A Randomized, Open-label, Safety and Efficacy Study of Ibrutinib in Pediatric and Young Adult Patients With Relapsed or Refractory Mature B-cell non-Hodgkin Lymphoma.

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Run-in Part (Part 1)Objectives Primary* Confirm that the pharmacokinetics in pediatric subjects is consistent with that in adults Secondary* Evaluate the safety and tolerability of ibrutinib in combination with RICE or RVICI background therapy in...

Ethical review	Approved WMO
Status	Completed
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON50711

Source
ToetsingOnline

Brief title
54179060LYM3003/Sparkle

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
B-AL), Burkitt leukemia (ie, Burkitt-like lymphoma (BLL), DLBCL, Relapsed/refractory BL

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: door de opdrachtgever

Intervention

Keyword: Ibrutinib, Mature B-cell non- Hodgkin-Lymphoma, Pediatric, Relapsed or refractory

Outcome measures

Primary outcome

Run-in Part (Part 1):

* Exposure (area under the plasma concentration-time curve [AUC])

* Apparent (oral) plasma clearance (CL/F), apparent (oral) volume of distribution (Vd/F), and derived measures of exposure such as maximum observed plasma concentration (Cmax)

* Relationship between pharmacokinetic parameters and age or measure of body size

Randomized Part (Part 2):

* Difference in EFS between the 2 treatment groups (an event is defined as the time from randomization to death, disease progression, or lack of CR or PR after 3 cycles of treatment based on blinded independent event review)

Secondary outcome

Run-in Part (Part 1):

* Safety parameters, including gastrointestinal effects, immune function, intensified cardiac monitoring (in particular, after previous anthracycline exposure)
* Overall response (complete response [CR], including CR biopsy-negative [CRb] and unconfirmed CR [CRu]) and partial response [PR])
* Phosphor BTK, as well as SYK, STAT3, caspase-3, BCL-xL, and cIAP1 expression at baseline and during treatment
* B-cell receptor (BCR)/CD79B, CARD11, and MYD mutations
* c-MYC, immunoglobulin, and T-cell receptor gene rearrangements at baseline
* BTK occupancy
* Visual analog scale score for palatability

Randomized Part (Part 2):

* Safety parameters, including gastrointestinal effects, immune function, intensified cardiac monitoring (in particular, after previous anthracycline exposure)
* The proportion of subjects who achieve CR, (including CRb and CRu) and PR
* Percent decrease in the sum of the products of the lesion diameters at Day 14
* Number and proportion of subjects who proceed to stem cell transplantation
* The time interval from the first dose of ibrutinib to the first documented response for those subjects who respond

* Duration calculated from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease (PD) or death

* Proportion of subjects with EFS at 2 and 3 years

* The duration from the date of randomization to the date of the subject*s death

* Phospho-BTK, as well as SYK, STAT3, caspase-3, BCL-xL, and cIAP1 expression at baseline and during treatment

* BCR/CD79B, CARD11, and MYD mutations

* c-MYC, immunoglobulin, and T-cell receptor gene rearrangements at baseline

* BTK occupancy

* Population pharmacokinetic parameters and derived systemic exposure to ibrutinib such as AUC

* Relationship between pharmacokinetic parameters and age or measure of body size

* Visual analog scale score for palatability

Study description

Background summary

Ibrutinib (IMBRUVICA®; PCI-32765; JNJ-54179060) is an orally-administered, covalently-binding small molecule Bruton*s tyrosine kinase (BTK) inhibitor currently being co-developed by Janssen Research & Development, LLC and Pharmacyclics LLC for the treatment of B-cell malignancies.

In children, mature B-cell non-Hodgkin lymphomas (NHLs) occur rarely; the most common types are Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL). Although these are aggressive lymphomas that are fatal in weeks to months if untreated, the cure rate in children with BL and DLBCL is between 85% to 90% after initial treatment. Given this high cure rate, the incidence of

relapsed or refractory BL and DLBCL within the broader pediatric population of NHL is very small.Relapse of pediatric BL most commonly occurs within 6 months of the end of treatment and has a poor prognosis. A review of children with mature B-cell NHL who relapsed or progressed following treatment with frontline pediatric B cell NHL protocols had survival rates of less than 20%; however, these data were not summarized by the individual subtypes of BL or DLBCL. Despite the reported overall response rate (ORR) of over 50% in most of these series, the overall mortality of this population is high and the 1- and 2-year event-free survival (EFS) rates are approximately 40% and 20%, respectively. Long-term survival beyond 2 years is poor, with only 10% to 20% of these patients surviving, underscoring the unmet medical need in this patient population.

Historically, RICE has been the most commonly used treatment regimen for DLBCL and BL in the relapsed/refractory pediatric population. However, among members of the European Intergroup Collaboration for Childhood non-Hodgkin Lymphoma (EICNHL), an alternative treatment regimen (the rituximab, vincristine, ifosfamide, carboplatin, and idarubicin [RVICI] regimen) is being increasingly used in BL patients.

