ASX Announcement

AZD0466 clinical data presented by AstraZeneca at EHA Congress

Melbourne, Australia; 14 June 2023: Starpharma (ASX: SPL, OTCQX: SPHRY) today announces the presentation of AZD0466 clinical data by AstraZeneca at the European Hematology Association 2023 Hybrid Congress (EHA Congress), which was held from 8 - 11 June 2023. The scientific poster and corresponding abstract are appended.

AZD0466 is a highly optimised dendrimer nanoparticle formulation of AstraZeneca's dual Bcl-2/xL inhibitor, AZD4320, which utilises Starpharma's DEP® technology and is being developed by AstraZeneca under their multi-product DEP® license with Starpharma for patients with advanced blood cancers. AZD0466 is the first candidate under Starpharma's multi-product license with AstraZeneca whereby Starpharma is eligible to receive development, launch and sales milestones, in addition to royalties.

The EHA Congress is an international haematology conference that brings together clinicians, researchers, and other industry stakeholders to showcase the latest advances in haematology clinical research.

The AZD0466 clinical data presented by AstraZeneca at the EHA Congress are from the ongoing global Phase 1/2 dose escalation and expansion study in patients with advanced haematological malignancies – relapsed/refractory acute myeloid leukaemia (AML) or acute lymphocytic leukaemia (ALL) (NCT04865419). As of the poster data cutoff date[1], 26 patients had received ≥1 dose of AZD0466 up to 3600mg. AZD0466 continues to be well tolerated in patients with relapsed/refractory acute leukaemia, with adverse events matching expected toxicity based on data from preclinical studies, and evidence of Bcl/xL on-target anti-leukaemia clinical activity in line with preclinical models. This study continues to enrol patients at 20 international trial sites.

In parallel with the ongoing study in patients with acute leukaemias, AZD0466 is also being evaluated in patients with advanced non-Hodgkin lymphoma (NCT05205161), with recruitment ongoing at over 20 sites globally.

Starpharma's dendrimer drug delivery technology, known as DEP®, is used to enhance the therapeutic properties of drugs to improve solubility, efficacy, pharmacokinetics, targeting, and to reduce certain toxicities. Starpharma has established partnerships with three of the world's largest pharmaceutical companies – AstraZeneca, MSD, and Genentech – and has also developed three clinical-stage anticancer products based on its DEP® technology, with others in preclinical development.

Starpharma CEO, Dr Jackie Fairley, commented: "We are delighted to see AstraZeneca publicising AZD0466 at international conferences. This poster presentation at the European Hematology Association Hybrid Congress is just one of a number of poster presentations and journal articles published by AstraZeneca over the last year for AZD0466, which is being progressed through two global clinical trials in patients with advanced blood cancers. We look forward to seeing additional clinical data from these clinical trials."

About AZD0466 and Starpharma's multi-product DEP® license with AstraZeneca

AZD0466 is a highly optimised dendrimer nanoparticle formulation of AstraZeneca's dual Bcl-2/xL inhibitor, AZD4320, which utilises Starpharma's DEP® technology and is being developed by AstraZeneca under their multi-product DEP® license with Starpharma. AZD0466 is in a novel class of oncology drugs called dual Bcl-2/xL inhibitors which seek to overcome drug

[1] 9 March 2023

resistance which occurs in treatment with BcL-2-specific inhibitors including venetoclax. AZD0466 allows for efficient delivery of AstraZeneca's dual Bcl-2/xL inhibitor, with an optimised release profile also designed to reduce the potential for toxicities associated with dual Bcl-2/xL inhibition. Dual Bcl-2/xL inhibition with AZD0466 also has the potential for broader activity than the marketed Bcl-2-specific inhibitor, venetoclax (Venclexta®).

AZD0466 is the first candidate under Starpharma's multi-product license with AstraZeneca. Starpharma is eligible to receive development, launch and sales milestones, in addition to royalties. To date, Starpharma has received US$7M in milestones for AZD0466, with the potential to receive milestones of up to US$124M, plus royalties.

