Clinical Study Report	
Drug Substance	Acalabrutinib + Multiple Agents
Study Code	D9820C00001/ACE-LY-111
Edition Number	1
Date	15 March 2022
EudraCT Number	2017-004191-63
NCT Number	03527147

PRISM: A Platform Protocol for the Treatment of Relapsed/Refractory Aggressive Non-Hodgkin's Lymphoma

Study dates: First patient enrolled: 19 June 2018
Last patient last visit: 31 March 2021

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator: [redacted]
Sarah Cannon Center for Blood Cancer

Sponsor's Responsible Medical Officer: [redacted]
Cambridge, CB2 8PA, United Kingdom

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

2. SYNOPSIS

Study centers

The study was sponsored by Acerta Pharma BV and was conducted in 10 centers in total, across the United States (8 centers) and the United Kingdom (2 centers).

Publications

Roschewski M, Munugalavadla V, Nuttall B, Burke K, Acar M, White R, et al. A phase 1 study of the combination of acalabrutinib and AZD9150 in patients with relapsed/refractory diffuse large B-cell lymphoma. Blood. 2021;138 Suppl 1:1418.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables – Master protocol

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	• To evaluate the safety of targeted agents for the treatment of relapsed/refractory aggressive non-Hodgkin's lymphoma (NHL)	Type, frequency, severity, and relationship to study treatment(s) of any treatment-emergent adverse events (TEAEs) or abnormalities of laboratory tests, serious adverse events (SAEs), dose-limiting toxicities (DLTs), or adverse events (AEs) leading to discontinuation of study treatment(s).
Secondary	Efficacy	• To evaluate the clinical activity of targeted agents for the treatment of relapsed/refractory aggressive NHL	Clinical activity endpoints: • Overall response rate (ORR) • Duration of response (DOR) • Progression-free survival (PFS) • Overall survival (OS)
Secondary	Pharmacokinetics	• To assess PK of study drugs	• Standard pharmacokinetic (PK) and appropriate PK parameters defined in each respective study arm
Exploratory	Pharmacodynamics	• Pharmacodynamic (PD) effects of the study treatment(s) in surrogate tissues and biopsies (when available).	• Results to be summarized outside of the Clinical Study Report (CSR) as a report or part of a publication
Exploratory	Efficacy	• Measurable residual disease (MRD) assessments and longitudinal monitoring of MRD.	• Results to be summarized outside of the CSR as a report or part of a publication

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Biomarker	• Investigate markers associated with sensitivity or innate or acquired resistance to the study treatment(s) that may have been observed in circulating tumor deoxyribonucleic acid (ctDNA), tumor tissue or serum/plasma. May have been protein, messenger ribonucleic acid (mRNA) or DNA markers.	• Results to be summarized outside of the CSR as a report or part of a publication
Exploratory	Biomarker	• Collect for long-term storage and/or analyze tumor biopsies and surplus plasma/serum or tissue (including patient-specific archival tumor tissue, if available) for potential future exploratory research into factors that may have influenced development of lymphoma and/or response to study treatments (where response was defined broadly to include distribution, efficacy, pharmacodynamic activity, tolerability, or safety). Included the analysis of tumor and circulating biomarkers, such as DNA, mRNA, proteins or metabolites.	• Results to be summarized outside of the CSR as a report or part of a publication

Refer to each respective study module in Appendix 16.1.1 for objectives and outcome variables.

Study design

The PRISM study was an exploratory Phase I platform protocol design to evaluate various targeted agents for the treatment of relapsed/refractory (R/R) aggressive non-Hodgkin's lymphoma (NHL). In this open-label, multi-drug, multi-center, and non-randomized platform protocol the common objectives and evaluations to be assessed were defined in the core protocol. Separate "modules" describing the particular treatment or combination of treatments, as well as procedures and assessments were provided as a series of modules to the Master platform protocol as appendices. The Master protocol was amended during the life of the

study to enable modules to be added. Any differences from the Master protocol related to a specific module have been described in the module annexes.

At the Investigator's discretion, patients were screened for more than one module at a time.

