Phase 1/2 Dose Finding, Safety and Efficacy Study of Ibrutinib in Pediatric Subjects with Chronic Graft Versus Host Disease (cGVHD)

Published: 22-08-2019
Last updated: 21-09-2024

This study has been transitioned to CTIS with ID 2023-507330-24-00 check the CTIS register for the current data. Part A - Dose Finding/SafetyPrimary Objective:* To determine the recommended pediatric equivalent dose (RPED; based on pharmacokinetic [...

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

Summary

ID

NL-OMON54762

Source
ToetsingOnline

Brief title
PCYC-1146-IM

Condition

- Other condition

Synonym
Chronic Graft Versus Host Disease

Health condition

Chronic Graft Versus Host Disease

Research involving

Human

Sponsors and support

Primary sponsor: Pharmacyclics
Source(s) of monetary or material Support: Industry

Intervention

Keyword: alloimmunity, graft versus host disease, inflammatory response, stem cell transplants

Outcome measures

Primary outcome

Primary Endpoints:

Part A: PK (area under the plasma concentration-time curve [AUC]) to determine

the RPED of ibrutinib for use in pediatric subjects (age >= 1 to

< 12 years) with cGVHD.

Part B: PK (AUC) and safety (treatment-emergent AEs and laboratory

abnormalities) of ibrutinib in pediatric subjects (age >= 1 and < 22 years)

with cGVHD.

Secondary outcome

Secondary Endpoints:

Part A:

* Safety, including treatment-emergent AEs, laboratory abnormalities and other

safety endpoints.

* Pharmacodynamics (Bruton*s tyrosine kinase occupancy)

* For those subjects continuing therapy after dose escalation (Part A

Continuation Cohort), secondary endpoints will be the same as

outlined under Part B below.

Part B:

* Response rate at 24 weeks

* Duration of response

* Overall survival rate

* Growth and development

* Immune reconstitution

Study description

Background summary

Although cGVHD is less common in children than in adults, they nonetheless represent a significant proportion of the overall cGVHD population, and have substantial morbidity and mortality associated with the disease (Baird 2010). Based on pediatric-specific data, the pathogenesis of cGVHD, although not yet fully understood, appears to be essentially the same in adults and pediatric patients. Recent information implicates B-cells as well as T-cells in the generation of cGVHD (Sarantopoulos 2015, Allen 2014, Flynn 2014, Johnston 2014). This was
first recognized in adult populations and confirmed in a biomarker study of children with cGVHD by the Children*s Oncology Group. The investigators demonstrated that plasma biomarkers influencing both B-cell and T-cell function were highly expressed when compared to
children who had undergone transplant without cGVHD (Fujii 2008, She 2007). Children and adolescents develop cGVHD symptomatology in a manner analogous to that of adults. Clinical manifestations of cGVHD are similar in adults and children, and most commonly involve the skin, eyes, oral cavity, gastrointestinal (GI) tract, liver, and lungs (Baird 2010). The primary difference between the pediatric and adult population is that cGVHD occurs in children who are still growing and developing and who generally have a longer life expectancy. For example, cGVHD of the GI tract can lead to malnutrition and poor weight gain and linear growth while sclerotic skin changes and joint contractures can lead to musculoskeletal deformities as a child grows. Complications of cGVHD in children may lead to significant long-term morbidity.

Chronic GVHD Treatment in Pediatric Patients:
Currently, there are no therapies indicated for the treatment of pediatric patients with cGVHD, and ibrutinib is the only therapy indicated for adult patients with cGVHD (after failure of one or more lines of systemic therapy). A significant proportion of pediatric patients do not maintain sufficient disease control with existing treatments, or experience toxicities that limit their effectiveness (Jacobsohn 2010). Choice of treatment in pediatric patients is mostly based on experience in adults, and often includes prednisone and cyclosporine in the frontline setting (Baird 2010, Zecca 2002).

Study objective

This study has been transitioned to CTIS with ID 2023-507330-24-00 check the CTIS register for the current data.