About Starpharma

Starpharma Holdings Limited (ASX:SPL, OTCQX:SPHRY) is a biopharmaceutical company, focussed on the development of pharmaceutical and medical products for unmet patient needs, including in the areas of oncology and infectious diseases.

Starpharma's innovative technology is based on proprietary polymers called dendrimers, which are precise, synthetically manufactured, nanoscale molecules. The unique properties of dendrimers – including their size, structure, high degree of branching, polyvalency, and water solubility – are advantageous in medical and pharmaceutical applications.

Starpharma uses its dendrimer technology to develop novel therapeutics and to improve the performance of existing pharmaceuticals. Starpharma's portfolio includes multiple clinical stage oncology products, which utilise its Dendrimer Enhanced Product ('DEP®') drug delivery technology; and marketed products, including VIRALEZE™ and VivaGel® BV, which utilise SPL7013, a proprietary dendrimer with antimicrobial properties.

Starpharma's DEP® drug delivery platform is being used to enhance the effectiveness of existing and novel therapies and to reduce drug-related toxicities through controlled and specified drug delivery.

In addition to Starpharma's internal DEP® programs, Starpharma has multiple DEP® partnerships with international biopharmaceutical companies including AstraZeneca (oncology); MSD (antibody drug conjugates); Chase Sun (anti-infectives); and other world leading pharmaceutical companies. Due to the broad applicability and optionality of Starpharma's DEP® platform, partnered DEP® programs have the potential to generate significant future milestones and royalties.

Starpharma's topical antiviral nasal spray, VIRALEZE™, is now registered in more than 35 countries*, including in Europe, in the UK, and in Asia. Starpharma's novel non-antibiotic vaginal gel, VivaGel® BV, for treatment of bacterial vaginosis (BV) and prevention of recurrent BV, is registered in more than 50 countries, including in the UK, in Europe, in Southeast Asia, South Africa, Australia and New Zealand.

* Note: VIRALEZE™ is not approved for use or supply in Australia.

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Disclosure
This ASX Announcement was authorised for release by the Chairman, Mr Rob Thomas.

Forward Looking Statements

This document contains certain forward-looking statements, relating to Starpharma's business, which can be identified by the use of forward-looking terminology such as "promising", "plans", "anticipated", "will", "project", "believe", "forecast", "expected", "estimated", "targeting", "aiming", "set to", "potential", "seeking to", "goal", "could provide", "intends", "is being developed", "could be", "on track", or similar expressions, or by express or implied discussions regarding potential filings or marketing approvals, or potential future sales of product candidates. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no assurance that any existing or future regulatory filings will satisfy the FDA's and other authorities' requirements regarding any one or more product candidates nor can there be any assurance that such product candidates will be approved by any authorities for sale in any market or that they will reach any particular level of sales. In particular, management's expectations regarding the approval and commercialization of the product candidates could be affected by, among other things, unexpected trial results, including additional analysis of existing data, and new data; unexpected regulatory actions or delays, or government regulation generally; our ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry, and general public pricing pressures; and additional factors that involve significant risks and uncertainties about our products, product candidates, financial results and business prospects. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected. Starpharma is providing this information as of the date of this document and does not assume any obligation to update any forward-looking statements contained in this document as a result of new information, future events or developments or otherwise. Clinical case studies and other clinical information given in this document are given for illustrative purposes only and are not necessarily a guide to product performance and no representation or warranty is made by any person as to the likelihood of achievement or reasonableness of future results. Nothing contained in this document nor any information made available to you is, or shall be relied upon as, a promise, representation, warranty or guarantee as to the past, present or the future performance of any Starpharma product.