Target patient population and sample size

This master platform protocol was conducted in 10 centers across the United States and Europe. The total number of patients enrolled to each study module was not to exceed 40.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Refer to the Clinical Study Report (CSR) for each module.

Duration of treatment

Patients continued to receive study treatment until disease progression, or discontinuation criteria were met.

Statistical methods

No formal statistical hypothesis testing was to be conducted for this protocol. The safety analyses were the primary endpoints of this study. Safety assessments consisted of monitoring and recording dose-limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs) and AEs leading to discontinuation of study treatment(s); measurements of protocol-specified hematology, clinical chemistry, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that were deemed critical to the safety evaluation of the study treatments. All safety analyses were performed on the safety population defined as all patients who received at least 1 dose of study treatments.

Patient population

In total 50 patients were screened, and 30 patients were treated in the study; 17 patients in Module 1, 2 patients in Module 2, 7 patients in module 3, and 4 patients in module 4.

Summary of efficacy results

The limited number of patients in this study and the short duration of follow up preclude meaningful interpretation of efficacy. Please refer to the CSR for each module.

Summary of pharmacokinetic results

Refer to the CSR for each module.

Summary of safety results

Refer to the CSR for each module.

Conclusions

The PRISM study was an exploratory Phase I platform protocol design to evaluate various targeted agents for the treatment of R/R aggressive NHL. The study was terminated prematurely due to the Sponsor's decision because of either safety/tolerability of the investigated combinations or because of modest clinical activity reported (refer to individual modules for details).

- Module 1 was closed on 06 December 2019 as the Steering Committee agreed to permanently close module 1 to enrolment following discussion of the durability of response to the combination.
- Module 2 was closed on 25 February 2019 [redacted]
- Module 3 was closed prematurely on 31 March 2021 as the sponsor decided not to pursue the development of this triplet combination for the indication of R/R DLBC
- Module 4 was closed prematurely on 13 April 2020 following safety data review [redacted]

Refer to the CSR for each module for details full.

None of the explored combinations in modules 1- 4 will continue subsequent clinical development.

Clinical Study Report Module 1	
Drug Substance	Acalabrutinib + AZD9150
Study Code	D9820C00001/ACE-LY-111
Edition Number	1
Date	15 March 2022
EudraCT Number	2017-004191-63
NCT Number	03527147

PRISM: A Platform Protocol for the Treatment of Relapsed/Refractory Aggressive Non-Hodgkin's Lymphoma

Study Module 1: AZD9150 plus Acalabrutinib in Relapsed/Refractory Diffuse Large B-cell Lymphoma

Abbreviated CSR

Study dates: First patient enrolled: 10 August 2018
Last patient last visit: 11 August 2020
The analyses presented in this report are based on a clinical data lock date of 31 March 2021

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator:
[redacted]
Sarah Cannon Center for Blood Cancer
[redacted]

Sponsor's Responsible Medical Officer:
[redacted]
Cambridge, CB2 8PA,
United Kingdom

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study centre(s)

Refer to Section 2 of the master clinical study report (CSR).

Publications

Refer to Section 2 of the master CSR.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints – Study Module 1 (AZD9150 [a] and Acalabrutinib) Subprotocol

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To evaluate the safety of AZD9150 and acalabrutinib for the treatment of relapsed/refractory DLBCL.	Type, frequency, severity, and relationship to study treatment(s) of any TEAEs or abnormalities of laboratory tests, SAEs, DLTs, or AEs leading to discontinuation of study treatment(s).
Secondary	Efficacy	To evaluate the clinical activity of AZD9150 and acalabrutinib for the treatment of relapsed/refractory DLBCL.	Clinical activity endpoints: ORR, DOR, PFS, OS.
Secondary	PK	To assess PK of AZD9150 and acalabrutinib.	Standard and appropriate PK parameters.
Secondary	Immunogenicity	To assess immunogenicity of AZD9150.	[redacted]
Exploratory	PK-PD	PD and PK-PD effects of the study treatments(s) in surrogate tissues and/or biopsies (when available).	[redacted]

Table S1 Objectives and Endpoints – Study Module 1 (AZD9150 [a] and Acalabrutinib) Subprotocol

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Efficacy	MRD assessments and longitudinal monitoring of MRD.	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Exploratory	Biomarker	Collect for long-term storage and/or analyse tumor biopsies and surplus plasma/serum or tissue for potential future exploratory research into factors that may influence development of lymphoma and/or response to study treatments. Included the analysis of tumor and circulating biomarkers, such as DNA, mRNA, proteins or metabolites.	[redacted]

[a] AZD9150 is also referred to as danvatirsen.