As described above, long-term survival for patients with relapsed or refractory BL and DLBCL is poor, with only 10% to 20% of these patients surviving beyond 2 years, underscoring the unmet medical need in this patient population. Ibrutinib is an oral agent with an acceptable safety profile and novel mechanism of action. The drug inhibits the B-cell receptor pathway via BTK inhibition, thereby overcoming the B-cell receptor (BCR)- and chemokine-controlled retention of malignant B cells in their supportive microenvironments. It has been shown to disrupt the pathogenesis of several B-cell malignancies. Therefore, the addition of ibrutinib to a salvage regimen like RICE/RVICI may provide some advantages for the pediatric population given its non-overlapping mechanism of action and toxicity profile. Although there is no clinical pediatric experience with ibrutinib, translational models demonstrate activity of ibrutinib in BL and DLBCL. Clinical data also demonstrate the safety and activity of ibrutinib in adult subjects with relapsed DLBCL. No effect of the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) on ibrutinib pharmacokinetics was observed, nor did ibrutinib affect the pharmacokinetics of vincristine, also a CYP3A substrate. Therefore, an open label study of ibrutinib in combination with RICE/RVICI in pediatric subjects with relapsed or refractory BL or DLBCL is planned. The available safety and pharmacokinetic information combined with the unmet medical need support foregoing a stepwise approach and support starting treatment using the body surface area (BSA)-derived equivalent of the 560 mg ibrutinib dose used in adults with lymphomas. In all 3 pediatric age groups, the first 2 evaluable subjects will start treatment with the equivalent of 420 mg, followed by up titration to the 560 mg equivalent guided by safety and pharmacokinetic evaluation.

Study objective

Run-in Part (Part 1)
Objectives
Primary
* Confirm that the pharmacokinetics in pediatric subjects is consistent with that in adults
Secondary
* Evaluate the safety and tolerability of ibrutinib in combination with RICE or RVICI background therapy in pediatric subjects with B-cell malignancies
* Assess anti-tumor activity of ibrutinib as add on to RICE or RVICI regimens
* Assess disease-specific biomarkers
* Assess the pharmacodynamic response
* Acceptability and palatability assessment of all ibrutinib formulations
Exploratory
* Evaluate other response biomarkers
* Explore the exposure-response relationships

2.1.2. Randomized Part (Part 2)
Objectives
Primary
* Assess efficacy (EFS) of ibrutinib in combination with RICE or RVICI background therapy compared to RICE or RVICI background therapy alone * Difference in EFS between the 2 treatment groups (an event is defined as the time from randomization to death, disease progression, or lack of CR or PR after 3 cycles of treatment based on blinded independent event review)
Secondary
* Evaluate the safety and tolerability of ibrutinib in combination with RICE or RVICI background therapy in pediatric subjects and young adults with B-cell malignancies * Safety parameters, including gastrointestinal effects, immune function, intensified cardiac monitoring (in particular, after previous anthracycline exposure)
* Determine the ORR * The proportion of subjects who achieve CR, (including CRb and CRu) and PR
* Evaluate tumor volume reduction at Day 14 * Percent decrease in the sum of the products of the lesion diameters at Day 14
* Determine the number and proportion of subjects who proceed to stem cell transplantation * Number and proportion of subjects who proceed to stem cell transplantation
* Evaluate the time to response * The time interval from the first dose of ibrutinib to the first documented response for those subjects who respond
* Measure the duration of response * Duration calculated from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of PD or death
* Evaluate long-term survival (EFS at 2 and 3 years) * Proportion of subjects with EFS at 2 and 3 years

* Evaluate overall survival * The duration from the date of randomization to the date of the subject*s death
* Assess disease-specific biomarkers * Phosphor-BTK, as well as SYK, STAT3, caspase-3, BCL-xL, and cIAP1 expression at baseline and during treatment
* BCR/CD79B, CARD11, and MYD mutations
* c-MYC, immunoglobulin, and T-cell receptor gene rearrangements at baseline
* Assess the pharmacodynamic response, if deemed appropriate based on Part 1 results * BTK occupancy
* Assess the population pharmacokinetics of ibrutinib in pediatric subjects and young adults * Population pharmacokinetic parameters and derived systemic exposure to ibrutinib such as AUC
* Relationship between pharmacokinetic parameters and age or measure of body size
* Acceptability and palatability assessment of all ibrutinib formulations * Visual analog scale score for palatability
Exploratory
* Evaluate other response biomarkers * Other biomarkers, as applicable
* Explore the exposure-response relationships * Potential relationships between systemic exposure and response