Safety and Tolerability of AZD0466 as Monotherapy for Patients with Advanced Hematological Malignancies – Preliminary Results from an Ongoing Phase I/II Trial

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Background

- The B-cell lymphoma 2 (BCL-2) family of proteins regulate apoptosis via caspase activation and are increasingly being targeted in hematologic malignancies using inhibitors such as venetoclax, which blocks the anti-apoptotic activity of BCL-2[1]
- However, BCL-2-selective inhibition can lead to drug resistance through upregulation of anti-apoptotic proteins such as B-cell lymphoma-extra large (BCL-xL)[1]
- To broaden therapeutic activity, we developed AZD0466, a drug-dendrimer conjugate in which the BCL-2/xL dual inhibitor AZD4320 is covalently conjugated to Starpharma's clinically validated DEP® dendrimer platform and gradually released by hydrolysis[2]
- The drug-dendrimer conjugation leads to lower peak plasma levels compared to direct infusion of AZD4320 at similar doses, thus reducing the on-target toxicity that can be associated with Bcl-xL inhibition[2,3]
- Preclinically, AZD4320 showed activity in patient-derived acute myeloid leukemia (AML) xenografts and tumor growth inhibition superior to that of venetoclax and navitoclax in venetoclax-resistant xenograft models[3]
- Preliminary results from a first-in-human study (NCT04214093) in patients with solid malignancies indicated that AZD0466 is well tolerated, with no dose-limiting toxicities (DLTs) reported
- We report preliminary data of Module 1 Part A of an ongoing, modular, non-randomized Phase I/II dose escalation and expansion study, NIMBLE – drug deNdrIMer targeting BCL-2/xL in acute LEukemias (NCT04865419)

Methods

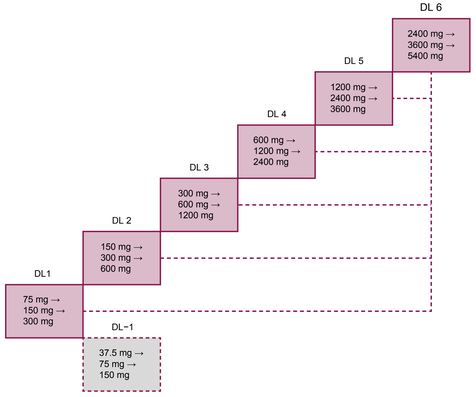
Study design

- Module 1 Part A of NIMBLE is a dose-escalation study of AZD0466 monotherapy in patients who meet the following eligibility criteria:
  - Age ≥18 years
  - Eastern Cooperative Oncology Group (ECOG) performance status ≤2
  - Relapsed/refractory AML, acute lymphocytic leukemia (ALL), or intermediate or higher risk myelodysplastic syndrome (MDS) as defined by >10% blasts, and/or risk score >3 per Revised International Prognostic Scoring System (IPSS-R)
  - Received ≥1 prior line of therapy
  - No standard-of-care treatment available
  - No active central nervous system involvement
  - No treatment with reversible CYP3A inhibitors and moderate or strong mechanism-based inhibitors or inducers of CYP3A4 which cannot be discontinued within 14 days prior to the first dose of study treatment and withheld throughout the study until 14 days after the last dose of AZD0466
  - Adequate organ function; adequate cardiac function measured by left ventricular ejection fraction >50%
  - Predicted life expectancy ≥8 weeks
- No minimum platelet count at study entry is specified but patients must have a white blood cell count <10 x 10^9/L, and transfusions are permitted as part of supportive care

Dose escalation of AZD0466

- AZD0466 IV administration starts with a dose ramp-up on days 1 and 4 and continues with weekly administration of the target dose from day 8 of cycle 1 onwards (**Figure 1**)
- Cycle length: cycle 1 (DLT evaluation period) = 35 days; subsequent cycles = 28 days
- Decisions on escalation/de-escalation are based on an mTPI-2 design[4]
- Patients are treated until disease progression, unacceptable toxicity, or withdrawal of consent