Part A - Dose Finding/Safety
Primary Objective:
* To determine the recommended pediatric equivalent dose (RPED; based on pharmacokinetic [PK] and, if applicable, pharmacodynamic data) for use in pediatric subjects (age >=1 to <12 years) with cGVHD as defined by the 2014 NIH Consensus Development Project Criteria
Secondary Objectives:
* To determine the safety of ibrutinib in pediatric subjects with cGVHD.
* To assess pharmacodynamics (BTK occupancy) of ibrutinib in pediatric subjects with cGVHD.
Part A Continuation Cohort
* For those subjects continuing therapy after dose escalation (Part A Continuation Cohort), secondary endpoints will be the same as outlined under Part B below.
Part B - Pharmacokinetics and Safety Study
Primary Objective:
* To assess the PK and safety of ibrutinib in pediatric subjects (age >=1 to <22 years) with cGVHD.
Secondary Objectives:
* To evaluate the efficacy of ibrutinib treatment at 24 weeks in pediatric subjects with cGVHD.
* To evaluate the duration of response to ibrutinib treatment in pediatric subjects with cGVHD.
* To evaluate the overall survival rate in pediatric subjects with cGVHD treated with ibrutinib
* To evaluate safety by assessing the potential impact of ibrutinib on late effects (including effects on growth and development and immune reconstitution) in pediatric subjects with cGVHD.

Study design

Open label, multicenter, Phase 1/2 dose finding, safety and efficacy study of oral ibrutinib in pediatric subjects with moderate or severe cGVHD. The study is divided into 2 parts:
Part A - dose finding and safety study for subjects >=1 to <12 years, and Part B - PK, safety and
efficacy study for subjects >=1 to <22 years. Enrollment will be concurrent into Part A (for subjects < 12 years only),
and into Part B (for subjects >= 12 years old only). Once the RPED (for subjects < 12 years) has been established in Part A, enrollment for all
subjects (age >= 1 to < 22 years) will continue in Part B. The RPED for subjects >=1 to <12 years of age with cGVHD is targeted
to be the dose that will achieve approximately the equivalent exposure to that seen in adult subjects with cGVHD who received 420 mg of
ibrutinib daily. Subjects age >= 12 years will receive the adult fixed dose of 420 mg orally daily in Part B of the study.

Part A - Dose Finding/Safety Study
A minimum of 12 subjects >=1 to <12 years with moderate or severe cGVHD after failure of 1 or more lines of systemic therapy will be enrolled. Intra-subject dose escalation will occur in order to determine the RPED. Subjects will receive oral ibrutinib once daily, starting with a dose of 120 mg/m2 (equivalent to approximately 50% of the adult cGVHD dose calculated using mg/m2) and escalate to 240 mg/m2 (approximately 100% of the adult cGVHD dose) after 14 days of treatment at the lower dose level, provided there are no safety concerns. Doses may exceed an absolute dose of 420 mg.
Pharmacokinetic data and, if applicable, pharmacodynamic data, from Part A will be used to determine the RPED to be carried forward for
subjects >=1 to <12 years in Part B. If analysis of PK data after the initial 3 subjects treated at the 50% dose level confirms sub-therapeutic
exposure, then dose levels may be adjusted for all subsequent subjects who begin Part A.
The RPED will be determined after PK (and, if applicable, pharmacodynamic) data are evaluated on a minimum of 12 subjects in
Part A (>=1 to<12 years) including a minimum of 3 subjects in the younger age group (>=1 to < 6 years). If the older age group (age >=6 to
<12 years) enrolls 9 subjects before 3 subjects in the younger age group are enrolled, RPED will be determined based on available data, and
subsequent enrollment for the older age group will be in Part B while the younger age group continues to recruit subjects in Part A. Safety
will be monitored until 30 days after the last ibrutinib dose.

Part A Continuation Cohort:
Subjects participating in Part A may continue receiving daily ibrutinib at the

240 mg/m2 dose (or maximal achieved dose) until the RPED is determined, at which time their dose may be adjusted. This cohort will be treated and evaluated in the same fashion as for Part B subjects. Evaluation of these subjects will include safety and efficacy as in Part B subjects.

