A first-in-human dose escalation and expansion study with the SIRPα-directed monoclonal antibody BYON4228 alone and in combination with rituximab to evaluate the safety, pharmacokinetics, pharmacodynamics and efficacy in patients with relapsed/refractory CD20 positive B-cell Non-Hodgkin*s Lymphoma (NHL)

Published: 22-12-2022
Last updated: 25-09-2024

This study has been transitioned to CTIS with ID 2024-512390-27-00 check the CTIS register for the current data. The primary objectives of this trial are:• Part 1 (dose escalation): To evaluate the safety of BYON4228 alone and in combinationwith...

Ethical review	Approved WMO
Status	Pending
Health condition type	Lymphomas non-Hodgkin's unspecified histology
Study type	Interventional

Summary

ID

NL-OMON56086

Source
ToetsingOnline

Brief title
BYON4228

Condition

- Lymphomas non-Hodgkin's unspecified histology

Synonym
lymphoma, NHS, Non-Hodgkin Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Byondis Bv.
Source(s) of monetary or material Support: by the sponsor;Byondis B.V.

Intervention

Keyword: BYON4228, NHL, Non-Hodgkin

Outcome measures

Primary outcome

Primary endpoints

The primary endpoint for Part 1 of the trial is:

• Incidence of dose limiting toxicity (DLT), or

• Optimal biological dose (OBD).

The primary endpoint for Part 2 of the study is:

• Objective response rate (ORR).

Optimal biological dose (OBD) is defined as the dose level where no DLTs were experienced, providing maximal target engagement over the full dosing interval (28 days for the 4-weekly cohorts, 14 days for the 2-weekly cohorts) an acceptable benefit/risk profile for all evaluable patients in the dose-cohort.

Objective response rate (ORR) is defined as the percentage of patients with a

best overall tumor response of complete response (CR) or partial response (PR) according to the Lugano classification.

Secondary outcome

Safety endpoints

The endpoints related to safety include:

• Incidence and severity of (serious) AEs;

• Changes in vital signs and weight;

• Changes in ECOG performance status;

• Changes in laboratory parameters;

• Percentage of patients with confirmed anti-BYON4228 and anti-rituximab antibodies;

• Number of patients with dose modifications due to AEs.

Efficacy endpoints

Preliminary efficacy will be assessed by:

• ORR (Part 1);

• Clinical benefit rate (CBR);

• Number of patients with CR, PR, stable disease (SD) and progressive disease (PD);

• Best percent change in target lesion measurements;

• Time to response;

• Duration of response (DOR);

• Progression-free survival (PFS);

• Overall survival (OS).

Clinical benefit rate (CBR) is defined as the percentage of patients with CR, PR, SD or non-CR/non-PD (SD or non-CR/non-PD for 6 or more months).

Time to response (TTR) is defined as the time from first day of IMP treatment to first observation of CR or PR.

Duration of response (DOR) is defined as the duration from first observation of response (CR or PR) to the time of disease progression or death from any cause.

Progression-free survival (PFS) is defined as the time from first day of IMP treatment to disease progression or death from any cause.

All above described responses will be calculated using the Lugano classification first and subsequently using the LYRIC criteria.

Overall survival (OS) is defined as the time from first day of IMP treatment to death from any cause.

14.2.3. Pharmacokinetic endpoints

PK endpoints will include standard parameters such as Cmax, tmax, area under the curve (AUC), Cmin (trough-levels), terminal half-life (t*), volume of distribution, and drug clearance.

14.2.4. Other endpoints

The exploratory pharmacodynamic and predictive biomarker endpoints will include, but are not limited to:

• SIRPα receptor occupancy (RO) on peripheral blood monocytes over time;

• Tumor DNA/RNA whole exome sequencing;

• Blood transcriptional profiling (RNA sequencing);

• Proteolytic serum fragments;

• Histamine.

Study description

Background summary

BYON4228 is a monoclonal antibody, a type of protein designed to recognize and attach to a specific target substance in the body. BYON4228 attaches to a target protein called SIRPα, which is present on immune cells. Normally, SIRPα binds to a protein CD47 present on NHL tumour cells. Binding results in a *don*t-eat-me-signal* which prevents the immune system from attacking the tumor cell. BYON4228 treatment aims to block the binding between the immune cell and the tumor cell. As a result, the *don*t-eat-me-signal* is suppressed which may enhance the tumor cell killing activity of other therapeutic anticancer treatments like rituximab.

Study objective

This study has been transitioned to CTIS with ID 2024-512390-27-00 check the CTIS register for the current data.