Figure 1. Study design showing the dose escalation of AZD0466



DL, dose level

Study objectives

- Primary objectives [endpoints]:
  - Safety and tolerability of AZD0466 in patients with advanced hematological malignancies [incidence of adverse events (AEs) and serious AEs (SAEs), DLTs according to predefined criteria and occurring during cycle 1, maximum tolerated dose (MTD), recommended phase II dose (RP2D), changes from baseline in laboratory findings, physical examinations, performance status, electrocardiograms, and vital signs]
- Secondary objectives:
  - Pharmacokinetic (PK) profile of AZD0466 following IV administration via the PK profile of the active moiety AZD4320 in plasma
  - Preliminary antitumor activity of AZD0466 by assessment of complete response, time to response, duration of response, and overall survival in patients with advanced hematological malignancies
- Exploratory objectives:
  - Risk of potential heart rate-corrected QT interval (QTc) prolongation of AZD0466 by concentration-QTc modeling
  - PK of AZD0466 in urine following IV administration
  - Presence, identity, and PK of plasma AZD4320 metabolites
  - Hematological improvement in patients with intermediate and higher risk MDS
  - Pharmacodynamic (PD) effects of AZD0466 by assessment of biomarkers (cell counts, DNA, RNA, and/or protein) in longitudinal bone marrow and/or blood samples
  - Relationship between baseline peripheral and/or bone marrow characteristics and efficacy outcomes
  - Explore mechanisms of acquired resistance to treatment through analysis of longitudinal peripheral and/or bone marrow samples

Results

- As of the data cutoff date of March 09, 2023, 26 patients had received ≥1 dose of AZD0466 in Module 1, Part A
- Patients had been treated for a median (range) of 4.2 weeks (1.1–11.1)

Table 1. Patient characteristics at baseline*

AZD0466 dose	300 mg (N=4)	600 mg (N=4)	1200 mg (N=7)	2400 mg (N=4)	3600 mg (N=7)	Total (N=26)
Median age, years (range)	67.5 (33–77)	71.0 (69–78)	66.0 (37–82)	61.0 (41–80)	72.0 (45–78)	69.5 (33–82)
Male, n (%)	3 (75.0)	2 (50.0)	4 (57.1)	1 (25.0)	4 (57.1)	14 (53.8)
Female, n (%)	1 (25.0)	2 (50.0)	3 (42.9)	3 (75.0)	3 (42.9)	12 (46.2)
Race, n (%)						
Asian	0	1 (25.0)	1 (14.3)	0	0	2 (7.7)
Black/African American	1 (25.0)	0	0	0	0	1 (3.8)
White	1 (25.0)	3 (75.0)	6 (85.7)	4 (100)	6 (85.7)	20 (76.9)
Other	1 (25.0)	0	0	0	0	1 (3.8)
Not reported	1 (25.0)	0	0	0	0	1 (3.8)
Missing	0	0	0	0	1 (14.3)	1 (3.8)
Ethnicity, n (%)						
Hispanic/Latino	2 (50.0)	0	1 (14.3)	0	1 (14.3)	4 (15.4)
Not Hispanic/Latino	2 (50.0)	4 (100)	6 (85.7)	4 (100)	5 (71.4)	21 (80.8)
Missing	0	0	0	0	1 (14.3)	1 (3.8)
ECOG performance status, n (%)						
0	0	0	3 (42.9)	2 (50.0)	4 (57.1)	9 (34.6)
1	1 (25.0)	4 (100)	3 (42.9)	2 (50.0)	3 (42.9)	13 (50.0)
2	3 (75.0)	0	0	0	0	3 (11.5)
Missing	0	0	1 (14.3)	0	0	1 (3.8)

*Information reflects data as of March 09, 2023. ECOG, Eastern Cooperative Oncology Group

Table 2. Disease characteristics at baseline*

	Total (N=26)
Disease, n (%)	
AML/secondary AML	21 (80.8)
ALL	5 (19.2)
AML or acute leukemia of ambiguous lineage	
AML subtype, n (%)	
M2 – Myeloblastic leukemia with maturation	1 (3.8)
M4 – Myelomonocytic leukemia	2 (7.7)
M5 – Monocytic leukemia	1 (3.8)
M6 – Erythroleukemia	1 (3.8)
M7 – Megakaryoblastic leukemia	1 (3.8)
Myeloblastic leukemia minimal maturation	4 (15.4)
Not applicable	6 (23.1)
Undifferentiated AML	4 (15.4)
AML type, n (%)	
De novo AML	8 (30.8)
Other	3 (11.5)
Prior history of myeloproliferative neoplasm	4 (15.4)
Secondary to chemotherapy	5 (19.2)
ALL	
B-cell ALL lineage, n (%)	
Common ALL	3 (11.5)
T-cell ALL lineage, n (%)	
Pre–T ALL	1 (3.8)