Part B - Pharmacokinetics, Safety, and Efficacy
Part B will enroll a minimum of 10 and up to 32 subjects with moderate or severe cGVHD after failure of 1 or more lines of systemic therapy or with newly diagnosed moderate or severe cGVHD. Efficacy assessments will be made at weeks 5, 13, 25 and every 12 weeks subsequently. PK and pharmacodynamic data will be assessed on Week 3 Day 1. Treatment with ibrutinib will continue until:
* The subject*s cGVHD no longer requires treatment (subject has received at least 36 weeks of ibrutinib and has been off immunosuppressants for a minimum of 12 weeks)
* The subject begins a new systemic immunosuppressive agent for treatment of cGVHD
* Progressive cGVHD
* Unacceptable toxicity
* Recurrence of the underlying disease, or
* Subject dies
In addition to regular assessments of safety and efficacy, subjects in Part A and B will continue to be followed every 12 months until 60 months post-enrollment, to assess for potential late effects of ibrutinib,including effects on growth and development as well as immune reconstitution.

Intervention

see section study design

Study burden and risks

Chronic GVHD Treatment in Pediatric Patients
Currently, there are no therapies indicated for the treatment of pediatric patients with cGVHD, and ibrutinib is the only therapy indicated for adult patients with cGVHD (after failure of one or more lines of systemic therapy). A significant proportion of pediatric patients do not maintain sufficient disease control with existing treatments, or experience toxicities that limit their effectiveness (Jacobsohn 2010). Choice of treatment in pediatric patients is mostly based on experience in adults, and often includes prednisone and cyclosporine in the frontline setting (Baird 2010, Zecca 2002).

Contacts

Public
Pharmacyclics

Gateway Boulevard 1000
South San Francisco 94080
US
Scientific
Pharmacyclics

Gateway Boulevard 1000
South San Francisco 94080
US

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

1. Part A: Subjects with moderate or severe cGVHD after failure of 1 or more lines of systemic therapy.
2. Part B: Subjects with moderate or severe cGVHD after failure of 1 or more lines of systemic therapy, or subjects with new onset moderate or severe cGVHD and in need of systemic immunosuppression.
a. Subjects with new onset moderate or severe cGVHD must not have received previous systemic therapy for cGVHD with the exception of corticosteroids received within 72 hours prior to signing the informed consent form.

b. Subjects with newly diagnosed cGVHD may be receiving other immunosuppressants for the prophylaxis or treatment of acute GVHD, but if the subject is receiving prednisone for prophylaxis or treatment of acute GVHD it must be at or below 0.5 mg/kg/d at the time of enrollment.
3. History of allogeneic stem cell transplantation
4. Age
• Part A: >=1 to <12 years of age at the time of enrollment
• Part B: >=1 to <22 years of age at the time of enrollment
5.Written informed consent or parental or guardian permission and assent of children capable of understanding the nature of the study, per country-specific or site-specific standards
6. Ability of subject or, if a minor, parent/guardian to understand the purpose and risks of the study and to provide a signed and dated parental permission and authorization to use protected health information (in accordance with national and local subject privacy regulations); willingness of child to provide an assent, if developmentally able to do so.

Exclusion criteria

Disease-Related
1. Presence of single organ genito-urinary involvement as the only manifestation of cGVHD.
Concurrent Conditions
2. Received an investigational agent within 28 days before enrollment.
3. Received donor lymphocyte infusion (DLI) within 56 days before enrollment.
4. Progressive underlying malignant disease or active post-transplant lymphoproliferative disease.
5. Ongoing anticoagulation treatment with warfarin or equivalent vitamin K antagonist.
6. History of other malignancy (not including the underlying malignancy that was the indication for transplant), with the following exceptions:
• Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to enrollment and felt to be at low risk for recurrence by treating physician
• Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma without current evidence of disease
• Adequately treated cervical carcinoma in situ without current evidence of disease
7. History of major surgery within 28 days before enrollment or lack of full recovery from surgery.
8. Any life-threatening illness, medical condition, or organ system

dysfunction that, in the investigator*s opinion, could compromise the subject*s safety or put the study outcomes at undue risk.
9. Female subject who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 3 months of the last dose of study drug. Male subject who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.
10. Unwilling or unable to participate in all required study evaluations and procedures.

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):	13-01-2020
Enrollment:	2
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	22-08-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-11-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	15-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-05-2023
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
EU-CTR	CTIS2023-507330-24-00
EudraCT	EUCTR2017-004558-41-NL
CCMO	NL67071.041.19