The primary objectives of this trial are:
• Part 1 (dose escalation): To evaluate the safety of BYON4228 alone and in combination
with rituximab to determine the maximum tolerated dose (MTD), or optimal biological dose
(OBD) if the MTD is not reached, and recommended combination dose regimen for expansion (RDE);
• Part 2 (expansion): To evaluate the objective tumor response rate (ORR) of the combined
BYON4228/rituximab dose regimen.

The secondary objectives of this trial are to evaluate the BYON4228/rituximab combination
with respect to:
• Safety (Part 2);
• Pharmacokinetics (PK);
• Immunogenicity;
• Preliminary efficacy

Other exploratory objectives of this trial (Part 1 and 2) are to evaluate:
• Pharmacodynamic (PD) and predictive biomarkers.

Study design

This is the first-in-human study with BYON4228, a humanized monoclonal antibody (mAb) directed against SIRPα.
This study includes a dose escalation part (Part 1) in which the MTD or OBD and RDE will be determined, and an expansion part (Part 2) to evaluate efficacy and safety in specific patient cohorts. Eligible patients with CD20 positive B-cell NHL will participate. The trial will investigate administration of BYON4228 as single agent and in combination with rituximab.

Intervention

BYON4228 will be given by intravenous infusion. Different doses of BYON4228 will be given to different patients. The first patient will receive the lowest dose 7 mg and will be escalated for the following patients as presented in Table 2 (page 6 of the protocol). The maximum dose of BYON4228 will be 1500 mg. The patient will continue with the same dose that they started with, so the dose will not be increased for them.

In this study patients will receive BYON4428 alone in the first cycle (four weeks) and the combination of BYON4228 + Rituximab from cycles 2 to 7. Rituximab will be given to the patient for what is standard for treating NHL, this will be the same dose for all patients for a total of 6 treatment cycles. Thereafter, from cycle 8 onwards, the patient will continue treatment with BYON4228 alone.

In this study there are 2 possible schedules for the administration of BYON4228, once every 4 weeks or once every 2 weeks

Study burden and risks

For the study, the patient needs to visit the hospital approximately 7 times during the first cycle of 4 weeks, followed by approximately 5 times in the second cycle, and 1 or 2 times per cycle thereafter, depending on which schedule the patient is in. Patients who are eligible will be treated until disease progression or unacceptable toxicity.
A follow-up visit is planned 30 days after the treatment discontinuation visit. Patients will subsequently be contacted every 3 months to collect survival data.

The following procedures will take place during the hospital visits:
- Physical exam, Vital signs, demographics, medical history, weight
- Blood and urine tests
- ECOG performance status
- ECG
- Pregnancy tests in women of childbearing potential
-PET-CT/MRI scan
- Buccal swab
-infusion of study drugs. For the first two infusions the patient will need to

stay overnight in the hospital.
-A tumor biopsy sample will be required at screening in case no recent archival material is available.

Contacts

Public
Byondis Bv.

Microweg 22
Nijmegen 6545 CM
NL
Scientific
Byondis Bv.

Microweg 22
Nijmegen 6545 CM
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Male or female, age >= 18 years at the time of signing informed consent; 2. Patient with: a. Part 1 only: (Aggressive or indolent) B-cell NHL expressing CD20 by immunohistochemistry (IHC) or flow cytometry, R/R to at least 2 prior lines of therapy or autologous CAR-T cell therapy; b. Part 2 cohort A only: Histologically confirmed aggressive B cell NHL (e.g., DLBCL, MCL) expressing CD20 by IHC or flow cytometry, R/R to frontline therapy, or second line salvage regimens or autologous hematopoietic cell transplantation, or autologous CAR-T therapy; c. Part 2 cohort B only: Histologically confirmed indolent B-cell NHL