*Information reflects data as of March 09, 2023. ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia

Table 3. Molecular characteristics at baseline*

Molecular characteristics ALL, n (%)	N=5
t (v;11q23.3); *KMT2A* rearranged	1 (20.0)
Other	3 (60.0)
Molecular characteristics AML, n (%)	**N=21**
inv(3) (q21.3q26.2) or t(3;3) (q21.3;q26.2);	
GATA2, MECOM	1 (4.8)
ASXL1	1 (4.8)
BCR-ABL1	1 (4.8)
NPM1	1 (4.8)
RUNX1	2 (9.5)
TP53	1 (4.8)
Other	12 (57.1)

*Information reflects data as of March 09, 2023. ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia

Table 4. Previous anticancer therapy*

	AZD0466 dose					
	300 mg (N=4)	600 mg (N=4)	1200 mg (N=7)	2400 mg (N=4)	3600 mg (N=7)	Total (N=26)
Previous HSCT, n (%)	2 (50.0)	2 (50.0)	1 (14.3)	1 (25.0)	1 (14.3)	7 (26.9)
Prior venetoclax treatment, n (%)	2 (50.0)	3 (75.0)	3 (42.9)	3 (75.0)	6 (85.7)	17 (65.4)
Number of prior therapy lines, n (%)						
1	0	1 (25.0)	2 (28.6)	3 (75.0)	0	6 (23.1)
2	1 (25.0)	2 (50.0)	1 (14.3)	0	3 (42.9)	7 (26.9)
>2	1 (25.0)	1 (25.0)	3 (42.9)	1 (25.0)	3 (42.9)	9 (34.9)
Number of prior therapy regimens, n (%)						
1	0	1 (25.0)	2 (28.6)	3 (75.0)	0	6 (23.1)
2	1 (25.0)	2 (50.0)	0	0	2 (28.6)	5 (19.2)
>2	1 (25.0)	1 (25.0)	4 (57.1)	1 (25.0)	5 (71.4)	12 (46.2)

*Information reflects data as of March 09, 2023. HSCT, hematopoietic stem cell transplant.

- No DLTs or treatment-related deaths had been observed as of the data cutoff date (**Table 5**)
- Three patients experienced a SAE possibly related to AZD0466 as assed by the investigator (**Table 5**) (1 ALT increase in the 2400 mg cohort, 1 pneumonia and 1 uncoded SAE in the 3600 mg cohort)
- One patient in the 3600 mg group experienced a SAE (cerebral hemorrhage) assessed by the investigator as unrelated to AZD0466, but which led to the discontinuation of AZD0466 (**Table 5**)

Table 5. Safety summary*

	AZD0466 dose					
	300 mg (N=4)	600 mg (N=4)	1200 mg (N=7)	2400 mg (N=4)	3600 mg (N=7)	Total (N=26)
Any AE, n (%)	4 (100)	4 (100)	6 (85.7)	4 (100)	6 (85.7)	24 (92.3)
Any treatment-related AE**, n (%)	3 (75.0)	2 (50.0)	3 (42.9)	2 (50.0)	5 (71.4)	15 (57.7)
Any SAE, n (%)	4 (100)	0	3 (42.9)	1 (25.0)	6 (85.7)	14 (53.8)
Any treatment-related SAE**, n (%)	0	0	0	1 (25.0)	2 (28.6)	3 (11.5)
DLTs, n (%)	0	0	0	0	0	0
Treatment-related death**, n (%)	0	0	0	0	0	0
AE leading to dose interruption, n (%)	0	1 (25.0)	2 (28.6)	1 (25.0)	4 (57.1)	8 (30.8)
AE leading to treatment discontinuation, n (%)	0	0	0	0	1 (14.3)	1 (3.8)
Any Grade ≥3 AE, n (%)	4 (100)	2 (50.0)	5 (71.4)	1 (25.0)	6 (85.7)	18 (69.2)

