This should be discussed with
sponsor before the roll-over of patient.

For patients who prematurely discontinued treatment permanently in 1199-0337 but are potentially
eligible and for completed patients from parent trial not able to roll-over into the extension trial within 12 weeks following their End of Treatment visit:

All exclusion criteria for new patients are applicable. In addition, following additional exclusion
criterion is applicable for patients who prematurely discontinued treatment permanently in 1199-0337:
21. Patients who experienced drug-related adverse events during parent trial leading to
permanent study treatment discontinuation.

See protocol section 3.3.3.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-08-2022
Enrollment:	1
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ofev
Generic name:	Nintedanib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	04-11-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-05-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
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Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
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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	EUCTR2020-005554-23-NL
ClinicalTrials.gov	NCTnummerisnognietbekend
CCMO	NL79059.018.21