AE = Adverse Event; BTK = Bruton tyrosine kinase; CRR = Complete response rate; ctDNA = circulating tumor DNA; DLBCL = Relapsed/refractory diffuse large B-cell lymphoma; DLT = Dose-limiting toxicity; DNA = Deoxyribonucleic acid; DOR = Duration of response; MRD = Measurable Residual Disease; ORR = Overall response rate; OS = Overall Survival; PD = Pharmacodynamics; PFS = Progression-free survival; PK = Pharmacokinetic; SAE = Serious Adverse Event; TEAE = Treatment emergent adverse event

Study design

Module 1 was a single-arm, open-label study evaluating the combination of AZD9150 [redacted] with acalabrutinib (Bruton tyrosine kinase [BTK] inhibitor) for the treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL).

Target population and sample size

Module 1 was designed to enroll up to 21 patients who were diagnosed with relapsed/refractory DLBCL.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Study module 1 (AZD9150 + acalabrutinib) Subprotocol

- AZD9150 [redacted] was administered as a [redacted] intravenous (IV) infusion.
- Acalabrutinib was administered orally [redacted]

AZD9150

AZD9150 was administered, by the site study staff, as an IV infusion [redacted]

Acalabrutinib

Acalabrutinib was administered with [redacted] water.
Acalabrutinib was administered without regard to food. Doses should be administered [redacted] at approximately the same times each day.

AZD9150 and acalabrutinib were administered until disease progression, unacceptable toxicity or the patient discontinued treatment for any other reason.

Individual investigational product (IP) batch numbers and further information is located in Appendix 16.1.6b (refer to module 1).

Table S2

Investigational Product	Dose, Regimen, Route of Administration	Manufacturer	Manufacturer/ Bulk Lot Number	Primary lot number	Expiry date
AZD9150 [redacted] **Vial Labeled Kit**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZD9150 [redacted] **Vial Labeled Kit**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZD9150 [redacted] **Vial Labeled Kit**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted] IV, intravenous(ly)

Duration of treatment

Patients continued to receive study treatment until disease progression or discontinuation criteria were met.

Statistical methods

Demographic and other baseline disease characteristics, protocol deviations, concomitant medications, dosing, exposure, safety, tolerability, dose-limiting toxicity (DLT), and response data were listed as defined by the current AstraZeneca standards.

Study population

Seventeen patients were enrolled in module 1 of the study.

Summary of efficacy results

In this Phase I study on 17 patients with advanced, pre-treated DLBCL, the combination of acalabrutinib and AZD9150 showed limited efficacy with an ORR 23.5% (CR rate of 11.8%) and median DOR1.9 months.

Summary of pharmacokinetic results

Overall, the PK data of acalabrutinib, [redacted] and AZD9150 were consistent with historical data, suggesting no drug-drug interaction.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

- [redacted]
- [redacted]
- No AEs with fatal outcome were reported in this study.
- [redacted]

- [redacted]
- [redacted]
- In general, there were no clinically meaningful changes from baseline in clinical laboratory data, vital signs, ECG results, or physical findings.

Conclusion(s)

- The primary endpoint of this Phase I study was to investigate the safety of acalabrutinib in combination with AZD9150 for the treatment of relapsed/refractory DLBCL.
- [redacted]
- The safety profile of the individual investigational drugs acalabrutinib and AZD9150 was generally consistent with the safety profile as per Acalabrutinib IB and AZD9150 IB.
- In the evaluable population and with the caveat of the small sample size, efficacy was modest both in terms of response rate (ORR 23.5%) and durability (median DOR 1.9 months, median PFS 2 months).
- The decision to stop recruitment into module 1 was based on an interim analysis of the efficacy data. [redacted]
- No future studies are planned to further investigate this combination.