*Patient treatment is ongoing and safety data up to March 09, 2023 are captured. **Reasonable possibility that the AE was caused by AZD0466, as assessed by the investigator. AE, adverse event; DLT, dose-limiting toxicity; SAE, serious adverse event

- AEs occurred in 24/26 patients (**Table 5**). The most frequently observed AE by preferred term were AST increase (26.9%), ALT increase, hypokalemia, and pyrexia (23.1% each) (**Table 6**)
- AZD0466 treatment-related AEs were reported in 15 patients (57.7%), the most common of which were AST and ALT increases (all Grade 1 or 2) (**Table 7**)
- Grade ≥3 treatment-related AEs were reported in 8 patients (30.8%) including Grade 3 Pneumonia (n=1), Grade 3 febrile neutropenia (n=3), Grade 3 diarrhea (n=1), Grade 4 thrombocytopenia (n=1), Grade 4 platelet count decrease (n=1), and Grade 3 gamma-glutamyltransferase increase (n=1)

Table 6. AEs observed in >10% of patients*

Preferred Term, n (%)	Total (N=26)		Preferred Term, n (%)	Total (N=26)	
	Any Grade	Grade ≥3		Any Grade	Grade ≥3
AST increase	7 (26.9)	0	Hypomagnesemia	4 (15.4)	0
ALT increase	6 (23.1)	0	Nausea	4 (15.4)	0
Hypokalemia	6 (23.1)	1 (3.8)	ALP increase	3 (11.5)	0
Pyrexia	6 (23.1)	1 (3.8)	Amylase increase	3 (11.5)	0
Diarrhea	5 (19.2)	1 (3.8)	Constipation	3 (11.5)	0
Pneumonia	5 (19.2)	5 (19.2)	Decreased appetite	3 (11.5)	0
Fatigue	4 (15.4)	0	Dyspnoea	3 (11.5)	0
Asthenia	4 (15.4)	0	Febrile neutropenia	3 (11.5)	3 (11.5)
Cough	4 (15.4)	0	Hypoalbuminemia	3 (11.5)	0
GGT increase	4 (15.4)	1 (3.8)	Hypertriglyceridemia	3 (11.5)	0
Hyperglycemia	4 (15.4)	0	Hyponatremia	3 (11.5)	0
Hypocalcemia	4 (15.4)	0	LDH increase	3 (11.5)	0
			Edema peripheral	3 (11.5)	0

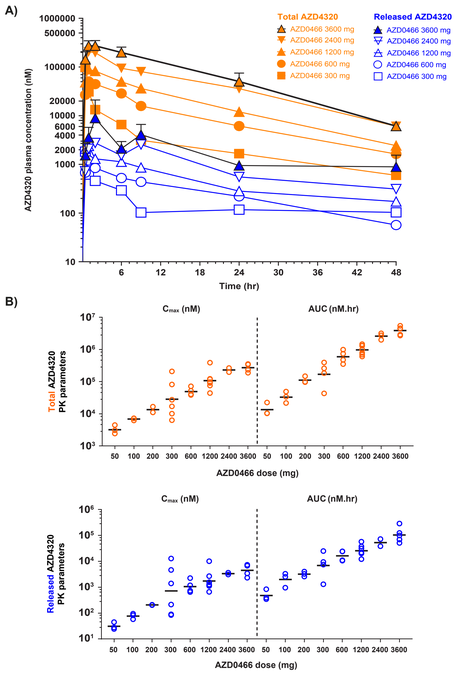
*Patient treatment is ongoing and safety data up to March 09, 2023 are captured. AE, adverse event; ALP, alkaline phosphatas; ALT, alanine aminotransferase; AST, Aspartate aminotransferase; GGT, Gamma-glutamyltransferase; LDH, lactate dehydrogenase