Study design

This is a 2-part, multicenter study. A safety and pharmacokinetic run-in part (Part 1) will be conducted before starting the randomized part (Part 2) of the study. Part 2 is a randomized, open-label, Phase 3 study to compare the safety and efficacy of ibrutinib in combination with CIT (RICE or RVICI) versus CIT alone in children and young adult subjects with relapsed or refractory mature B-cell NHL. All subjects in Part 1 will receive ibrutinib in combination with CIT (investigator choice of RICE or RVICI); 6 to 12 pediatric subjects (1 to <18 years) will be enrolled to allow confirmation of the dose regimen. In Part 2, approximately 72 additional subjects will be randomized in a 2:1 ratio to receive ibrutinib in combination with CIT (investigator choice of RICE or RVICI) or CIT alone; at least 40 subjects are targeted to be of age 1 to <18 years and at least 10 of the 40 subjects are targeted to be age <11 years. Subjects will be stratified by histology (Burkitt lymphoma [BL]/Burkitt leukemia [B AL] versus other) and by background therapy (RICE versus RVICI). Pharmacokinetic samples will be obtained during Part 2 of the study to characterize the pharmacokinetics in pediatric subjects.
Part 1 and Part 2 of the study will be conducted in 3 phases: a Pretreatment (Screening) Phase, a Treatment Phase, and a Posttreatment Phase. The Treatment Phase will extend from enrollment/randomization until 1 of the following: 1) completion of 3 cycles of therapy, 2) transplantation, if clinically indicated, or 3) disease progression, whichever comes first. Subjects will begin the Posttreatment Phase after completion of combination therapy. During the Posttreatment Phase, subjects on ibrutinib with a response of PR or better and have completed 3 cycles of combination treatment will continue on ibrutinib monotherapy for up to three 28-day cycles as described below (see Dosage and

Administration). All subjects will be followed to assess disease progression as described below (see Efficacy Evaluations/Endpoints). The Posttreatment Phase will continue until death, loss to follow up, consent withdrawal, or study end, whichever occurs first. The end of study is defined as when approximately 60 EFS events have occurred in Part 2 (death, disease progression, or lack of CR or PR after 3 cycles of treatment based on blinded independent event review), or the sponsor terminates the study, whichever comes first.

Intervention

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. The IDMC will review the safety and
efficacy data during the study and make recommendations as to the further conduct of the study.

Study burden and risks

Safety evaluations will include adverse events (AEs) (incidence, intensity, and type), vital sign measurements, clinical
laboratory test results, and limited physical examinations.

Contacts

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Scientific
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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)
Elderly (65 years and older)

Inclusion criteria

- 1 to <18 years of age enrollment will begin with children in the 2 older age groups (6-11, 12-17 years) to assess pharmacokinetics and safety data before allowing enrollment of children in the youngest age group (1-5 years) (Part 1 only), or 1 to 30 years of age, inclusive, if initial diagnosis of mature B-cell NHL occurred at <18 years of age (Part 2 only)
- Relapsed/refractory BL, Burkitt-like lymphoma (BLL), Burkitt leukemia (ie, B-AL) with FAB3 morphology or presence of surface immunoglobulin by flow cytometry, DLBCL, DLBCL not otherwise specified (NOS), or other pediatric mature B-cell NHL
- Must be in first recurrence and have received only one prior line of therapy or have disease that is primarily refractory to conventional therapy
- Must have at least 1 of the following:
a) 1 site of measurable disease >1 cm in the longest diameter and >1 cm in the shortest diameter by radiological imaging
b) bone marrow involvement
c) cerebrospinal fluid with blasts present
- Lansky-Karnofsky score of *50
- Adequate organ function
- Must have recovered from the acute toxic effects of prior chemotherapy, immunotherapy, or radiotherapy, in the opinion of the investigator, prior to entering this study.
- signed, written, informed consent or assent as applicaple.
- Adolescents/young women of childbearing potential must be practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method throughout the study and for at least 3 months after the last dose of ibrutinib and 1 year after the last dose of the background CIT.
- Must be willing and able to adhere to the prohibitions and restrictions specified in this protocol

Exclusion criteria

- Ongoing anticoagulation treatment with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon), or ongoing treatment with agents known to be strong CYP3A4/5 inhibitors, or has taken any disallowed therapies, Prohibited Medications, before the planned first dose of study drug
- Inherited or acquired bleeding disorders
- Clinically significant arrhythmias, complex congenital heart disease, or left ventricular ejection fraction (LVEF) <50% or shortening fraction (SF) *28%
- Known history of human immunodeficiency virus (HIV) or active Hepatitis B or C virus
- Any condition that could interfere with the absorption or metabolism of ibrutinib including malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel
- Known allergies, hypersensitivity, or intolerance to ibrutinib or its excipients (refer to Investigator's Brochure)
- Known allergy, hypersensitivity, or intolerance to any of the backbone CIT
- Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned first dose of study drug, or is - currently being treated in an investigational study
- Pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study drug
- Plans to father a child while enrolled in this study or within 3 months after the last dose of study drug
- Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
- Had major surgery, (eg, requiring general anesthesia) within 4 weeks before enrollment/randomization, or has not fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 4 weeks after the last dose of study drug administration. Lumbar puncture, bone marrow aspiration/biopsy, or placement of central venous access device are not considered major procedures.
- A diagnosis of post-transplant lymphoproliferative disease (PTLD)
-Patients who are within 6 months of an allogeneic bone marrow transplant

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	17-02-2020
Enrollment:	2
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	23-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	24-04-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-05-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	05-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-02-2021
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	EUCTR2016-000259-28-NL
CCMO	NL57075.078.16

Study results

Date completed: 11-06-2021

Results posted: 07-06-2022

First publication
22-12-2021

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File