ARM 2 ADDENDUM

Clinical Study Report	
Drug Substance	Acalabrutinib + AZD6738
Study Code	D9820C00001/ACE-LY-111
Edition Number	1
Date	05 March 2021
EudraCT Number	2017-004191-63
NCT Number	03527147

PRISM: A Platform Protocol for the Treatment of Relapsed/Refractory Aggressive Non-Hodgkin's Lymphoma

Study Arm 2: AZD6738 plus Acalabrutinib in Relapsed/Refractory Diffuse Large B-cell Lymphoma

Study dates: First subject enrolled: 19 June 2018
Last subject last visit: 08 January 2019

Phase of development: I

International Co-ordinating Investigator: [redacted]
Sarah Cannon Center for Blood Cancer
[redacted]

Sponsor's Responsible Medical Officer: [redacted]
Acerta Phama LLC
[redacted]
South San Francisco, CA 94080

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

2. SYNOPSIS

Study centre(s)

See Section 2 of the master CSR.

Publications

See Section 2 of the master CSR.

Objectives and criteria for evaluation-Arm 2-Specific

Table S1 Objectives and outcome variables – Study Arm 2 (AZD6738 and acalabrutinib) Subprotocol

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To evaluate the safety of AZD6738 and acalabrutinib for the treatment of relapsed/refractory DLBCL	Type, frequency, severity, and relationship to study treatment(s) of any TEAEs or abnormalities of laboratory tests, SAEs, DLTs, or AEs leading to discontinuation of study treatment(s).
Secondary	Efficacy	To evaluate the clinical activity of AZD6738 and acalabrutinib for the treatment of relapsed/refractory DLBCL	Clinical activity endpoints: ORR, DOR, PFS, OS
Secondary	PK	To assess PK of AZD6738 and acalabrutinib	Standard and appropriate pharmacokinetic parameters
Exploratory	PK-PD	PD and PK-PD effects of the study treatments(s) in surrogate tissues and/or biopsies (when available).	[redacted]
Exploratory	Efficacy	MRD assessments and longitudinal monitoring of MRD.	
Exploratory	Biomarker	Investigate markers associated with sensitivity or innate or acquired resistance to the study treatment(s) that may be observed in ctDNA, tumor tissue or serum/plasma. May behave been protein, mRNA or DNA markers.	

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Biomarker	Collect for long-term storage and/or analyse tumor biopsies and surplus plasma/serum or tissue for potential future exploratory research into factors that may influence development of lymphoma and/or response to study treatments. Included the analysis of tumor and circulating biomarkers, such as DNA, mRNA, proteins or metabolites.	[redacted]

The study was discontinued after enrolment of 2 patients. Therefore, none of the exploratory objectives were evaluated.

Study design

Arm 2 of this master platform protocol was an open-label study evaluating the combination of AZD6738 [redacted] with acalabrutinib (BTK inhibitor) for the treatment of patients with relapsed/refractory DLBCL or aggressive Non-Hodgkin's lymphoma (i.e., B-cell NHL).

Target subject population and sample size

[redacted]

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Study Arm 2 (AZD6738 + acalabrutinib) Subprotocol

- AZD6738 was administered orally [redacted]
- Acalabrutinib was administered orally [redacted]

AZD6738 and Acalabrutinib were administered with [redacted] of water. Patients were instructed to fast [redacted] Patients were instructed to take doses at approximately the same times each day.

Treatment was administered in [redacted] cycles. Study treatment was administered until disease progression, unacceptable toxicity or the patient discontinued treatment for any other reason.

Individual investigational product (IP) batch numbers and further information is located in Appendix 16.1.6b.

Duration of treatment

Patients continued to receive study treatment until disease progression or discontinuation criteria were met.

Statistical methods

Demographic and other baseline disease characteristics, protocol deviations, concomitant medications, dosing, exposure, safety, tolerability, DLT, and response data were listed as defined by the current AZ standards.