(e.g., marginal zone, follicular lymphoma (Grade 1-3a) expressing CD20 by IHC or flow cytometry, R/R to at least 2 prior lines of therapy; For both parts: autologous hematopoietic stem cell transplantation (HSCT) and autologous CAR-T cell therapy (if more than 3 months prior to start IMP), and allogeneic HSCT (if more than 6 months prior to start IMP) are allowed as prior lines. 3. Eastern Cooperative Oncology Group (ECOG) performance status <= 1; 4. For Part 2 only: Disease that is measurable or assessable for response per Lugano Classification for lymphomas; 5. Laboratory measurements, blood counts (Growth Factor (GF) support and blood transfusions are not allowed within 2 weeks prior to this assessment): a. Hemoglobin >= 8.5 g/dL (> 5.28 mmol/L); b. Absolute neutrophil count (ANC) >= 1.0 × 109/mL; c. Platelet counts >= 50 × 109/mL; If bone marrow involvement: >= 25 × 109/mL;
6. Laboratory measurements, hepatic function: a. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < 5 × upper limit of normal (ULN); b. Total bilirubin <= 1.5 × ULN or 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert*s syndrome or a genetic equivalent; 7. Laboratory measurements, renal function: Serum creatinine <= 1.5 × ULN or calculated glomerular filtration rate (GFR) >30 mL/min/1.73 m2 (calculated with CKD-EPI formula); 8. Females of childbearing potential must be willing to use a highly effective method of contraception during the study and for 12 months after the last dose of rituximab or for 6 months after the last dose of BYON4228, whichever takes longer; 9. Part 1: Willing to consent to 1 pre-treatment tumor biopsy. If a recent (<= 2 months) archival tumor biopsy sample is available prior to signing the ICF and the patient did not have anticancer treatment (including steroids) since the biopsy was performed, this could be used as the pre-treatment tumor biopsy; 10. Part 2: Willing to consent to 1 pre-treatment and 1 on-treatment tumor biopsy. If a recent (<= 2 months) archival tumor biopsy sample is available prior to signing the ICF and the patient did not have anticancer treatment (including steroids) since the biopsy was performed, this could be used as the pre-treatment tumor biopsy.

Exclusion criteria

1. Having been treated with:
a. CD47 or SIRPα targeting agents at any time;
b. Other anticancer therapy including investigational agents within 2 weeks prior to start of BYON4228 treatment or within 4 times the elimination half-life (up to a maximum of 4 weeks) whichever is longer.
Note: treatment with hormonal therapy with LHRH agonists for localized prostate cancer, and treatment with bisphosphonates and RANKL inhibitors are not criteria for exclusion;
c. Radiotherapy within 1 week prior to start of BYON4228;
d. Autologous HSCT or CAR-T cell therapy within 3 months prior to start IMP, or allogeneic HSCT within 6 months prior to start IMP.
In addition, the patient must have sufficiently recovered from any

treatment-related toxicities or CTCAE Grade <= 1 or baseline, except for toxicities not considered a safety risk for the patient at the investigator's discretion;
2. Any contraindication to rituximab treatment;
3. History of hypersensitivity or allergic reaction to any of the excipients of BYON4228 or rituximab which led to permanent discontinuation of the treatment;
4. Currently diagnosed or suspected CNS involvement;
5. Burkitt's lymphoma;
6. Known active or chronic (DNA or RNA positive) hepatitis B, C or E infection or human immunodeficiency virus (HIV);
7. Red blood cell (RBC) transfusion dependence, defined as requiring more than 2 units of RBC transfusions during the 4-week period prior to screening;
8. Patients with active graft versus host disease (GVHD) or ongoing immunosuppression for GVHD;
9. History of autoimmune hemolytic anemia or autoimmune thrombocytopenia that in the investigator's opinion is likely to jeopardize patient safety;
10. History of autoimmune disorders (including but not limited to: Crohn's disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Grave's disease) or other conditions that compromise or impair the immune system (except for hypogammaglobulinemia) and that in the investigator's opinion is likely to jeopardize patient safety;
11. Second malignancy, other than the one treated in this trial, in the last 3 years before signing ICF. Except, if appropriately treated: basal cell or localized squamous skin carcinomas, localized prostate cancer or localized cervical cancer. Any other indolent malignancy may be allowed upon discussion with the medical monitor;
12. History (within 6 months prior to start of BYON4228 treatment) or presence of clinically significant cardiovascular disease such as unstable angina, congestive heart failure, myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication. Presence of atrial fibrilation may be allowed upon discussion with the medical monitor;
13. Severe active infection or other severe uncontrolled systemic disease (e.g., advanced renal disease, pulmonary, uncontrolled diabetes mellitus, severely immunocompromised state, or metabolic disease) at screening;
14. Major surgery within 4 weeks prior to start of BYON4228 treatment;
15. Pregnancy or active breastfeeding;
16. Other condition that in the investigator's opinion is likely to jeopardize patient safety or interfere with the patient's ability to comply with trial requirements.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	23-08-2023
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	BYON4228
Generic name:	BYON4228
Product type:	Medicine
Brand name:	Truxima
Generic name:	Rituximab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-12-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-04-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-10-2023

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-11-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-01-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-02-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	CTIS2024-512390-27-00
EudraCT	EUCTR2022-002018-18-NL
CCMO	NL82832.091.22