Table 7. Summary of treatment-related AEs occurring in >1 patient*

Treatment-related AEs+, n (%)	AZD0466 dose					
	300 mg (N=4)	600 mg (N=4)	1200 mg (N=7)	2400 mg (N=4)	3600 mg (N=5)	Total (N=24)
AST increase	2 (50.0)	1 (25.0)	0	1 (25.0)	1 (14.3)	5 (19.2)
ALT increase	1 (25.0)	1 (25.0)	0	1 (25.0)	1 (14.3)	4 (15.4)
Febrile neutropenia	1 (25.0)**	0	2 (28.6)**	0	0	3 (11.5)
Diarrhea	0	0	1 (14.3)	0	1 (14.3)**	2 (7.7)
GGT increase	0	1 (25.0)**	0	0	1 (14.3)	2 (7.7)

*Reasonable possibility that the AE was caused by AZD0466, as assessed by the investigator; patient treatment is ongoing and safety data up to March 09, 2023 are captured; patients with multiple AEs are counted once per system organ class and Preferred Term regardless of the number of occurrences. **Grade 3 event. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase

Figure 2. Pharmacokinetics of AZD4320 following IV administration of AZD0466



A) Plasma concentrations of total and released AZD4320. B) C_{max} and AUC of total and released AZD4320. Horizontal line represents median; AUClast is shown

Preliminary efficacy

- As of March 09 2023, bone marrow (BM) assessment at screening and ≥1 follow-up were available from 11 patients
- None of the patients met the formal criteria of a response
- Preliminary anti-leukemia activity based on BM blast reduction was observed in 1 patient with AML in the 1200 mg group (51% at screening vs. 32% at cycle 2 day 23) and 1 patient with AML in the 2400 mg group (35% at screening vs. 25% at cycle 1 day 30)

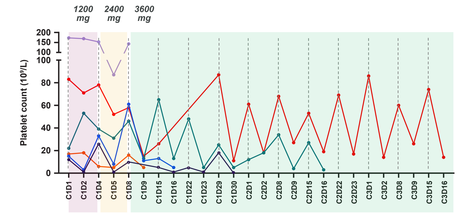
Pharmacokinetics

- Following administration of AZD0466 3600 mg by IV infusion:
  - A dose-proportional increase in area under the concentration time curve (AUC) and maximum concentration (C_{max}) was observed (**Figure 2**)
  - Released AZD4320 represents 1–5% of total AZD4320 (AUC and C_{max})
  - Released AZD4320 has a longer $T_{1/2}$ (~20 hours) relative to total AZD4320 (~10 hours)

Pharmacodynamics

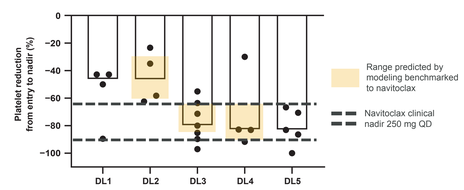
- As a marker of BCL-xL on-target activity, transient worsening of thrombocytopenia post-dose, with rapid platelet recovery prior to the next dose, was observed (**Figures 3** and **4**)
- This was in line with preclinical modeling showing a decrease in platelets post-dose vs. pre-dose starting at lower doses (300/600mg), with a ceiling effect after 1200 mg

Figure 3. BCL-xL on-target activity in individual patients in the 3600 mg group



The administration of platelet transfusion is not included due to missing data at this data capture. C, cycle; D, day

Figure 4. Observed platelet reduction is in line with predictions: evidence of dose response, nadir similar to navitoclax



DL, dose level, QD; once daily

Conclusions

- Treatment with AZD0466 is well tolerated in patients with R/R acute leukemia, with AEs matching expected toxicity based on data from preclinical studies
- Preclinical efficacy modeling and clinical PK data suggest further dose escalation is warranted to explore clinical activity, as well as the safety and tolerability of AZD0466
- The study continues to enrol

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Conflict of interest disclosures

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P537 SAFETY AND TOLERABILITY OF AZD0466 AS MONOTHERAPY FOR PATIENTS WITH ADVANCED HEMATOLOGICAL MALIGNANCIES - PRELIMINARY RESULTS FROM AN ONGOING PHASE I/II TRIAL