Subject population

Two patients were enrolled on Arm 2 of the study. The cohort was closed on 25 February 2019 [redacted]

Summary of efficacy results

[redacted]

Summary of safety results

[redacted]

Conclusion(s)

[redacted]

Clinical Study Report	
Drug Substance	Hu5F9-G4/rituximab +acalabrutinib
Study Code	ACE-LY-111
Edition Number	1
Date	15 March 2022
EudraCT Number	2017-004191-63
NCT Number	03527147

PRISM: A Platform Protocol for the Treatment of Relapsed/Refractory Aggressive Non-Hodgkin's Lymphoma

Study Module 3: Hu5F9-G4/Rituximab plus Acalabrutinib in Relapsed/Refractory Diffuse Large B-cell Lymphoma

Abbreviated CSR

Study dates: First patient enrolled: 13 August 2019
Last patient last visit: 31 March 2021
The analyses presented in this report are based on a data cutoff of 31 March 2021

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator:
[redacted]
Sarah Cannon Center for Blood Cancer

Sponsor's Responsible Medical Officer:
[redacted]
Cambridge, CB2 8PA, United Kingdom

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study center(s)

See Section 2 of the Core Clinical Study Report (CSR).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S 1 Objectives and Endpoints

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To evaluate the safety of Hu5F9-G4/rituximab and acalabrutinib for the treatment of relapsed/refractory DLBCL	Type, frequency, severity, and relationship to study treatment of any TEAEs or abnormalities of laboratory tests, SAEs, DLTs, or AEs leading to discontinuation of study treatment(s).
Secondary	Efficacy	To evaluate the clinical activity of Hu5F9-G4/rituximab and acalabrutinib for the treatment of relapsed/refractory DLBCL	Clinical activity endpoints: ORR, CRR, DOR, PFS, OS
Secondary	PK	To assess PK of Hu5F9-G4/rituximab and acalabrutinib	Standard and appropriate PK parameters
Secondary	Immunogenicity	To assess immunogenicity of Hu5F9-G4	[redacted]
Exploratory	PK-PD	PD and PK-PD effects of the study treatments(s) in surrogate tissues and/or biopsies (when available).	[redacted]
Exploratory	Efficacy	MRD assessments and longitudinal monitoring of MRD.	Correlations of MRD detectability using DNA based methods to response depth and DOR, PFS and OS.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Biomarker	Investigate markers associated with sensitivity or innate or acquired resistance to the study treatment(s) that may be observed in ctDNA, tumor tissue or serum/plasma. These may be protein, mRNA or DNA markers..	[redacted]
Exploratory	Biomarker	Collect for long-term storage and/or analyze tumor biopsies and surplus plasma/serum/saliva or tissue (including patient-specific archival tumor tissue, if available) for potential future exploratory research into factors that may influence development of lymphoma and/or response to study treatments (where response is defined broadly to include distribution, efficacy, pharmacodynamic activity, tolerability, or safety). This may include the analysis of tumor and circulating biomarkers, such as DNA, mRNA, proteins, or metabolites.	Correlative analysis with treatment effects to determine if any recurrent biomarkers could predict response, as well as any relationship to study drug exposure levels.

AE = Adverse Event; BTK = Bruton tyrosine kinase; CRR = Complete response rate; ctDNA = circulating tumor DNA; DLBCL = Relapsed/refractory diffuse large B-cell lymphoma; DLT = Dose-limiting toxicity; DNA = Deoxyribonucleic acid; DOR = Duration of response; MRD = Measurable Residual Disease; ORR = Overall response rate; OS = Overall Survival; PD = Pharmacodynamics; PFS = Progression-free survival; PK = Pharmacokinetic; SAE = Serious Adverse Event; TEAE = Treatment emergent adverse event

Study design

Module 3 of the master platform protocol was a Phase 1, single-arm, open-label study evaluating the combination of Hu5F9-G4 [redacted]/rituximab (anti-CD20 antibody) with acalabrutinib (Bruton tyrosine kinase inhibitor) for the treatment of relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL).

Target population and sample size

Module 3 was conducted at 5 study sites in the United States. It was planned to enroll up to 21* patients with R/R DLBCL.

* Note: The protocol states this number as 25; this is a typographical error in the protocol, which was identified at the time of writing the CSR.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Hu5F9-G4 [redacted] and rituximab [redacted] were administered as intravenous (IV) infusions. Acalabrutinib was administered orally [redacted]

Table S 2 Details of study treatments

Investigational Product	Dose, Regimen, Route of Administration	Manufacturer	Manufacturer/ Bulk Lot Number	Primary lot number	Expiry date
Hu5F9-G4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hu5F9-G4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hu5F9-G4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]	-	-	-
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Duration of treatment

Acalabrutinib dosing could continue until disease progression or unacceptable toxicity; Hu5F9-G4 and rituximab dosing could continue until disease progression, unacceptable toxicity or up to 2 years of treatment.

Statistical methods

No formal statistical hypotheses testing was planned. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals for discrete variables) were used to summarize data as appropriate.

Study population

Seven patients were treated in module 3 at 5 US Sites. The first patient was enrolled into the study on 13 August 2019.

Summary of efficacy results

The median follow-up was 8.30 months (range: 0.7 to 16.1 months).

[redacted]

The limited number of patients and short duration of follow-up preclude meaningful interpretation of efficacy.

Summary of pharmacokinetic results

Overall, the pharmacokinetic data were consistent with historical monotherapy data, which suggested no drug-drug interaction. No anti-Hu5F9-G4 antibodies were detected.

Summary of safety results

[redacted]

[redacted]

No AEs with a fatal outcome and no dose-limiting toxicities (DLTs) or concerning safety signals were reported in this study.

[redacted]

In general, there were no clinically meaningful changes from baseline in clinical laboratory data, vital signs, electrocardiogram results, or physical findings.

Conclusion(s)

The combination of acalabrutinib, Hu5F9-G4, and rituximab (N = 7) in the Platform Protocol for the Treatment of Relapsed/Refractory Aggressive Non-Hodgkin's Lymphoma (PRISM), Module 3 study was tolerable and safe (no DLTs reported) in patients with R/R DLBCL not previously exposed to chimeric antigen receptor T-cell therapy, however the triplet did not demonstrate significant synergy in terms of clinical activity, with the caveat that the small sample size precludes meaningful interpretation of efficacy data.

The sponsor decided not to pursue the development of this triplet combination for the indication of R/R DLBCL; therefore, there is no detailed presentation of efficacy data in this abbreviated CSR.

Clinical Study Report	
Drug Substance	AZD5153 + acalabrutinib
Study Code	D9820C00001/ACE-LY-111
Edition Number	1
Date	15 March 2022
EudraCT Number	2017-004191-63
NCT Number	03527147

PRISM: A Platform Protocol for the Treatment of Relapsed/Refractory Aggressive Non-Hodgkin's Lymphoma

Study Module 4: AZD5153 plus Acalabrutinib in Relapsed/Refractory Diffuse Large B-cell Lymphoma

Abbreviated CSR

Study dates: First patient enrolled: 05 September 2019
Last patient last visit: 25 July 2020
The analyses presented in this report are based on a clinical data lock date of 31 March 2021

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator: [redacted]
Sarah Cannon Center for Blood Cancer

Sponsor's Responsible Medical Officer: [redacted]
Cambridge, CB2 8PA,
United Kingdom

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2 SYNOPSIS

Study centre(s)

Please refer to Section 2 of the master clinical study report (CSR).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To evaluate the safety of AZD5153 and acalabrutinib for the treatment of relapsed/refractory DLBCL	Type, frequency, severity, and relationship to study treatment(s) of any TEAEs or abnormalities of laboratory tests, SAEs, DLTs, or AEs leading to discontinuation of study treatment(s).
Secondary	Efficacy	To evaluate the clinical activity of AZD5153 and acalabrutinib for the treatment of relapsed/refractory DLBCL	Clinical activity endpoints: CRR, ORR, DOR, PFS, OS
Secondary	PK	To assess the PK of AZD5153 and acalabrutinib	Standard and appropriate PK parameters
Exploratory	PK-PD	PD and PK-PD effects of the study treatments(s) in surrogate tissues and/or biopsies (when available).	[redacted]