Topic: 4. Acute myeloid leukemia - Clinical

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Background:

The BCL2 family of proteins induce apoptosis via caspase activation and are being increasingly targeted in hematologic malignancies by small molecules such as venetoclax (VEN). However, BCL2-selective inhibition can often lead to drug resistance mediated by upregulation of anti-apoptotic proteins such as BCLxl. To broaden therapeutic activity, we developed AZD0466, a drug-dendrimer conjugate in which the BCL-2/xL dual inhibitor AZD4320 is covalently conjugated to a pegylated poly-L-lysine dendrimer and gradually released by hydrolysis. Preclinically, AZD4320 showed activity in patient (pt)-derived AML xenografts and superior tumor growth inhibition to VEN and navitoclax in VEN-resistant xenograft models (Balachander et al. Clin Cancer Res 2020).

Aims:

To report preliminary data from an ongoing Phase 1/2 dose escalation and expansion study, NIMBLE - drug deNdrIMer targeting BCL2/xL in acute LEukemias (NCT04865419) - designed to evaluate preliminary safety and tolerability (primary objectives), and pharmacokinetics (PK) and preliminary efficacy (secondary objectives).

Methods:

Module 1, Part A dose escalation evaluated target doses of 300–3600mg, with escalation/de-escalation per a mTPI-2 design. AZD0466 is administered intravenously with a ramp-up on d1, d4, d8 in cycle 1, reaching target dose on d8, and weekly administrations thereafter. Duration of cycle 1 is 35 days; subsequent cycles are 28 days. Module 2 investigates drug-drug interactions between AZD0466 and voriconazole. Pts remain on study until progressive disease, withdrawal of consent, or unacceptable toxicity. Eligible pts are ≥18 years old with relapsed/refractory (R/R) acute leukemia without active CNS disease, or with intermediate- or high-risk myelodysplastic syndrome. We report results from Module 1, part A.

Results:

As of 24 Jan 2023, 24 pts (n=20 AML, n=4 ALL; median age 69.5 yrs; ECOG 1–2 in 67% of pts) had received ≥1 dose of AZD0466 (300mg, n=4; 600mg, n=4; 1200mg, n=7; 2400mg, n=4; 3600mg, n=5). Median treatment duration was 4.1 (0.9–8) weeks. No dose-limiting toxicities (DLTs) were observed in the DLT-evaluable population (n=19).

Any-grade AZD0466-related adverse events (AEs) were reported for 50% of pts (n=12), with related AEs grade ≥3 in 25% (n=6) of pts and any AE leading to discontinuation in 1 pt. The most common related any-grade AEs were aspartate aminotransferase (n=5, 21%) and alanine aminotransferase level elevations (n=4, 17%), followed by febrile neutropenia (n=3, 13%) and diarrhea (n=2, 8%). Serious AZD0466-related AEs were reported in one pt (4%). One AE of intracranial bleeding deemed not related to AZD0466 was reported.

As a marker of BCLxL on-target activity, transient worsening of thrombocytopenia post-dose, with rapid platelet recovery prior to the next dose, was observed. This was in line with preclinical modeling showing a decrease in platelets post-dose compared to pre-dose starting at lower doses (300/600mg), with a ceiling effect after 1200mg and little further reduction at higher doses. Among pts with ≥1 follow-up bone marrow (BM) assessment available, preliminary anti-leukemia activity based on BM blast reduction at 1200 and 2400mg was observed in 2 pts. Based on clinical and PK data, and comparison of exposures observed in the clinic and predicted from preclinical murine models, further dose escalation to 5400mg is planned to evaluate safety and clinical efficacy. Enrollment is ongoing.

Summary/Conclusion:

Treatment with AZD0466 is well tolerated in pts with R/R acute leukemia, with AEs matching expected toxicity from preclinical data. Preclinical efficacy modeling and clinical PK data suggest further dose escalation is warranted to explore clinical activity.