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Immunogenicity	Pharmacodynamic and pharmacokinetic-pharmacodynamic effects of the study treatment(s) in surrogate tissues and/or biopsies (when available).	[redacted]
Exploratory	Efficacy	MRD assessments and longitudinal monitoring of MRD.	Correlations of MRD detectability using DNA based methods to response depth and DOR, PFS and OS.
Exploratory	Biomarker	Investigate markers associated with sensitivity or innate or acquired resistance to the study treatment(s) that may be observed in ctDNA, tumor tissue or serum/plasma. May have been protein, mRNA or DNA markers.	[redacted]
Exploratory	Biomarker	Collect for long-term storage and/or analyse tumor biopsies and surplus plasma/serum or tissue for potential future exploratory research into factors that may influence development of lymphoma and/or response to study treatments. Included the analysis of tumor and circulating biomarkers, such as DNA, mRNA, proteins or metabolites.	Correlative analysis with treatment effects to determine if any recurrent biomarkers could predict response, as well as any relationship to study drug exposure levels.

AE = Adverse Event; BTK = Bruton tyrosine kinase; CRR = Complete response rate; ctDNA = circulating tumor DNA; DLBCL = Relapsed/refractory diffuse large B-cell lymphoma; DLT = Dose-limiting toxicity; DNA = Deoxyribonucleic acid; DOR = Duration of response; MRD = Measurable Residual Disease; ORR = Overall response rate; OS = Overall Survival; PD = Pharmacodynamics; PFS = Progression-free survival; PK = Pharmacokinetic; SAE = Serious Adverse Event; TEAE = Treatment emergent adverse event

Study design

The PRISM master platform protocol was a Phase I study, designed to evaluate various targeted agents for the treatment of relapsed/refractory (R/R) aggressive Non-Hodgkin's lymphoma (NHL). Module 4 of this master platform protocol was an open-label module evaluating the combination of AZD5153 [redacted] with acalabrutinib (Bruton tyrosine kinase [BTK] inhibitor) for the treatment of relapsed/refractory DLBCL.

Target population and sample size

It was planned that this module would be conducted in the United States and Europe with approximately 25 sites participating. It was planned to enrol up to 21* patients with R/R DLBCL.

*Note: The protocol states this number as 25, this is a typographical error in the protocol which was identified at the time of writing the CSR.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

AZD5153 was administered orally [redacted] Acalabrutinib was administered orally [redacted]

Table S 2 Details of study treatments

Investigational Product	Dose, Regimen, Route of Administration	Manufacturer	Packaging Lot Number/ Bulk Lot Number	Primary lot number	Expiry Date
AZD5153	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZD5153	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZD5153	[redacted]	[redacted]		[redacted]	[redacted]
AZD5153	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZD5153	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Investigational Product	Dose, Regimen, Route of Administration	Manufacturer	Packaging Lot Number/ Bulk Lot Number	Primary lot number	Expiry Date
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PO = per os (oral); QD = once daily

Duration of treatment

AZD5153 dosing could continue at the [redacted] up to 2 years, or until disease progression or other study discontinuation criteria were met. Acalabrutinib was administered orally at [redacted] until disease progression, unacceptable toxicity or the patient discontinued treatment for any other reason.

Statistical methods

No formal statistical testing was planned. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals for discrete variables) were used to summarize data as appropriate.

Study population

A total of 4 patients were enrolled and treated into module 4 at 4 US Sites. The first patient was enrolled on 05 September 2019 and received treatment with AZD5153 and acalabrutinib on 02 September 2019.

Summary of efficacy results

The median follow-up was 5.70 months (range: 0.8 to 13.6 months).

No patient experienced meaningful disease response. [redacted] The limited number of patients and short duration of follow-up preclude interpretation of efficacy data.

Summary of pharmacokinetic results

Overall, the pharmacokinetic data were consistent with historical monotherapy data, suggesting no drug-drug interaction with the combination.

Summary of safety results

[redacted]

No AEs with fatal outcome were reported in this study.

[redacted]

Conclusion(s)

Four patients were treated on Module 4. The cohort was closed prematurely on 13 April 2020 following safety data review [redacted] The limited number of patients and short duration of follow up preclude the interpretation of efficacy data. No future studies exploring the combination of AZD5153 and acalabrutinib in R/R DLBCL are planned.